A COMPREHENSIVE REVIEW OF MOLD RESEARCH LITERATURE FROM 2011 – 2018

Authors
[1]Ming Dooley
[2]Scott W. McMahon, MD

Affiliations
[1]Holistic Resonance Center, San Diego, California
[2]Whole World Health Care and FHL Pediatrics, Roswell, New Mexico

Correspondence
Ming Dooley
Email: ming@holisticresonancecenter.com

ABSTRACT

Background

Increasing evidence is reported supporting associations between exposure to indoor microbial growth/dampness in water-damaged buildings (WDB) and increased respiratory and allergic symptoms. Less attention is paid to associations between indoor microbial growth/dampness with multi-system and non-respiratory adverse health effects. Contrary to the medical literature, testimony is given in court that it is very unlikely for sufficient mycotoxin to amass in WDB to cause multi-system illness. We reviewed epidemiological evidence of multi-system associations between exposure and adverse health effects published from 2011-2018.

Methods

We performed a comprehensive PubMed literature search targeting epidemiological articles referencing indoor microbial growth/dampness and adverse human health effects. We reviewed articles using a pre-determined format. Articles were sorted into 2 classes, non-supportive and supportive. Supportive articles were sorted into reports demonstrating statistically significant associations between indoor microbial growth/dampness and adverse human health at levels of: i) at least one association with OR (odds ratio) or RR (relative risk) ≥2.0; ii) an OR or RR ≥1.5; iii) an OR or RR ≥1.25; or iv) the inability to calculate an OR or RR from the published data.

Results

One hundred fourteen epidemiological articles were identified referencing chronic indoor microbial growth/dampness exposure with adverse human health effects. One hundred twelve (98.2%) were supportive linking chronic exposure to the interior of WDB and altered human health. Results referenced numerous systems including respiratory, neurological, immunologic (allergic and non-IgE mediated), cognitive, ophthalmologic and dermatologic among others. Seventy-nine articles reported one or more statistically significant OR or RR ≥2.0. Ninety-eight studies reported one or more OR or RR ≥1.50. Thirteen studies were supportive without adequate data to calculate OR or RR.

Conclusions
Of 114 epidemiological articles, 112 (98.2%) were supportive of single/multi-system symptoms. The current literature supports multi-system adverse human health effects in those chronically exposed to indoor microbial growth/dampness.

Keywords
Mold, microbial growth, dampness, water-damaged buildings, adverse health effects, Chronic Inflammatory Response Syndrome, innate immune system, Sick Building Syndrome, comprehensive review, systematic review

Abbreviations Used
List of acronyms:

AAAAI	American Academy of Allergy, Asthma and Immunology
ACTH	Adrenocorticotrophic hormone
ACOEM	American College of Occupational and Environmental Medicine
ADH	Antidiuretic hormone
CBAI	Chronic biotoxin-associated illness
CDC	Centers for Disease Control and Prevention
CIRS	Chronic inflammatory response syndrome
ERMI	Environmental Relative Moldiness Index
GAO	Government Accountability Office of the United States
HLA	Human leukocyte antigen
IOM	Health Committee of the Institute of Medicine
MMP9	Matrix metalloproteinase 9
MSH	α-melanocyte stimulating hormone
MSQPCR	Mold specific quantitative polymerase chain reaction
NIOSH	National Institute of Occupational Safety and Health
NQ	NeuroQuant®
OR	Odds ratio
RR	Relative risk
SAIIE	Sequential activation of innate immune elements
TGF-β1	Human transforming growth factor – beta1
WDB	Water-damaged building(s)
WHO	World Health Organization
VCS	Visual contrast sensitivity

BACKGROUND

Respiratory System Adverse Health Effects

While there is increasing evidence supporting associations between exposure to dampness and microbes with respiratory health, adverse health effects on other body systems have been less studied and are contested in few publications. An ongoing area of controversy is the assertion of causation that adverse human health effects are acquired following exposure to damp indoor environments. A WDB is defined as a structure with water intrusion not resolved within 2 days followed by microbial growth/amplification as evidenced by visible mold, bacteria and/or actinomycetes; musty smells; or abnormalities in mold testing such as DNA-based mold specific quantitative polymerase chain reaction (MSQPCR). While there is a paucity of prospective experimental studies that could confirm risk, there exists a robust epidemiologic literature examining the association of a diversity of symptoms acquired following exposure to WDB.

Since the publication of the Health Committee of the Institute of Medicine (IOM)[1] in 2004, there is little argument that damp indoor spaces are associated with an increase in respiratory and allergic health problems. By 2009, the World Health Organization's report[2] concluded that the level of evidence was almost sufficient to establish causality for asthma exacerbation. They agreed with the IOM (2004) Damp Indoor Spaces report[1] findings that sufficient evidence of an association with upper respiratory tract symptoms, cough and wheeze existed. Between 2009 and 2018, further data in meta-analyses and reviews investigating the increased risk of asthma or rhinitis associated with exposure to mold concluded that sufficient evidence of an association between qualitative mold exposure and asthma development also existed.[3] Caillaud et al., 2018, went further and concluded in their review "Indoor Mould Exposure, Asthma and Rhinitis: Findings From Systematic Reviews and Recent Longitudinal Studies", that in children there was both sufficient evidence of a causal relationship for asthma development and exacerbation as well as sufficient evidence of an association with allergic rhinitis.[3]

Adverse Health Effects Associated with Other Systems

While the association between mold exposure and respiratory symptoms has grown in certainty, broader health effects from exposure have fewer data and are still contested. In 2008, the Government Accountability Office of the United States (GAO), published the following table documenting the potential adverse health effects of exposure to indoor mold, citing data only from Federal guidance documents.[4] (**Figure 1).**

Table 1: Potential Adverse Health Effects of Exposure to Indoor Mold Cited in Six or More Guidance Documents, by Federal Agency

Potential adverse health effects of exposure to indoor mold	Number of documents reviewed, by agency					Total number of documents citing the health effects
	CPSC[a] (2)	EPA (12)	FEMA (8)	HHS (6)	HUD (6)	
	Number of documents citing the health effects					
Asthma, asthma triggers, or asthma symptoms (such as episodes or attacks)	2	11	6	4	6	27[b]
Upper respiratory tract symptoms[c]	2	4	6	6	5	21[b]
Eye symptoms[d]	2	3	6	6	5	20[b]
Skin symptoms[e]	1	2	5	5	4	16[b]
Allergies or allergic reactions (symptoms not otherwise specified)	0	7	4	3	1	15
Wheeze	1	1	5	5	2	13[b]
Cough	2	2	4	2	2	10[b]
Difficulty breathing or trouble breathing	1	1	3	2	4	10[b]
Infections (including those affecting people who have chronic lung disease)	0	1	3	6	0	10
Adverse effects to the nervous system[f]	1	1	3	0	4	8[b]
Shortness of breath	1	1	3	3	0	7[b]
Fungal colonization or opportunistic infections in immune-compromised individuals	0	1	0	5	1	6[b]
Hypersensitivity pneumonitis	1	4	0	2	1	6[b]

Source: GAO analysis of selected federal guidance.

Figure 1. GAO Table of Potential Adverse Health Effects of Exposure to Indoor Mold

Although they were not listed in the table (as they were only cited in five or fewer guidance documents), the report also referenced fatigue, fever, dizziness, and gastrointestinal tract problems as adverse health effects resulting from exposure to indoor mold.[4] The GAO report was not intended to be comprehensive; it reviewed only governmental "fact sheets" and 20 mold review articles. A more comprehensive review was penned by Shoemaker et al., in 2010, citing 632 papers.[5]

Independently, from 1997 on, Shoemaker noted many patients with a syndrome often triggered by chronic exposure to the interior of WDB. In a retrospective study of one thousand consecutive patients seen at a single medical clinic specializing in diagnosis and treatment of patients made ill by exposure to WDB, 37 symptoms were identified (35 out of 37 symptoms were statistically significant) as differentiating cases from controls.[6] The identified symptoms were fatigue, weakness, aches, cramps, unusual pain (including ice pick pain and lightning bolt pain), joint pain, morning stiffness, headache, skin sensitivity, light sensitivity, red eyes, blurred vision, tearing, sinus problems, cough, shortness of breath, abdominal pain, diarrhea, numbness, tingling, metallic taste, vertigo, memory loss, decreased focus/concentration, confusion, decreased assimilation of new knowledge, decreased word finding ability,

disorientation, excessive thirst, frequent urination, static shocks, night sweats, mood swings, temperature regulation and appetite swings.

Chronic Inflammatory Response Syndrome, a Dysregulated Chronic Innate Immune Activation

As a result of this ongoing research, in 2006 Shoemaker published a case definition for CBAI (chronic biotoxin-associated illness)[6] requiring i) exposure to a WDB, ii) presence of symptoms in four of eight systems, iii) absence of confounders, iv) abnormalities in three of six objective parameters including visual contrast sensitivity (VCS), α-melanocyte stimulating hormone (MSH), matrix metalloproteinase 9 (MMP9), human leukocyte antigen (HLA) DR haplotypes, dysregulation of antidiuretic hormone (ADH)/osmolality, and dysregulation of adrenocorticotropic hormone (ACTH)/cortisol, and v) response to appropriate therapy.[7-9] The GAO 2008 report also offered a case definition for all WDB-based illnesses which exactly paralleled the 2006 case definition of CBAI.[4]

The mechanism of illness proposed for CBAI was dysregulated chronic innate immune activation.[10] This multi-symptom multi-system illness became known as Chronic Inflammatory Response Syndrome (CIRS) in 2010. When the exposure was from WDB, it was called CIRS-WDB.[11] Recent research in a mouse model by Harding et al. (2019), provided testing of this very hypothesis; that repeated, quantified doses of both toxic and nontoxic mold stimuli would cause innate immune activation with concomitant neural effects and cognitive, emotional, and behavioral symptoms.[12] Understanding that data in a mouse does not always translate to data in a human, Harding et al. (2019) provided prospective data consistent with both prospective and retrospective data previously presented in humans.[12] This is another study demonstrating exposure to known quantities of both toxic and nontoxic mold spores activates a central neural immune response with concomitant cognitive and emotional dysfunction.

Harding et al.'s[12] research confirmed that innate immune system activation occurred as a direct result of indoor mold exposure which is the central tenet of the pathophysiology of CIRS. Chronic innate immune system activation paired with an HLA predisposing hole in antigen presentation in most CIRS patients leads to eventual innate immune system dysregulation. Almost all CIRS patients are MSH deficient causing numerous other regulatory abnormalities (sleep cycles, ADH and ACTH production, presence of multiply antibiotic resistant biofilm-forming coagulase-negative *Staphylococci* in nasal carriage, interference with beta-endorphin production, leptin resistance and more). Capillary hypoperfusion is seen in almost all patients in the extremities but also in some with brain MR spectroscopy. Dysregulations of ADH with osmolality with/or dysregulations of ACTH with cortisol are seen in almost every CIRS patient along with some grouping of sleep, appetite, temperature perception and autonomic abnormalities. Hypothalamic function impairment appears to extend beyond decreased MSH production alone.[13]

As early as 2006, Shoemaker and Maizel presented experimental evidence for causality for CIRS through prospective exposure studies in patients who had previously improved with CIRS treatment. They used controlled repetitive exposure protocols and meticulous documentation of baseline and worsening of symptoms, VCS testing and objective lab parameters when re-exposed to a WDB.

Patient exposures were controlled. Symptoms and objective parameters returned to control levels with re-treatment. Several repetitive re-exposure trials were conducted over a course of six days documenting sequential activation of innate immune elements (SAIIE).[9,14,15] This research served to support the potential for causation of indoor microbial exposure and multi-symptom illness.

Use of Flawed Position Statements in Litigation

Despite this growing literature supporting the associations between indoor microbial growth/dampness and multi-system symptoms, medical experts testify in courts that chronic exposure to indoor mold cannot cause health problems beyond infection, (IgE-mediated) allergy, and direct toxicity from toxins, contrary to what GAO, WHO (World Health Organization) and other governmental review positions state. [2,4,16] In litigation, experts testifying for defense interests often cite former position statements from professional academies that previously supported the position that microbial growth could only cause allergic symptoms and not immune-related symptoms such as chronic fatigue or cognitive effects.[17]

The American College of Occupational and Environmental Medicine (ACOEM) published such a statement in 2002[18] and again in 2011. The American Academy of Allergy, Asthma and Immunology (AAAAI) also published such an article in 2006.[19] Not one of the three opinion statements currently serves as the position statement for either of these organizations. These former position statements claim there is little or no medical literature that supports inhaled microbial products, especially mold and fragments of mold spores, causing expanded symptoms, and are cited as authoritative.

Craner, (2008) in "A Critique of the ACOEM Statement on Mold: Undisclosed Conflicts of Interest in the Creation of an 'Evidence-based' Statement," described the ACOEM 2002 position paper as resembling a litigation "defense report" which omitted or inadequately acknowledged research validating the association between mold and building-related symptoms[20] but this appeared to have had little impact on the use of the ACOEM and AAAAI statements in litigation. The US GAO called out and criticized the AAAAI 2006 paper for failure to include assessment of known immunological effects (pg. 16).[4] The American College of Medical Toxicology created a position statement which was also strongly based on the flawed ACOEM 2002 paper and cited the AAAAI 2006 paper too. This statement was toxicologically based and also failed to mention the immune effects the AAAAI 2006 paper was criticized for not including.

We sought to evaluate the sources of conflicting opinions by reviewing published literature to determine the current state of the medical literature. We searched published data to answer two key questions: Is there adequate evidence supporting causation of multi-system illnesses from exposure to the interior of WDB? What organ systems show association of adverse effects following exposure(s)?

METHODS

Search Strategy

We performed a systematic literature search of PubMed database from 2011 through November 2018, using the following search terms - Mold/Mould/Dampness (no MESH search terms) AND each of the following (with MESH search terms) listed in **Table 1**. We did not search for unpublished articles. **Figure 2** describes the methods for article selection.

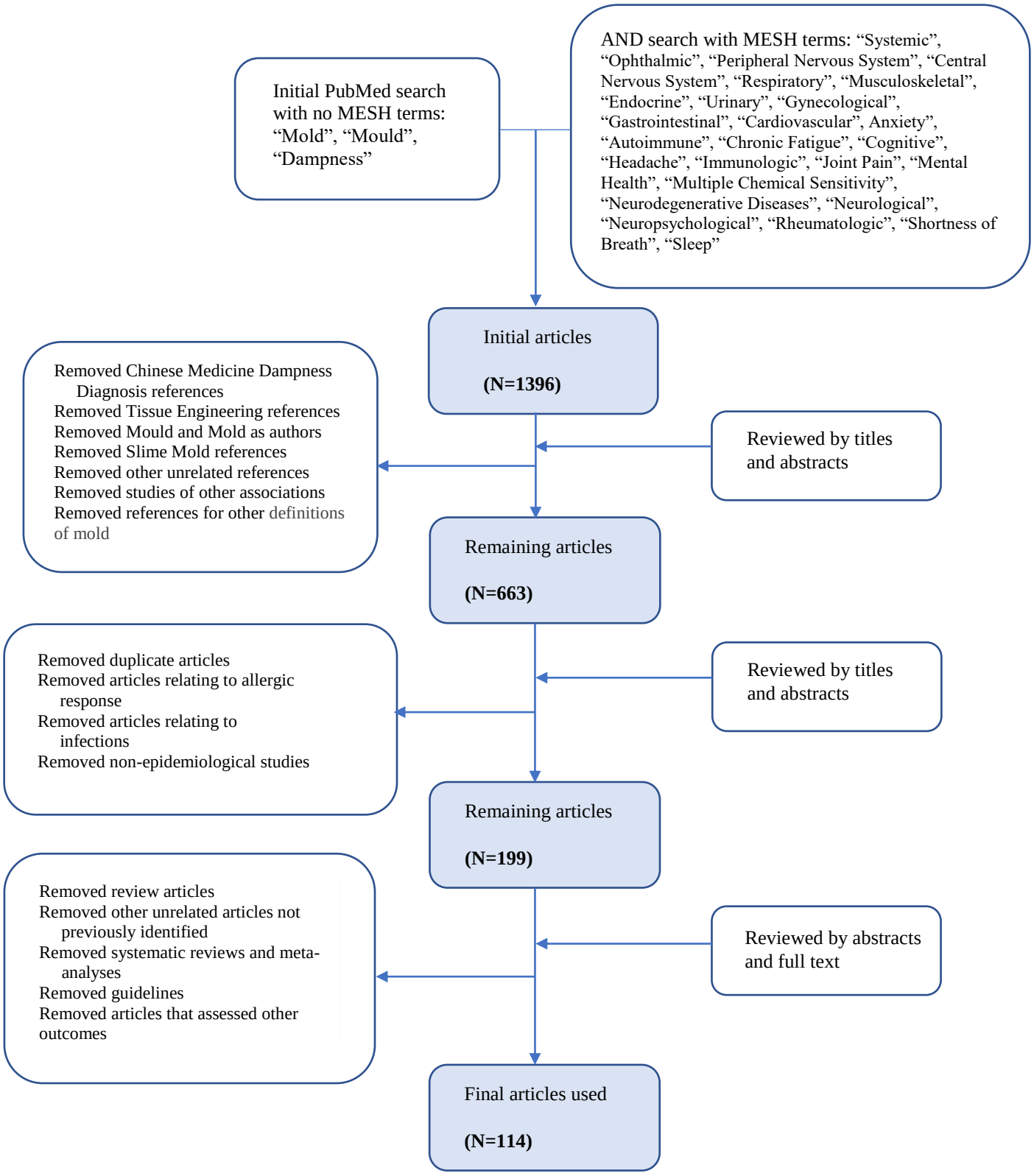

Figure 2. Methods for Article Selection

Table 1. List of Search Terms used with Mold/Mould/Dampness

Systemic	Ophthalmic	Peripheral Nervous System	Central Nervous System
Respiratory	Musculoskeletal	Endocrine	Urinary
Gynecological	Gastrointestinal	Cardiovascular	Anxiety
Autoimmune	Chronic Fatigue	Cognitive	Headache
Immunologic	Joint Pain	Mental Health	Multiple chemical sensitivity
Neurodegenerative diseases	Neurological	Neuropsychological	Rheumatologic
Shortness of Breath	Sleep		

The initial search yielded 1396 articles. For this study we identified the following *a priori* eligibility criteria: the study (i) was an original study, (ii) was a cohort/longitudinal, cross-sectional, case/control or case series/case history (iii) reported on the relationship between mold or dampness with any adverse human health effect, without regard to method for quantifying exposure and (iv) was published in the peer reviewed literature between 2011 and November of 2018. Studies were excluded if not epidemiological, not available in English (with two exceptions, see Results - Literature Search) or if only abstracts were available (with one exception, see Results - Literature Search).

Data Extraction and Quality Assessment

We reviewed eligible studies, and the relevant characteristics were recorded in a standard form for data extraction. These forms were used to populate data synthesis tables. In observational studies, risk of bias assessment is more complex than in randomized control trials and can be prone to bias and confounders.[21] At present, there is not an international standard for assessing bias in human observational studies and available tools have serious limitations such as lacking adequate description and evaluation, and time-consuming and cumbersome to implement.[22] Consequently, although we had initially planned a quality assessment for each article, since we were unsuccessful in finding a reliable tool to objectively evaluate each report, we did not perform a formal bias or quality assessment.

Data Analysis

For studies or case histories that did not contain a Relative Risk or Odds Ratio, we calculated them using standard OR formulas where the data allowed. Studies with calculated ORs can be found in **Table 2**. Details of the calculations are available upon request. Calculations and statistics were performed using Excel (Office 365). Chi-squared calculations were performed on the online chi-squared calculator at www.socscistatistics.com/tests/chisquare/default2.aspx. Findings were considered statistically significant if they met 95% confidence level or had p-values <0.05.

Table 2. Author Calculated OR*

Author	Study name	Type of Study	# of Parti-cipants	# of Cases	# of Controls	Data used	OR ≥2.0	OR ≥1.5
Sinclair et al., 2018[23]	Asthma Risk Associated with Indoor Mold Contamination in Hispanic Communities in Eastern Coachella Valley, California	Cross-sectional	695			Mean % of children in Mecca with asthma or resp ill = 17.5% (OR>2), p<0.05 Mean % of children in Coachella City with asthma or resp ill = 17.5% (OR>2), p <0.05	Yes	
Celtik et al., 2011[24 i]	Investigation of indoor molds and allergic diseases in public primary schools in Edirne city of Turkey	Cross-sectional	1,374			An OR of 1.74 and p = .0044. Association of increased spore counts with asthma symptoms in the previous 12 months		Yes
Norback et al., 2017[25]	Ocular symptoms and tear film break up time (BUT) among junior high school students in Penang, Malaysia - Associations with fungal DNA in school dust	Cross-sectional	368			Non-Invasive Tear Breakup Times associated with total Fungal DNA - drop of 4.2 seconds - lowest quartile – OR = 3	Yes	
Karvala et al., 2013[26]	Quality of life of patients with asthma related to damp and moldy work environments	Cross-sectional	1,267			Decreased quality of life with occupational asthma and work exacerbated asthma – OR = 1.5		Yes
Tuuminen and Rinne, 2017[27]	Severe Sequelae to Mold-Related Illness as Demonstrated in Two Finnish Cohorts	Cohort	89			6 in 30 with hypothyroidism – OR= 3.4 Two cancers in 50 kids – OR = 6 3 breast cancers in 25 female teachers – OR = 6	Yes	
Shoemaker et al., 2014[28]	Structural brain abnormalities in patients with inflammatory illness acquired following exposure to water-damaged buildings: a volumetric MRI study using NeuroQuant®	Case/Control		17	18	Abnormalities in MSH – OR = 7.3, abnormalities in ADH/osmolality – OR = 7.3, headache –OR = 5.33, memory – OR = 16, focus/concentration – OR = 17, word selection – OR = 16, decreased assimilation – OR = ∞, confusion – OR = ∞, disorientation – OR = ∞, numbness – OR = ∞, tingling – OR = 16, vertigo – OR = 13, metallic taste – OR = ∞, tremor – OR = ∞	Yes	

[i] Celtik et al., reported there were no associations between measured amounts of mold spores in 10 schools and human health effects, but an analysis of the data showed at least one association existed. (25) The 10 schools were evaluated by total mold spore counts. Data inspection revealed the two schools with the highest spore counts (#2 and #8) both had more than double the spores of any other school. Those 2 schools also showed the highest and third highest percentage of children with asthma symptoms in the previous 12 months. There was an association between spore counts and asthma symptoms in the previous 12 months.

[*] Details of calculations available on request.

RESULTS

Literature Search

The sequential approach to the literature search is found in **Figure 2**. One hundred fourteen studies met the search parameters. Two articles were translated using Google Translate.[29,30] One abstract from an article published in Chinese was included, as detailed data with statistically significant results was listed in the abstract.[31]

Participant Characteristics of Included Studies

Eligible articles consisted of 78 Cross-Sectional Studies, 18 Cohort Studies, 15 Case/Control Studies and 3 Case Series/Case History. The combined total number of participants, households, and families, in the 114 studies was 270,454 with 1,493 additional cases and 1,846 controls (one study had >46,000 participants). Details can be found in **Appendix 1**. Two cross-sectional studies and three case/control studies assessing different parameters evaluated the same participants and are included only once in the total number of participants. Participant characteristics from errors in **Appendix 1** below**.**

Number of Studies by Geographic Location

The number of countries represented was over 30 from 5 continents. Details of the countries represented, and the number of studies associated with each country are listed in **Table 3** with a corresponding map in **Figure 3**.

Table 3. Geographic Locations and Number of Studies

Australia	1	Korea	7
Belgium	1	Malaysia	2
Canada	8	Menorca Island	1
Chile	1	Mexico	1
China	9	New Zealand	3
Denmark	1	Norway	1
2+ European Countries	6	Pakistan	1
Finland	9	Poland	2
France	4	Portugal	1
Georgia	2	Romania	1
Germany	3	Scandinavia	1
Great Britain	2	Serbia	1
International	1	Sweden	11
Italy	3	The Caribbean	1
Japan	2	Turkey	4
USA	23		

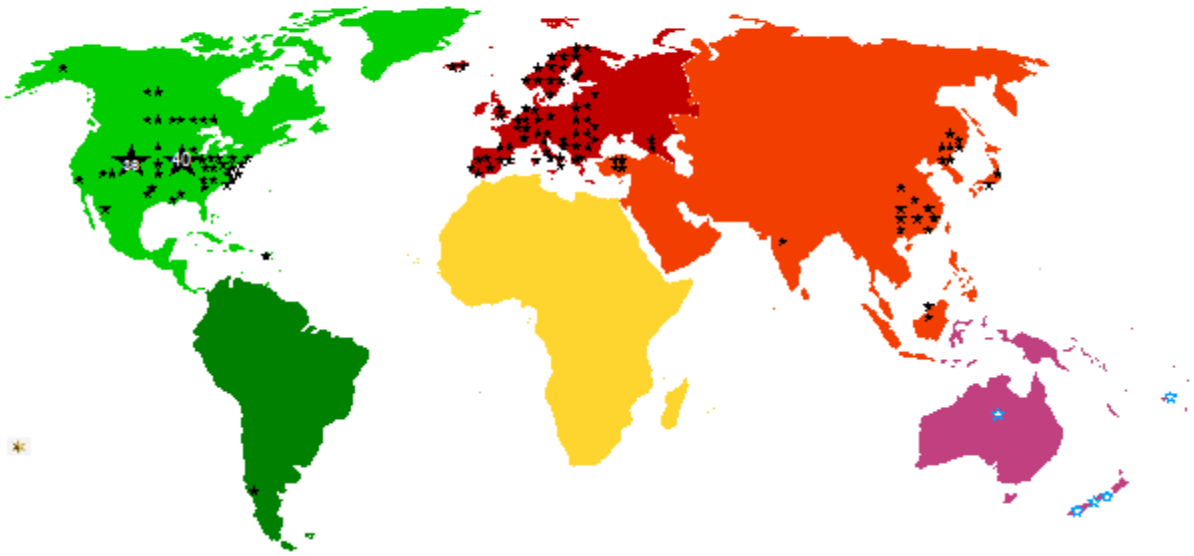

Figure 3. Map showing Geographical Distribution of Studies

Multi-system Associations

Adverse health effects were classified according to the eight body systems (**Table 4**) referenced in "Diagnostic Process for Chronic Inflammatory Response Syndrome (CIRS): A Consensus Statement Report of the Consensus Committee of Surviving Mold".[11] When adverse health effects did not fit in these categories, we created a new category **(Table 5).** Asthma and Allergies were included as immunologic in addition to the respiratory system because these illnesses incorporate deranged immunologic components. In articles that assessed a constellation of symptoms, including the imprecise appellation of "Sick Building Syndrome," or combined symptoms for statistical analysis, the statistically significant results were added to all appropriate categories referenced.

Upon analysis of the 114 articles, we found that 92 reported results with one of more statistically significant RR or OR (≥1.5) and 2 reported results with no associations. Six of the remaining 20 articles provided data enabling the authors to perform an OR calculation. All 6 articles had one or more statistically significant associations with OR >1.5. These studies are listed in **Table 2.**

Table 4. Eight Body Systems Used in Describing CIRS

General
Musculoskeletal
Eye
Respiratory
Gastrointestinal
Cognitive
Hypothalamic
Neurologic

Table 5. Additional Categories Identified in the Literature Beyond the 8 Systems

Immunologic
Dermatologic
Otolaryngologic
Mental Health
Infectious Disease
Pregnancy
Neonatal
Cardiovascular

Of the remaining 14 articles, 13 did not publish data allowing for OR calculation, and 1 article reported an OR ≥1.25. These studies' authors reported their findings supported adverse human health effects. Therefore, we found that 112 of the 114 articles were supportive of associations between exposure to the interior of WDB and adverse health effects. Further, we found i) 79 studies reported at least one statistically significant (at 95% confidence level) OR or RR of ≥2.0; ii) 98 reported an association with OR or RR of ≥1.50; and iii) 99 reported an association with OR or RR of ≥1.25. Two articles reported no associations and insufficient data was reported to calculate an OR or RR in 13. By individual findings, total statistically significant associations at 95% confidence level in these articles were: 1) OR or RR of ≥2.0, 251 associations; 2) OR or RR of ≥1.50, 384 associations; and 3) OR or RR of ≥1.25, 460 associations. References reporting no associations were 5. Results are summarized in **Table 6**.

Table 6. OR/RR Associations from 99 articles*

	OR/RR ≥2.0	OR/RR ≥1.5	OR/RR ≥1.25	No Assoc.
Number of articles	**79**	**98**	**99**	**2**
Number of references	**251**	**384**	**460**	**5**

***6 calculated by Authors**

The number of supportive studies and evidence varied for each system, as different systems were examined in each study. One hundred reports further supported previous works regarding respiratory, and 60 supported immunological effects. Twenty-four supported general adverse health effects and 16 studies supported cognitive decline. Fewer studies evaluated for the rest of the systems with only 2 studies showing no associations with respiratory and immunological symptoms. One of those two studies also showed no association with dermatologic symptoms. All other systems evaluated demonstrated zero (-0-) studies showing no associations with that system. Details of these references are summarized in **Table 7.**

Articles Referencing Associations of Non-Respiratory Systems

We prepared an in-depth analysis of the specific articles that referenced General, Cognitive, Neurological, Gastrointestinal, Musculoskeletal, and Dermatological systems (non-respiratory systems). Twenty-seven (23.7%) of the 114 studies met these criteria. These studies consisted of 17 cross-sectional studies, 6 cohort studies, and 4 case/control studies. The combined total number of participants, households, and

families, in these 27 studies was 73,304 along with 334 additional cases and 342 controls. From these 27 articles, 13 were from Europe (including 3 from Finland and 4 from Sweden), 5 were from the USA, 3 from Korea and 2 each from China and Japan. The remaining two were from Pakistan and Mexico. The largest single study was from China with 36,541 participants followed by a large study from the USA with 18,356 participants. Twenty-five of these studies had at least one association with OR/RR ≥2.0, 1 had an OR/RR ≥1.5 and the remaining one, where an OR/RR was not calculable, had statistically significant results with p≤0.05. Characteristics of these studies are listed in **Appendix 2**.

Articles Referencing Specific Statistically Significant Associations From 27 Studies of 6 Non-Respiratory Systems

We found that in some studies, individual associations were not calculated. Instead, symptoms were grouped together and often associations included symptoms from more than one system. For purposes of this review, if a symptom was included within a group of symptoms and statistically significant results were found for that group, it was considered an association in the combined category. Individually statistically significant associations were listed individually. A list of these articles and their references by categories are summarized in **Table 8.**

Table 7. Number of Studies Referencing Each System Found in the Literature Search*

	Supportive	No assoc.		Supportive	No assoc.
General	24		Immunologic	60	2
Musculoskeletal	7		Otolaryngologic	2	
Eye	16		Dermatologic	14	1
Respiratory	100	2	Mental Health	5	
Gastrointestinal	9		Infectious	5	
Cognitive	16		Pregnancy	1	
Hypothalamic			Neonatal	2	
Neurologic	10		Cardiovascular	1	

*not all references statistically significant, some statistically significant associations based on groups of symptoms

Table 8. Number of Specific Statistically Significant Associations From 27 Studies by System

Author/ Country	Title	General [iii]		Cognitive [iii]		Neuro-logical [iii]		Gastro-intestinal [iii]		Musculo skeletal [iii]		Dermato-logical [iii]	
	C are associations with any mention of a General Symptom and also includes the Individual Symptoms I is an Association with an Individual Symptom Only	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**
	Total	**12**	**10**	**5**	**7**	**4**	**5**	**5**	**0**	**3**	**1**	**4**	**6**
Sahlberg et al., 2012[32] Northern Europe	Airborne molds and bacteria, microbial volatile organic compounds (MVOC), plasticizers and formaldehyde in	Yes						Yes				Yes	

	dwellings in three North European cities in relation to sick building syndrome (SBS)												
Wen and Balluz, 2011[33] USA	Association between presence of visible in-house mold and health-related quality of life in adults residing in four U.S. states	Yes											
Arif and Korgaonkar, 2016[34] Pakistan	Association of childhood asthma with mental health and developmental comorbidities in low-income families		Yes		Yes								
Jedrychowski et al., 2011[35] Poland	Cognitive function of 6-year old children exposed to mold-contaminated homes in the early postnatal period. Prospective birth cohort study in Poland				Yes		Yes						
Thomas et al., 2012[36] USA [v]	Comparison of work-related symptoms and visual contrast sensitivity between employees at a severely water-damaged school and a school without significant water damage		Yes		Yes		Yes				Yes		Yes
Zhang et al., 2018 China[37]	Dampness and mold in homes across China: Associations with rhinitis, ocular, throat and dermal symptoms, headache and fatigue among adults		Yes	Yes				Yes					Yes
Zhang et al., 2012[38], Sweden	Dampness and moulds in workplace buildings: associations with incidence and remission of sick building syndrome (SBS) and biomarkers of inflammation in a 10-year follow-up study	Yes						Yes					
Casas et al., 2013[39] Menorca Island [ii]	Early life exposures to home dampness, pet ownership and farm animal contact and neuropsychological				Yes		Yes						

	development in 4-year-old children: a prospective birth cohort study												
Azuma et al., 2013[40] Japan	Effects of water-damaged homes after flooding: health status of the residents and the environmental risk factors		Yes			Yes							Yes
Lu et al., 2017[41] Romania	Evidence from SINPHONIE project: Impact of home environmental exposures on respiratory health among school-age children in Romania	Yes											
Hahm et al., 2016[42] Korea	Exposure to mould allergens and rhinoconjunctivitis in Korean children		Yes										
Tiesler et al., 2015[43] Korea	Exposure to visible mould or dampness at home and sleep problems in children: Results from the LISAplus study		Yes										
Lukcso et al., 2014[44] USA	Indoor environmental and air quality characteristics, building-related health symptoms, and worker productivity in a federal government building complex	Yes		Yes									
Casas et al., 2012[45] Germany	Indoor factors and behavioural problems in children: the GINIplus and LISAplus birth cohort studies				Yes								
Seo et al., 2014[46]	Infrared camera-proven water-damaged homes are associated with the severity of atopic dermatitis in children												Yes
Moniruzzaman et al., 2012[47] Sweden	Levels of endotoxin in 390 Swedish homes: determinants and the risk for respiratory symptoms in children												Yes
Roussel et al., 2012[48] France	Microbiological evaluation of ten French archives and a		Yes										

	link to occupational symptoms												
Abou-Donia et al., 2017[49] USA[vi]	Neural autoantibodies in patients with neurological symptoms and histories of chemical/mold exposures	Yes		Yes		Yes		Yes		Yes		Yes	
Sahlberg et al., 2012[50] Sweden	Onset of mucosal, dermal and general symptoms in relation to biomarkers and exposures in the dwelling: a cohort study from 1992 to 2002	Yes										Yes	
Lu et al., 2016[51] China	Outdoor air pollution, meteorological conditions and indoor factors in dwellings in relation to sick building syndrome (SBS) among adults in China		Yes										Yes
Oudin et al., 2016[52] Sweden	Poor housing conditions in association with child health in a disadvantaged immigrant population: a cross-sectional study in Rosengard, Malmo, Sweden	Yes	Yes										
Gonzalez-Casanova et al., 2018[53] Sweden	Prenatal exposure to environmental pollutants and child development trajectories through 7 years				Yes		Yes						
Karvala et al., 2011[54] Finland	Prolonged exposure to damp and moldy workplaces and new-onset asthma	Yes								Yes			
Karvala et al., 2013[26] Finland[i]	Quality of life of patients with asthma related to damp and moldy work environments	Yes											
Saijo et al., 2010[55] Japan	Relationships between mite allergen levels, mold concentrations, and sick building syndrome symptoms in newly built dwellings in Japan	Yes		Yes		Yes							
Tuuminen and Rinne, 2017[27] Finland[,vii]	Severe Sequelae to Mold-Related Illness as Demonstrated in	Yes		Yes		Yes		Yes		Yes		Yes	

	Two Finnish Cohorts												
Shoemaker et al., 2014[28] USA [i]	Structural brain abnormalities in patients with inflammatory illness acquired following exposure to water-damaged buildings: a volumetric MRI study using NeuroQuant(R)		Yes		Yes		Yes						

[i] OR calculated by author
[ii] Data had statistically significant associations with p<0.05 but OR/RR not calculable
[iii] Symptoms are classified as combined when RR/OR was based on an association with more than one symptom that includes an individual symptom included in the category. Symptoms were classified as Individual when one single symptom was found to have an association
[iv] General symptoms included headache, problems sleeping, flu-like symptoms, fatigue and others
[v] See discussion for details about this study
[vi] Abou-Donia's case/control study associated high levels of neural autoantibodies with exposure in a recorded incidence of symptoms but did not analyze associations between the high levels of neural autoantibodies with specific symptoms.
[vii] Our calculated ORs for Tuuminen and Rinne's study are not calculated for specific symptoms but for disease outcomes in a cohort that experienced associated symptoms.

From our finding of 24 articles referencing general symptoms, 12 (50%) were combined references and 10 (42%) were individual. The remaining 2 references were supportive studies where statistically significant results were not calculable, but both the reports' authors considered the studies supportive. For cognitive symptoms, out of 16 articles, 5 (31%) were combined references, and 7 (44%) were individual; for neurologic symptoms, out of 10 articles, 4 (40%) were combined references and 5 (50%) individual; for gastrointestinal, out of 9 articles, 5 (56%), references were combined and 0 individual; for musculoskeletal, out of 8 articles, 3 references (38%), were combined and 1 (13%) individual; and for dermatologic, out 14 articles, 4 (29%) references were combined, and 6 (43%) individual. The related references for 25 of the 27 articles all had OR or RR ≥2 except for one which had OR ≥1.5 and one for which an OR or RR could not be calculated from the data reported but had statistically significant results. These results are summarized in **Table 9**.

Table 9. Total Supportive References and Statistically Significant Combined and Individual Results for 6 Systems

System	Total	Combined		Individual	
General	24	12	(50%)	10	(42%)
Cognitive	16	5	(31%)	7	(44%)
Neurologic	10	4	(40%)	5	(50%)
Gastrointestinal	9	5	(55%)	0	
Musculoskeletal	7	3	(38%)	1	(13%)
Dermatologic	14	4	(29%)	6	(43%)

Studies with Multiple Associations for 6 Select Systems

Two studies, Abou-Donia, et al. (2017)[49] and Tuuminen and Rhine, (2017)[27] found statistically significant results for combined associations in all 6 systems included in this more detailed analysis. Since these were not individual associations, this may not represent statistically significant results for the individual system. Zhang, et.al (2018)[37] recorded multiple statistically significant associations in their cross-sectional study with 36,541 participants in 4 of the 6 select systems evaluated in their study, with 2 systems having individual associations and 2 systems having combined associations (two systems not evaluated).

For individual associations, Thomas, et. al (2012)[36] found statistically significant results in 5 of the 6 select systems. No data was collected for gastrointestinal symptoms. In order to be consistent with our categorization, we considered the symptom "aching all over" to be a musculoskeletal symptom, whereas Thomas et. al included it in constitutional (general). Shoemaker, et.al (2014)[28] also found statistically significant results for individual associations in 3 of the 6 select systems. In this particular study, data was not reported for the other 3 systems. Four other studies found statistically significant results in 2 of 6 systems (where 2 systems were reviewed and 4 systems were not evaluated).

Studies with No Associations

Two studies were non-supportive.[56,30] Choi et al. (2014)[56] evaluated the homes of 198 allergic children and 202 Swedish controls measuring cultured fungi, (1-3, 1-6)-β-d-glucan and ergosterol. The concentrations of cultured fungi were comparable between houses with parent reported and mold inspector reported mold issues. No associations with adverse health were associated with elevated levels of cultured fungi, (1-3, 1-6)-β-d-glucan and ergosterol.

Pegas et al. (2011)[30] looked at 342 students in Lisbon. Students ranged from 5-12 years old but 92% were between 6-8 years. The percentage of children with wheezing was an astonishing 43.3%, those with allergic rhinitis was 42.9% and the prevalence of asthma was 5.6%. Many factors were evaluated including origin country of birth, carpet on the floor of the child's room, presence of pets, heaviness of street traffic, presence of mold, tobacco exposure in the first year of life etc. The presence of mold or infiltration was noted in 19% of residences. Multi-variate linear regression was performed. While some environmental associations were found with adverse health effects, no associations were noted between presence of mold and increase of asthma.

DISCUSSION

Our Findings

Over the years, the body of knowledge has increased to the point where the association between adverse respiratory system health effects with microbial exposure is not doubted. Our research further supports that assertion. Our objective was to document associations in other published research that would corroborate or disprove the peer reviewed data published by Shoemaker beginning in 2005 confirming the multi-system, multi-symptom illness that later became known as CIRS, resulting from exposure to the interior of WDB.

We found that most peer reviewed research did not use the detailed symptom reporting that was used by Shoemaker. This was not

an unexpected finding given that CIRS research is in its infancy. This does not negate the possible impact from exposure to WDB; it is more probable that is was not assessed to the level of detail that Shoemaker observed and documented.

Nevertheless, one study that did use detailed reporting was the Thomas et al. (2012), case/control study performed by NIOSH, a division of the CDC. Two high schools were evaluated environmentally by visual inspection and multiple sample types [spore trap, bulk, swab and Environmental Relative Moldiness Index (ERMI)]. The medical team compared 95 occupants of the severely water-damaged school in New Orleans, Louisiana, with 110 occupants of a school that had not experienced significant water damage in Cincinnati, Ohio. The researchers found lower VCS scores in every column in the New Orleans school personnel and statistically significant increases in 18 of the 22 symptoms in every system they evaluated (neurobehavioral, upper and lower respiratory, dermatologic and constitutional systems). All of these ORs were ≥2. Multi-system illness and lowered VCS testing, as demonstrated in this NIOSH study, are hallmarks of CIRS.

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Work by two other groups, Tuuminen et al. (2017)[27] and Brewer, et al. (2013)[57], corroborated CIRS symptoms. Tuuminen et al. (2017)[27], part of a group in Finland, described a syndrome they called Dampness and Mold Hypersensitivity Syndrome[58] that they defined by the following 5 criteria: i) exposure to dampness microbiota; ii) recurrent and/ or unusual infections; iii) Sick Building Syndrome (SBS); iv) development of multiple chemical sensitivity and v) sensitized olfactory scenting.[59] Brewer et al. (2013)[57] described multiple symptoms and chronic illness associated with exposure to WDB, as well as referencing several publications by their group which also corroborated CIRS.

Correlating specific concentrations of fungi and fungal components has given mixed results in the literature when evaluating human health effects. Therefore, the Choi et al. (2014)[56] result showing no association is not surprising and does not degrade the otherwise very strong results reported above. Pegas et al. (2011),[30] also showing no association, gives results contrary to 30 years of epidemiological evidence regarding indoor microbial growth/dampness exposure and asthma. However, that does not mean the study is flawed. Instead, it suggests this study is an outlier. When one considers p-values, the understanding is that if a study was replicated 100 times, a p-value <0.05 means the same results will be obtained at least 95 times, but not necessarily 100 times. It is also possible that the high rate of wheezing and/or the relatively low prevalence of asthma, affected these results. The prevalence of infiltration/mold at 19% could have been underreported, which could also lead to a finding of no association.

Despite the preponderance of evidence supporting association between exposure to WDB and adverse health effects to the respiratory system, it took two decades for causality for asthma to appear in the published literature. Given this history, and that it is frequently stated that it takes an average of 17 years for research to translate into clinical practice,[60] we consider these initial findings documenting many associations with exposure to WDB and multi-system, multi-symptom illness, evidence of causation.

The core argument of the ACOEM 2002 article was the hypothesis that it would be

difficult to accumulate sufficient mycotoxin in a water-damaged room to give people significant illness. A mathematical model and proof were offered to make this point. Subsequent studies[2,4,61-64] have shown some assumptions made and some of the constants used in this proof were incorrect on the order of several magnitudes. The hypothesis itself has never been successfully tested. The AAAAI 2006 article was built on the same hypothesis. The evidence presented in our results documents that their hypothesis is incorrect and that the ACOEM and AAAAI articles do not reflect current evidence-based medicine.

Limitations

The limitations of the current study include one article that we were not able to obtain full text in English. Due to the science-wide lack of objective evaluation tools for the assessment of biases in observational studies[21,22] we did not perform a formal quality analysis and risk of bias assessment, nor did we attempt to search for unpublished data. It is not possible to assess the impact of this on our results as it could result in either an overstatement or an understatement.

This study reviewed case studies/series, case-control, nested case-control, cohort, and cross-sectional studies. Systematic reviews and meta-analyses were excluded, even though most of these supported the conclusions of this study. Further limitations included that some of the articles analyzed did not directly correlate symptoms with exposures, and some of the articles grouped symptoms together so associations were with symptom combinations. It could be inferred that an association with a group of symptoms includes an association with all symptoms in that group, however that is not explicitly stated in some articles and there may be an underrepresentation or overrepresentation of associations for these individual systems. Although most of the studies varied in design, number of subjects and assessment methods, because of the design of our study, it is likely these variations did not impact our results. Consequently, based on the total number of statistically significant results, the number of supportive articles, the very large number of subjects and the total number of supportive references we found, we believe that there is enough evidence to support our conclusions.

CONCLUSIONS

The proposition that inhaled mold, mold fragments, toxins and inflammagens, or other components of the air in WDB, cause single and multi-system illness, is supported by 112 of 114 (98.2%) epidemiological articles published between 2011 and 2018. The amount of evidence varied by system, as different systems were studied in each report. Seventy-nine studies (69.2%) had at least one association with an OR or RR ≥2.0 and 98 studies (85.9%) demonstrated an OR or RR ≥1.5. Two hundred fifty-one individual associations showed an OR or RR ≥2.0, 384 associations had OR or RR ≥1.5 and 460 associations noted OR or RR ≥1.25. All findings met 95% confidence. It is unclear why some give testimony in courts contrary to these findings.

One hundred (87.7%) of the entire 114 reports further supported previous works regarding respiratory symptoms along with 60 (52.6%) supporting immunological results. This was followed by 24 (21.1%) with reference to general symptoms. Sixteen (14.0%) studies supported cognitive decline. Varying numbers of articles supported neurologic, gastrointestinal, musculoskeletal, dermatologic, and other systems. Only 2 studies (1.8%) showed no associations with respiratory symptoms, and

immunological findings with one of the two also showing no association with dermatological findings. All other systems evaluated demonstrated zero (- 0 -) studies showing no associations with that system when that system was studied.

These percentages reflect the number of studies evaluating a particular system included in the 114 studies evaluated in this report. For instance, only 16 of the 114 studies (14.0%) reviewed cognitive decline. All 16 of those 16 reports (100%) were supportive of cognitive decline related to chronic exposure to indoor microbial growth/dampness. Those 16 papers made up 14.0% of all 114 articles evaluating all the previously noted body systems.

In a more detailed analysis of 27 (23.7%) of the total 114 articles looking at specific statistically significant associations with general, cognitive, neurologic, gastrointestinal, musculoskeletal, and dermatologic systems, of the total supportive articles for the specified system. Seven (44%) reported individual statistically significant references for cognitive symptoms, 4 (40%) reported individual statistically significant references for neurologic symptoms and 10 (40%) reported individual statistically significant references for general symptoms. Two studies reported statistically significant results in groups with a combination of symptoms that included all 6 systems. One study reported individual statistically significant results in 5 of the 6 systems (only 5 systems reviewed) with another finding individual association in 2 systems and combined associations in 2 systems (only 4 systems reviewed). An additional study found individually statistically significant results in 3 of the 6 systems (only 3 systems reviewed).

Peer-reviewed publications document that approximately 25% of the population have a genetic susceptibility for developing CIRS,[65] an estimated 50% of the buildings in the U.S. are water-damaged,[2] and the prevalence of CIRS is conservatively calculated at ≥ 7.01% in children and likely higher in adults due to the progressive nature of CIRS.[66] Nevertheless, CIRS is still an under-recognized syndrome, and those suffering from it frequently lack appropriate medical diagnosis and subsequent treatment. Therefore, it is critical that more research be done to further evaluate the multi-symptom, multi-system adverse human health effects from exposure to WDB and policies must be put into place to address the impact. We plan future data analysis in order to assess the feasibility of a meta-analysis and update to this review.

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Conflicts of Interest

Ming Dooley has no conflicts of interest to disclose. Dr. McMahon has no conflicts of interest to disclose and provides expert witness testimony in mold cases for both plaintiffs and defense.

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APPENDICES

Appendix 1. Study Characteristics

Author/Date	Country	Type of Study	# of Participants [iv]	# of Cases	# of Controls	OR/ RR ≥2.0	OR/ RR ≥1.5	OR/ RR ≥1.25
			270,454	1,493	1,846	79	98	99
Rath et al., 2011[67]	USA	Cross-sectional	1,243				Yes	
Sahlberg et al., 2012[32]	Northern Europe	Cross-sectional	159			Yes		
Holst et al., 2016[68]	Denmark	Cross-sectional	330			Yes		
Hoppe et al., 2012[69]	USA	Cross-sectional	71			Yes		
Claudio et al., 2016[70]	USA	Cross-sectional	797			Yes		
Wen and Balluz, 2011[33]	USA	Cross-sectional	18,356			Yes		
Arif and Korgaonkar, 2015[34]	Pakistan	Cross-sectional	400			Yes		
Atan Sahin et al., 2016[71]	Turkey	Cohort	384			Yes		
Kearney et al., 2014[72]	USA	Cross-sectional	352			Yes		
Norback et al., 2018[25iv]	China	Cross-sectional	39,782				Yes	
Hsu et al., 2018[73]	USA	Cross-sectional	14,076				Yes	
Karvala et al., 2014[74]	Finland	Cross-sectional	1,098			Yes		
Sinclair et al., 2018[23 i]	USA	Cross-sectional	695			Yes		
Hsu et al., 2016[75]	USA	Cross-sectional	14,585			Yes		
Karunanayake et al., 2017[76]	Canada	Cross-sectional	351			Yes		
Kielb et al., 2015[77]	USA	Cross-sectional	501			Yes		
Cibella et al., 2015[78]	Italy	Cross-sectional	2,150				Yes	
Beridze, et al., 2018[79]	Georgia	Cross-sectional	5,319				Yes	
Brewer et al., 2013[57]	USA	Case Series/Case History	3					
Clarhed et al., 2018[80]	Norway	Cross-sectional	16,099				Yes	
Jedrychowski et al., 2011[35]	Poland	Cohort	277			Yes		
Norback, et al., 2017[81 iv]	China	Cross-sectional	39,782				Yes	
Thomas et al., 2012[36]	USA	Case/Control		95	110	Yes		
Cable et al., 2014[82]	Great Britain	Cohort	7,320			Yes		
Wang et al., 2017[83]	Sweden	Cross-sectional	1,160			Yes		

Zhang et al., 2018[37]	China	Cross-sectional	36,541			Yes		
Borras-Santos et al., 2013[84]	Spain, The Netherlands and Finland	Cross-sectional	9,271				Yes	
Weinmayr et al., 2013[85]	International	Cross-sectional	46,051			Yes		
Zhang et al., 2012[38]	Sweden	Cohort	429			Yes		
Jacobs et al., 2014[86]	Netherlands and Spain	Cross-sectional	3843				Yes	
Moussu et al., 2014[87]	France	Cross-sectional	227			Yes		
Meszaros et al., 2014[88]	Australia	Cohort	5,729			Yes		
Casas et al., 2013[39]	Menorca Island	Cohort	424					
Yang et al., 2014[89]	Korea	Cross-sectional	7,389				Yes	
Stankovic et al., 2011[90]	Serbia	Cross-sectional	1,082				Yes	
Azuma et al., 2013[40]	Japan	Cross-sectional	379			Yes		
Boneberger et al., 2011[91]	Chile	Case/Control		188	294	Yes		
Hedman et al., 2015[92]	Sweden	Cohort	3,430					Yes
Lu et al., 2018[41]	Romania	Cross-sectional	280			Yes		
Punsmann et al., 2013[93]	Germany	Case/Control		25	25			
Seo et al., 2014[94]	Korea	Cross-sectional	511			Yes		
Weber et al., 2017[95]	Germany	Cross-sectional	4,732			Yes		
Kelly et al., 2013[96]	New Zealand	Cross-sectional	106				Yes	
Hahm et al., 2016[42]	Korea	Cross-sectional	3,852			Yes		
Tiesler et al., 2015[43]	Korea	Cross-sectional	1,719			Yes		
Martines et al., 2015[97]	Italy	Case/Control		204	204	Yes		
Lin et al., 2016[98]	China	Cross-sectional	4,246			Yes		
Norback et al., 2015[99]	Sweden	Cross-sectional	62					
Reponen et al., 2011[100]	USA	Cohort	176			Yes		
Hu et al., 2014[101]	China	Cross-sectional	13,335			Yes		
Gent et al., 2012[102]	USA	Cross-sectional	1,233			Yes		
Ware et al., 2013[103]	USA	Cross-sectional	561			Yes		
Harville et al., 2018[104]	Great Britain	Cohort	1927			Yes		
Levesque et al., 2018[105]	Canada	Cross-sectional	295			Yes		
Lukcso et al., 2016[44]	USA	Cross-sectional	7,637					
Jie et al., 2016[106]	China	Cross-sectional	610					

Casas et al., 2012[45]	Germany	Cohort	4,860			Yes		
Hernberg et al., 2014[107]	Finland	Cross-sectional	269					
Shorter et al., 2017[108]	New Zealand	Case/Control		150	298	Yes		
Reponen et al., 2012[109]	USA	Cross-sectional	289 Homes			Yes		
Seo et al., 2014[46]	Korea	Cross-sectional	52			Yes		
Celtik et al., 2011[24 i]	Turkey	Cross-sectional	1,374				Yes	
North et al., 2017[110]	Canada	Cohort	560			Yes		
Rea et al., 2018[111]	USA	Case Series/Case History	100					
Seo et al., 2014[112]	Korea	Case/Control		15	14	Yes		
Moniruzzaman et al., 2011[47 v]	Sweden	Case/Control		198	202	Yes		
Gargano et al., 2018[113]	USA	Cross-sectional	3,835			Yes		
Norback et al., 2011[114]	Finland	Cohort	6,443			Yes		
Hernberg et al., 2014[115]	Finland	Cross-sectional	521				Yes	
Keall et al., 2012[116]	New Zealand	Cross-sectional	891			Yes		
Roussel et al., 2012[48]	France	Cross-sectional	144			Yes		
Toyinbo et al., 2016[117]	Finland	Cross-sectional	4,248			Yes		
Karvonen et al., 2015[118]	Finland	Cohort	398			Yes		
Sahin et al., 2014[29 ii]	Turkey	Cross-sectional	63					
Norback et al., 2013[119]	10 European countries[vi]	Cohort	7,104				Yes	
Abou-Donia et al., 2017[49]	USA	Case/Control		24	12	Yes		
Dutmer et al.[120]	USA	Cross-sectional	29					
Akpinar-Elci et al., 2017[121]	The Caribbean	Cross-sectional	92					
Norback et al., 2017[122 i]	Malaysia	Cross-sectional	368			Yes		
Sahlberg et al., 2012[50]	Sweden	Cohort	452			Yes		
Lu et al., 2016[51]	China	Cross-sectional	3,485			Yes		
Pind et al., 2017[123]	Sweden	Cross-sectional	25,677				Yes	
Oudin et al., 2016[52]	Sweden	Cross-sectional	359			Yes		
Polyzois et al., 2016[124]	Canada	Cross-sectional	3,424			Yes		
Hulin et al., 2012[125]	France	Cross-sectional	727			Yes		
Tischer et al., 2015[126]	9 European countries[vii]	Cross-sectional	956				Yes	
Karunanayake et al., 2011[127]	Canada	Cross-sectional	871			Yes		

Gonzalez-Casanova et al., 2018[53]	Mexico	Cross-sectional	718			Yes		
Polyzoi et al., 2017[128]	Canada	Cross-sectional	3,424			Yes		
Pahwa et al., 2017[129]	Canada	Cross-sectional	874			Yes		
Karvala et al., 2011[54]	Finland	Cross-sectional	483			Yes		
Karvala et al., 2013[26 i]	Finland	Cross-sectional	1,267				Yes	
Vincent et al., 2018[130]	Belgium	Case/Control		32	32	Yes		
Saijo et al., 2010[55]	Japan	Cross-sectional	1,479			Yes		
Choi et al., 2014[56v,viii]	Sweden	Case/Control		198	202			
Lanthier-Veilleux et al., 2016[131]	Canada	Cross-sectional	2,097			Yes		
Kim et al., 2011[132]	Korea	Cross-sectional	1,915			Yes		
Fu et al., 2016[133]	Scandinavia	Cross-sectional	622			Yes		
Norback et al., 2016[134]	Malaysia	Cross-sectional	368			Yes		
Wang et al., 2014[135]	Sweden	Cross-sectional	5,775			Yes		
Park et al., 2012[136]	USA	Case/Control		131	161	Yes		
Pegas et al., 2011[30 ii,viii]	Portugal	Cross-sectional	342					
Ciebiada et al., 2014[137]	Poland	Cohort	68			Yes		
Civelek et al., 2010[138]	Turkey	Cross-sectional	6,963			Yes		
Zhu et al., 2012[31 iii]	China	Case/Control		271	271		Yes	
Abramidze et al., 2012[139]	Georgia	Cross-sectional	36			Yes		
Casas et al., 2017[140]	Spain, Netherlands, Finland	Cross-sectional	419					
Tuuminen and Rinne, 2017[27i]	Finland	Cohort	89			Yes		
Devien et al., 2018[141]	France	Cross-sectional	3,039			Yes		
Shoemaker et al., 2014[28 i]	USA	Case/Control		17	18	Yes		
Sun et al., 2011[142]	China	Case/Control		143	205	Yes		
Choi et al., 2016[143v]	Sweden	Case/Control		198	202	Yes		
Thrasher et al., 2011[144]	USA	Case Series/Case History	5					
Behbod et al., 2013[145]	USA	Cohort	499			Yes		

[i] OR calculated by author
[ii] Study translated using Google translate
[iii] Data based on abstract
[iv,v] These studies referenced the same populations but assessed different variables
[vi,vii] Study includes the following countries: Spain, France, Italy, United Kingdom, Germany, Estonia, Sweden, Switzerland, Iceland and others
[viii] No association found

Appendix 2. Characteristics of 27 Articles Referencing Non-Respiratory Systems

Author/ Date/ Country	Title	Type of Study	# of Partici-pants	# of Cases	# of Con-trols	OR/ RR ≥2.0	OR/ RR ≥1.5
			73,304	334	342	25	1
Sahlberg et al., 2013[32] Northern Europe	Airborne molds and bacteria, microbial volatile organic compounds (MVOC), plasticizers and formaldehyde in dwellings in three North European cities in relation to sick building syndrome (SBS)	Cross-sectional	159			Yes	
Wen and Balluz, 2011[33] USA	Association between presence of visible in-house mold and health-related quality of life in adults residing in four U.S. states	Cross-sectional	18,356			Yes	
Arif and Korgaonkar, 2015 Pakistan[34] [iii]	Association of childhood asthma with mental health and developmental comorbidities in low-income families	Cross-sectional	400			Yes	
Jedrychowski et al., 2011[35] Poland	Cognitive function of 6-year old children exposed to mold-contaminated homes in early postnatal period. Prospective birth cohort study in Poland	Cohort	277			Yes	
Thomas et al., 2012[36] USA [i]	Comparison of work-related symptoms and visual contrast sensitivity between employees at a severely water-damaged school and a school without significant water damage	Case/ Control		95	110	Yes	
Zhang et al., 2018[37] China	Dampness and mold in homes across China: Associations with rhinitis, ocular, throat and dermal symptoms, headache and fatigue among adults	Cross-sectional	36,541			Yes	
Zhang et al., 2012[38] Sweden	Dampness and moulds in workplace buildings: associations with incidence and remission of sick building syndrome (SBS) and biomarkers of inflammation in a 10 year follow-up study	Cohort	429			Yes	
Casas et al., 2013[39] Menorca Island [ii]	Early life exposures to home dampness, pet ownership and farm animal contact and neuropsychological development in 4 year old children: a prospective birth cohort study	Cohort	424				
Azuma et al., 2014[40] Japan	Effects of water-damaged homes after flooding: health status of the residents and the environmental risk factors	Cross-sectional	379			Yes	

Lu et al., 2018[41] Romania	Evidence from SINPHONIE project: Impact of home environmental exposures on respiratory health among school-age children in Romania	Cross-sectional	280			Yes	
Hahm et al., 2016[42] Korea	Exposure to mould allergens and rhinoconjunctivitis in Korean children	Cross-sectional	3,852			Yes	
Tiesler et al., 2015[43] Korea	Exposure to visible mould or dampness at home and sleep problems in children: Results from the LISAplus study	Cross-sectional	1,719			Yes	
Lukcso et al., 2014[44] USA	Indoor environmental and air quality characteristics, building-related health symptoms, and worker productivity in a federal government building complex	Cross-sectional	7,637			Yes	
Casas et al., 2012[45] Germany	Indoor factors and behavioural problems in children: the GINIplus and LISAplus birth cohort studies	Cohort	4,860			Yes	
Seo et al., 2014[46] Korea	Infrared camera-proven water-damaged homes are associated with the severity of atopic dermatitis in children	Cross-sectional	52			Yes	
Moniruzzaman et al., 2012[47] Sweden	Levels of endotoxin in 390 Swedish homes: determinants and the risk for respiratory symptoms in children	Case/ Control		198	202	Yes	
Roussel et al., 2012[48] France	Microbiological evaluation of ten French archives and link to occupational symptoms	Cross-sectional	144			Yes	
Abou-Donia et al., 2018[49] USA	Neural autoantibodies in patients with neurological symptoms and histories of chemical/mold exposures	Case/ Control		24	12	Yes	
Sahlberg et al., 2012[50] Sweden	Onset of mucosal, dermal, and general symptoms in relation to biomarkers and exposures in the dwelling: a cohort study from 1992 to 2002	Cohort	452			Yes	
Lu et al., 2016[51] China	Outdoor air pollution, meteorological conditions and indoor factors in dwellings in relation to sick building syndrome (SBS) among adults in China	Cross-sectional	3,485			Yes	
Oudin et al., 2016[52] Sweden	Poor housing conditions in association with child health in a disadvantaged immigrant population: a cross-sectional study in Rosengard, Malmo, Sweden	Cross-sectional	359			Yes	
Gonzalez-Casanova et	Prenatal exposure to environmental pollutants and	Cross-sectional	718			Yes	

al., 2018[53] Mexico	child development trajectories through 7 years						
Karvala et al., 2011[54] Finland	Prolonged exposure to damp and moldy workplaces and new-onset asthma	Cross-sectional	483			Yes	
Karvala et al., 2013 Finland[26 i]	Quality of life of patients with asthma related to damp and moldy work environments	Cross-sectional	1267				Yes
Saijo et al., 2011[55] Japan	Relationships between mite allergen levels, mold concentrations, and sick building syndrome symptoms in newly built dwellings in Japan	Cross-sectional	1,479			Yes	
Tuuminen and Rinne, 2017[27 i] Finland	Severe Sequelae to Mold-Related Illness as Demonstrated in Two Finnish Cohorts	Cohort	89			Yes	
Shoemaker et al., 2014 USA[28 i]	Structural brain abnormalities in patients with inflammatory illness acquired following exposure to water-damaged buildings: a volumetric MRI study using NeuroQuant®	Case/ Control		17	18	Yes	

[i] OR calculated by author
[ii] Data had statistically significant associations with p<.0.05 but OR/RR not calculable
[iii] Mold reported but reported ORs based on associations with asthma
[iv] Excludes number of cases and controls

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