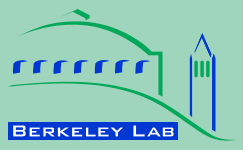

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A Research Agenda on Assessing and Remediating Home Dampness and Mold to Reduce Dampness-Related Health Effects

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List of Abbreviations

Aw	water activity
CI	confidence interval
D/M	dampness and mold
IgE	immunoglobulin E
IOM	Institute of Medicine
MVOC	microbial volatile organic compound
OR	odds ratio
QPCR	quantitative polymerase chain reaction
RR	relative risk
WHO	World Health Organization

Abstract

Background – An important proportion of human respiratory illness in the U.S. is considered attributable to residential dampness or mold (D/M), and thus potentially preventable. Developing effective public health policies for this problem has been challenging: current ability to define unhealthy levels of residential D/M and knowledge about effective remediation strategies for D/M to protect health are both limited. This report proposes a research agenda to improve understanding in these two areas, which are important components of the overall knowledge needed to reduce dampness-related health effects within housing.

Methods - This report briefly summarizes, based on recent review articles and selected more recent research reports, current scientific knowledge on two topics: assessing unhealthy levels of indoor D/M in homes and remediating home dampness-related problems to protect health. Based on a comparison of current scientific knowledge to that required to support effective, evidence-based, health-protective policies on home D/M, gaps in knowledge are highlighted, prior questions and research questions specified, and necessary research activities and approaches recommended.

Results - The suggested priority research activities include review and synthesis of the literature, epidemiologic studies, controlled intervention studies, field studies on building design and D/M, and development of improved semi-quantitative and quantitative assessment tools for D/M. The suggested epidemiologic studies would be iterative and coordinated with progressively refined D/M assessments that have increasingly stronger dose-response relationships with health.

Discussion - Available knowledge supports policies calling for remediation of residential D/M when apparent by sight or smell, not based on microbiologic measurements. However, this knowledge does not provide quantitative thresholds for action or explicit direction on the extent of needed remediation. Findings from the research recommended here would increase scientific support for evidence-based public health policies on residential D/M. Other research not covered here is also needed, to improve primary prevention of D/M through residential design, construction, and maintenance, and to improve the effectiveness of dampness-related public policies in achieving their desired goals.

Background

One current objective of public health research is to reduce dampness and mold (D/M) problems in homes and the resulting adverse health effects for occupants. This report proposes a health-related research agenda focused on two goals of improved understanding, as part of this larger objective: (a) how to *assess and detect* unhealthy levels of D/M in homes, and (b) how to *remediate* D/M problems in homes in a way that improves occupant health. These could be considered topics of "secondary prevention," aimed at reducing health effects from already existing conditions. Two other goals relevant for this broader objective are not included in this report: building-related research on how to improve "primary" prevention of dampness and mold in housing, before they occur at all, through improved design, construction, and maintenance, and policy research on how to improve the efficacy of D/M-related policy strategies (e.g., guidelines and regulations) intended to implement scientific knowledge, motivate actions, and achieve the desired changes in housing conditions.

Residential D/M have been consistently associated with increases in a variety of adverse health effects, including asthma, allergic rhinitis, and respiratory infections (WHO 2009; Mendell et. al. 2011; Institute of Medicine 2004). The widespread occurrence of indoor D/M, estimated to occur in up to 47% of U.S. homes (Mudarri and Fisk 2007), demonstrates that current public policies for controlling D/M are not adequate. Based on available data, an important proportion of human respiratory and allergic illness in the U.S. (e.g., 10-20% of current asthma, respiratory infections, and respiratory symptoms) has been estimated to be attributable to residential D/M, and thus potentially preventable (WHO 2009; Mendell et. al. 2011). Thus, more effective policies for reducing residential D/M (through detection and remediation) may prevent an important proportion of respiratory disease occurrence. Developing more effective public policy responses to this problem, however, has been challenging for two reasons: (a) the specific dampness-related agents causing health effects have not been identified, and (b) the specific remediation strategies for residential D/M that are necessary and sufficient to prevent D/M-related health effects have not been determined. Evidence-based public health advice is currently limited to recommendations to remediate indoor D/M that can be seen or smelled, quickly and safely. While this advice is important, and merits increased application in current policies, it has the limitation of lacking quantified D/M *thresholds* to trigger remedial actions or to quantify remediation effectiveness. Thus, the current ability to define unhealthy levels of D/M in homes, and the knowledge about effective remediation strategies for D/M, are both limited.

Ideally, health-protective policies for D/M in homes would be evidence based, i.e., supported by data showing consistent, dose-related health responses to measurable levels of specific dampness-related agents (e.g., total or specific fungi, or bioactive components of microorganisms such as allergens or toxins). However, other *quantifiable proxies* for causal exposures could also serve as thresholds for use in applications. The current lack of knowledge in this area hampers the development of more informed policies.

This report briefly summarizes, for the two topics of assessment and of remediation of unhealthy home D/M: (1) current scientific knowledge; (2) knowledge gaps that limit health-protective policies; and (3) suggested priority research questions and research activities.

The topics of documenting building design, construction, and maintenance strategies that *prevent* building dampness, both short- and long-term, and of optimizing D/M-related public policies that implement current knowledge in order to reduce home D/M, while important, are beyond the scope of this report. This is an initial thought piece intended to stimulate further multidisciplinary review, input, and expansion, in order to help focus future healthy housing-related research.

Approach

This paper summarizes current knowledge, knowledge gaps, recommended priority research questions, and proposed research activities on two topics: (a) how to assess and identify unhealthy levels of indoor dampness, mold, or dampness-related agents in homes that merit remediation; and (b) what remediation strategies for D/M in buildings can effectively protect health.

The paper deals with these two topics sequentially. For each topic it first briefly summarizes current scientific knowledge, based on recent review articles and selected, more recent research reports. The paper then describes the limitations of current knowledge relative to what is needed for health-protective actions and policies – i.e., the key *knowledge gaps* that limit our understanding and efforts. After summarizing key pre-research questions, based on a specific set of assumptions it specifies priority research questions, and recommends the most promising research activities and approaches to provide the information needed to support more effective actions and policies on home D/M. The focus is on respiratory and allergic health effects, which have been the focus of most prior research on indoor D/M and are the health effects most clearly linked to indoor D/M.

Results

How much evidence is needed to support health-protective actions/policies?

Etiologic epidemiology aims to identify true causal links between environmental exposures and disease. For each specific health effect, etiologic exploration is considered unfinished until demonstration of causal links, rather than mere statistical associations. Too strict a focus on etiologic epidemiology, however, can interfere with effective policy making (Brownson et. al. 2010). In fact, if sufficiently useful proxies for underlying causal agents have been identified, effective actions for public health prevention can proceed without requiring further etiologic research, even if better etiologic knowledge could further focus preventive actions. Making decisions on how much evidence is needed to justify public health actions involves a complex balancing of the available science, the public health benefits, and the costs of action and inaction (Gostin 2000). Although there is no “mold manufacturing” industry that would be disadvantaged by unnecessarily stringent policies on home D/M, inappropriately mandated D/M assessment and remediation would create unnecessary costs for building owners.

Ideally, strategies to detect unhealthy levels of indoor D/M would use assessment proxies documented to indicate, at least indirectly, the actual causal agents for D/M-related adverse health effects. The stronger the correlation of a proxy with the health effect, especially after

suitable analysis in a well-designed study, the better a proxy it is for the true causal agents. The strength of causal associations in epidemiology is generally evaluated separately for each specific health outcome, even those as related to each other as new asthma and asthma exacerbation, because different health effects may have different causes. For instance, cold air and exercise are known to cause exacerbations of existing asthma, but not to cause new asthma. And a symptom like cough or wheeze may indicate any of a number of disease processes, so that their demonstrated risk factors may not be directly relevant to any D/M-caused disease.

Assessing unhealthy levels of home D/M

Assessing unhealthy levels of D/M in homes: current knowledge

Documenting a method to detect unhealthy levels of D/M in homes requires, ideally, several steps: (1) identifying an assessment or measurement of home D/M that in reported scientific studies has a consistent, and if possible dose-related, relationship with a health effect of concern, and that can be considered a sufficiently useful proxy for the underlying causal exposures; (2) choosing a maximum acceptable increase in the health effect related to this condition; and (3) determining the corresponding maximum "acceptable" level of home D/M that corresponds with that maximum acceptable level of health effect. The first step requires a review of current knowledge about established relationships between indoor D/M, as assessed in specific ways, and various diseases or health effects of concern; the second step requires a value-based decision about acceptable impairments of health; and the third step involves combining results of the first two to provide a societal guideline. This last step may require adjustment based on economic or technologic feasibility. These steps are included in the larger process of using research and policy to reduce D/M-related health effects in housing, which also includes research on initial prevention of home D/M, and research on the effectiveness of policies to implement health-protective knowledge. Figure 1 shows a simple overall road map for developing health-protective public policies to reduce indoor D/M.

Over 25 years ago, Strachan et al. first reported an association between respiratory health effects (childhood wheeze and cough) and reported D/M in homes, but a lack of association between the respiratory health effects and culturable airborne fungi (as either total mold or individual species) or measured indoor relative humidity (Strachan and Elton 1986; Strachan and Sanders 1989; Strachan et. al. 1990). Since then, many studies have been conducted on the health effects of indoor D/M. The environmental assessments of D/M used in such studies can generally be grouped into two types, parallel to those used in the Strachan et al. studies – *subjective, qualitative indicators* of evident indoor D/M (e.g., visible water damage, visible moisture, visible mold, and moldy or musty odor) and *objective, quantitative microbial metrics* (e.g., concentrations of microorganisms, groups of microorganisms, or microbial compounds considered either bioactive or indicators of microbial presence) (WHO 2009; Mendell et. al. 2011; Kangchongkittiphon et. al. 2015). An intermediate category would include quantified nonmicrobial assessments of D/M, such as measured moisture content, area of visible mold, area of water damage, or relative humidity. Nonmicrobial dampness-related factors such as chemical emissions, although plausibly involved in dampness-related health effects, have been rarely measured (Norbäck et. al. 2000).

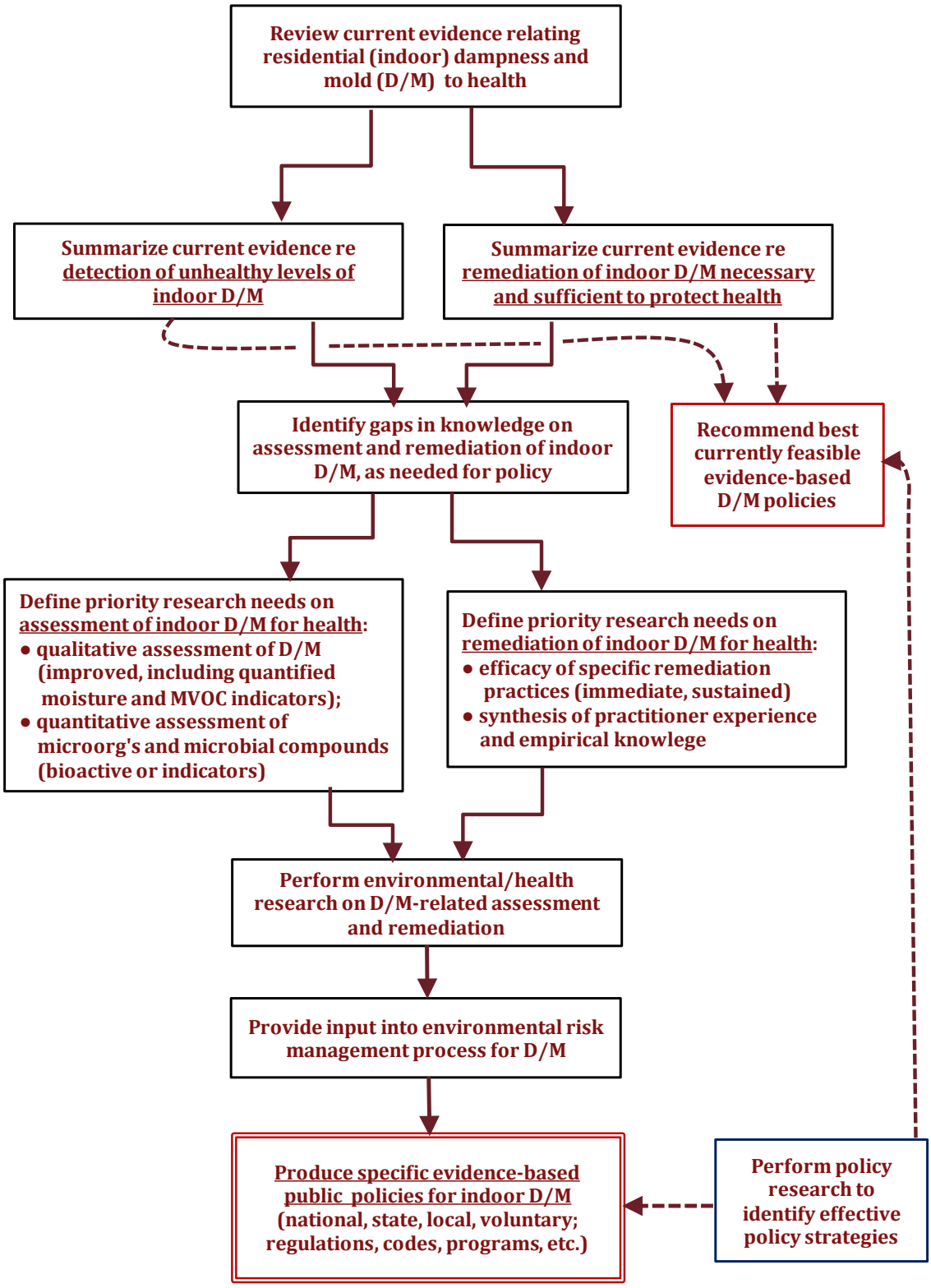


Figure 1. Road map of research to support public policies that reduce adverse health effects from home dampness and mold

Comprehensive reviews of studies that have evaluated the strength of etiologic (causal) evidence on D/M and health have been in general agreement. Until 2011 these reviews (WHO 2009; Institute of Medicine 2004; Mendell et. al. 2011) found consistent associations, but not clear causal links, between subjectively assessed indoor D/M factors and a growing variety of specific diseases and symptoms (Table 1). A recent focused review (Kangchongkittiphon et. al. 2015) has strengthened one conclusion, considering building D/M factors to be a demonstrated cause of asthma exacerbation in children (and to be associated with exacerbation in adults) (Table 1).

Table 1. Increasing strength of evidence* for association of subjectively assessed indoor dampness or mold with specific health effects (WHO 2009; Mendell et. al. 2011; Kangchongkittiphon et. al. 2015)

Health Effect	Reference			
	IOM 2004	(WHO 2009)	(Mendell et. al. 2011)	(Kangchongkittiphon et. al. 2015)
asthma exacerbation	⭘	⭘	⭘	●
asthma development (incidence)	○	⭘	⭘	---
asthma, current	---	⭘	⭘	---
allergic rhinitis	---	○	⭘	---
eczema	---	---	⭘	---
bronchitis	---	○	⭘	---
respiratory infections	---	⭘	⭘	---
wheeze	⭘	⭘	⭘	---
dyspnea	○	⭘	⭘	---
cough	⭘	⭘	⭘	---
upper respiratory tract symptoms	⭘	⭘	⭘	---

***Key**

- ● sufficient evidence for causation
- ⭘ sufficient evidence for association
- ○ limited or suggestive evidence for association
- --- not assessed

Two quantitative reviews have compared the health risks from specific *types* of qualitative assessments of D/M (Table 2). For both new asthma and rhinitis, mold odor was the qualitative D/M indicator with the strongest association with the health effect; visible mold and dampness had similar but slightly weaker associations, and water damage had the weakest associations, especially for new asthma (Table 2) (Quansah et. al. 2012; Jaakkola et. al. 2013). This suggests that some microbial emissions, in building locations that result in indoor air exposures for occupants, played an important role in the occurrence of asthma and rhinitis. Two studies have found that low outdoor air ventilation rates substantially increase the respiratory health risks to occupants associated with indoor dampness problems (Oie et. al. 1999; Sun et. al. 2011). The specific causal element in the emissions, however, is not yet clear.

Table 2. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for associations between specific qualitative metrics of dampness or mold and selected health outcomes (Quansah et. al. 2012; Jaakkola et. al. 2013)

Health Effect	Metric of Dampness or Mold				
	Any D/M Exposure	Mold Odor	Visible Mold	Dampness	Water Damage
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Asthma, new	1.3* (1.1-1.6)	1.7* (1.2-2.5)	1.3* (1.04-1.6)	1.3* (1.1-1.6)	1.1 (0.98-1.3)
Rhinitis (all)	2.1* (1.6-2.8)	2.2* (1.8-2.7)	1.8* (1.6-2.1)	1.8* (1.3-2.5)	1.7 (0.7-4.2)
Allergic rhinitis	1.5* (1.3-1.8)	1.9 (0.95-3.7)	1.5* (1.4-1.6)	1.5* (1.4-1.6)	1.5 (0.98-2.2)
Rhinoconjunctivitis	1.7* (1.4-2.0)	---	1.7* (1.3-2.2)	1.7* (1.4-2.0)	---

* $p<0.05$
--- not available

Some have suggested that the relatively strong association of health effects with mold odor strengthens a hypothesis that chemical compounds excreted by growing fungi (microbial volatile organic compounds, or MVOCs), which cause the sensation of moldy odors, are involved causally in the adverse health effects of indoor fungi. Alternatively, some propose that these MVOCs could serve as indicators of microbial growth and exposures to other microbial agents that actually cause health effects, even if MVOCs are not themselves the causal agents. However, according to a review of this issue, there is little evidence to support either of these concepts, for two reasons: these chemicals occur indoors at levels far below any known to produce human biological responses, and these chemicals are also produced by enough other indoor sources that they cannot be considered sufficiently specific to identify microbial presence (Korpi et. al. 2009). However, several later studies have suggested possible health effects of MVOCs (Hulin et. al. 2013; Inamdar et. al. 2013). The potential contribution of odorous MVOCs in assessment of D/M for health effects remains controversial, beyond their current role in the subjective assessment of mold odor and related health risks.

Most studies of D/M factors and health have used dichotomous qualitative assessments – yes or no. Assessments with multiple levels rather than just dichotomous values, however, are required to explore and demonstrate dose-response relationships. Some studies have used semi-quantitative metrics of single factors (e.g., approximate area of visible mold growth), semi-quantitative indices summarizing multiple factors (e.g., the size, number, or severity of visible water damage, dampness, mold growth, or mold odor), or more quantitative metrics of measured wall moisture to assess D/M factors that in earlier studies were only qualitative. Ten studies with semi-quantitative D/M metrics or indices, mostly in homes, are described in Table 3, and two studies using measured wall moisture in Table 4. (These tables provide examples to show the feasibility of this approach, but do not necessarily include all such studies available.)

Table 3. Example of reported positive dose-response associations with health effects for multi-level metrics or summary indices of indoor D/M in homes[a]

Reference	Exposure metric	Study group: health outcomes (adjusted ORs or RRs)
(Dales et. al. 1991)	Number of visible mold sites reported by parent: 0, 1, or 2	Children aged 5-8 years: diagnosed current asthma (1.0, 1.4*, 1.7*); wheeze with dyspnea (1.0, 1.6*, 2.0*); cough (1.0, 1.6*, 2.3*);[b]
(Haverinen et. al. 2001)	3-level index of overall home D/M, based on the most severe damage in the home and the number of damaged locations	Adults: respiratory infection scale (1.0, 1.3*, 1.4*); lower respiratory symptoms (1.0, 1.04, 1.3*); irritative symptoms, (1.0, 1.3*,1.6*); skin symptoms (1.0, 1.4, 1.6*)
(Pekkanen et. al. 2007)	3-level index of the maximum severity of inspector-observed moisture damage in the main living area and other specific rooms in the home	Infants and children: asthma development (1.0, 2.8*, 4.0*)
(Karvonen et. al. 2009)	3-level index of inspector-observed moisture damage (in the kitchen | in the whole home)	Infants up to 18 months of age: doctor-diagnosed wheeze (1.0, 2.1, 3.8* | 1.0, 1.7, 2.5); parent-reported wheeze (1.0, 2.0, 6.2* | 1.0, 1.9, 3.0*)
(Karvonen et. al. 2015)	3-level index of inspector-observed moisture damage and visible mold, at 5 months of age, for child's bedroom (and separately for living room, kitchen)	Children at age 6 years: (example ORs) Ever-diagnosed asthma (1.0, 0.81, 3.25) Persistent asthma (1.0, 0.76, 2.84) Wheezing (1.0, 0.72, 2.21)
(Iossifova et. al. 2007)	Visible mold at 8 months of age reported by parent: none, low visible mold area (<0.2 m^2), high visible mold area (≥0.2 m^2)	Infants at age 1 year: recurrent wheeze (1.0, 1.2, 4.4*). At age 1 year, with any positive skin prick test: recurrent wheeze (1.0, 2.6, 42.5*)
(Iossifova et. al. 2009)	Visible mold at 8 months of age reported by parent: none, low (moldy odor or moisture damage or visible mold <0.2 m^2), high (moisture damage and visible mold area ≥0.2 m^2)	Children at age 3 years: recurrent wheezing and atopy vs. neither (1.0, 1.9, 6.2*); positive asthma predictive index (1.0, 1.7, 7.1*)
(Biagini et. al. 2006)	At age 5-10 months, 3-level index of researcher-assessed visible home mold (no mold=no water damage, visible mold, moldy odor, or mold/water damage history; high mold= ≥0.2 m^2 area of mold in one room or of combined visible mold/water damage area on same surface; low mold=all others)	Infants up to age 1 year: more frequent upper respiratory infections (1.0, 1.5*, 5.1*)
(Norbäck et. al. 2013)	Multi-level dampness score (history of, or recent, water damage, or leaks in home) Mold score (history of, or recent, mold in home) Number of rooms with mold	Adults: new asthma, (1.0, 1.1, 1.3; dose-response p=0.047); (1.0, 1.05, 1.7; dose-response p=0.007); (1.0, 1.3, 1.4; dose-response p=0.01)

Reference	Exposure metric	Study group: health outcomes (adjusted ORs or RRs)
(Park et. al. 2004)[a]	Individualized, semi-quantitative exposure index for D/M, based on researchers' room-specific observations of the amount of water stains, moisture, visible mold, or mold odor, and weighted by time subject spent in each room	Adults: (ORs per unit increase in exposure index) wheeze (2.3*), chest tightness (2.2*), shortness of breath (2.7*), nasal symptoms (2.5*), and sinus symptoms (2.2*)

* $p<0.05$
[a] 1 study in offices
[b] unadjusted ORs; adjusted ORs similar but not reported

D/M indices described in Table 3 had different levels of specificity and complexity. For instance, Karvonen et al. (2009) and (2015) included room-specific D/M assessments to a greater degree than did Pekkanen et al. (2007). Haverinen et al. (2001) did not consider room location or size of the moisture damage. Park et al. (2004) constructed *individualized exposure indices* weighted by the time each subject spent in each room, the most complex semi-quantitative D/M indices yet reported, based on visual and olfactory observation by room for water stains, visible mold, mold odor, and moisture (with continuous rather than just several values). Such an approach seems likely to optimize exposure/response relations; however, the Park et al. (2004) approach in offices has not been studied in homes. Also, the more complex indices, such as used in Park et al. (2004) and Karvonen et al. (2009), may be currently of more scientific than practical application.

Studies investigating dose-response associations of D/M assessments with health effects have included different study designs, types and ages of subjects, and health outcomes, in addition to using different D/M indices, and no finding with a specific D/M index seems to have been replicated. This prevents the selection of the most effective overall D/M index that has been used, or selection of the most effective specific elements of each to combine in future metrics. Thus the available data are not yet sufficient to provide any specific, standardized assessment on which to base health-protective guidelines and standards. However, the multiple reported findings of dose-response relationships between D/M assessments and health effects demonstrate that developing D-M-related scales that correspond to increasing health risks is feasible. The various approaches used, together with their findings, need careful analysis, comparison, and evaluation to develop improved indices to examine in future studies. With respect to constructing the most effective index based on available knowledge, it should be noted that mold odor, the single D/M factor most strongly associated with specific adverse outcomes (Quansah et. al. 2012; Jaakkola et. al. 2013), was not included in seven of these ten indices in Table 3.

Although moisture is the key limiting factor for mold growth, moisture has, surprisingly, rarely been measured in health studies in buildings. While *investigations* of D/M problems in buildings (as opposed to in research studies) frequently include quantifying moisture in walls or building surfaces using moisture meters, this involves comparing multiple readings within a building to each other in order to identify relatively moist locations and thus moisture pathways. Investigation strategies do not now involve detecting absolute levels of material moisture documented to be associated with adverse health effects or with the growth of harmful microorganisms, because these levels have not been determined. The scientific evidence linking

measured moisture levels to health effects is limited to two studies from the United Kingdom (Williamson et. al. 1997; Venn et. al. 2003), summarized in Table 4. These studies both found dose-related associations between measured wall moisture and respiratory health effects (Mendell et. al. 2014).

Table 4. Summary of positive dose-response associations with health effects reported for quantified indoor moisture

Reference	Building Type	Exposure Metric	Health Outcomes (example ORs)
(Venn et. al. 2003)	Homes	Wall moisture measured by moisture meter in bedroom	Persistent wheezing (in living room, 1.0, 1.4, 1.6, 2.5); asthma exacerbation (in bedroom, 2.51* per increasing category) in children
(Williamson et. al. 1997)	Homes	Wall moisture measured by moisture meter	Asthma severity, model beta =2.3*

* p-value <0.05

Regarding *quantitatively* assessed microbiologic factors, published studies have investigated the associations of health effects with over 50 ways of assessing indoor microbial measurements; i.e., involving different combinations of specific sampling methods, analysis methods, and microbiologic targets (Table 5) (Mendell et. al. 2011).

The reviews by the Institute of Medicine (2004) and World Health Organization (2009) identified, informally, no consistent associations between measured indoor microbial exposures and health effects. The review by Mendell et al. (2011) explicitly evaluated the associations of health effects with diverse objective measures of D/M. This review found limited or suggestive evidence linking several quantified microbial compounds *in dust* with health effects, but no such evidence for quantified microorganisms or microbial compounds *in air*. In dust, increased ergosterol (considered not bioactive, but an indicator of total fungal biomass) was associated with increased current asthma, but in few studies. Increased endotoxin in dust was associated with increased wheeze, although higher endotoxin exposures were also associated with reduced allergy and asthma. Findings for (1→3)-β-d-glucans in dust were mixed, with medium concentrations associated with increased wheeze but the highest concentrations associated with decreased wheeze. These associations with microbial measurements were considered only suggestive, because of the limited number of studies, and the demonstrated complexity of some of these relationships (Mendell et. al. 2011; Douwes et. al. 2004; Douwes et. al. 2006).

Table 5. Types of quantitative microbial assessments in published studies on dampness, mold, and health (Mendell et. al. 2011)

Sampling Methods	Types of Analysis	Microbiologic Targets

• Air
  o impaction
  o impingement
• Surface dust
  o vacuumed
  o settled
  o wiped
	• Culture
	• Visual spore count
	• Quantitative polymerase chain reaction (QPCR)
	• Sequence-based methods (e.g., 454 pyrosequencing)
		• Fungi
		  o total species
		  o individual species
		  o hydrophilic species
		• Bacteria
		  o total species
		  o individual species
		• Ergosterol
		• Beta-1,3-glucans
		• Muramic acid
		• Extracellular polysaccharides

Along with the above-mentioned etiologic reviews, additional studies, reviews, or quantitative meta-analyses have been published, some reinforcing the conclusions of prior studies, e.g., (Tischer et. al. 2011a; Tischer et. al. 2011b; Tischer et. al. 2011c), and some providing novel findings. Several recent studies have shown strong relationships between fungi identified in home dust by quantitative polymerase chain reaction (QPCR) assays (either as individual species or in summary fungal indices) and development of asthma, although the fungal species implicated have varied across studies (Reponen et. al. 2012; Reponen et. al. 2011). QPCR-based fungal identification in dust is thus a very promising strategy, although the fungal species or groups of most interest require confirmation. The review by Kanchongkittiphon et al. (2015) concluded that recent studies provide limited or suggestive evidence (i.e., somewhat stronger evidence than found in the prior reviews) that indoor concentrations of culturable airborne fungi were associated with asthma exacerbation in children who were fungally sensitized. This is surprising, since microbial assessments based on culture, especially when using brief air samples, have been documented repeatedly as incompletely representing fungal exposures for building occupants; e.g., (Pitkaranta et. al. 2011). The findings reviewed in Kanchongkittiphon et al. include statistically significant, positive dose-response associations, in asthmatic children, of indoor airborne, culturable *Penicillium* species with persistent cough and wheeze (Gent et. al. 2002), frequent asthma symptoms (Turyk et. al. 2006), and symptomatic days and unscheduled medical visits (Pongracic et. al. 2010), with the latter outcome also having dose-response associations with total indoor fungi (Pongracic et. al. 2010). (However, indoor concentrations of airborne culturable *Penicillium* have been shown to be strongly correlated with dampness and mold factors, relative humidity, and cockroaches (Crawford et. al. 2015) and thus may simply be a signal for other key exposures.) Thus, quantified microbiologic assessments, while not yet having enough consistent associations with health effects to be used in standardized D/M assessments, now have enough small sets of positive findings to show future promise.

There is substantial uncertainty about the range of biologic mechanisms through which dampness-related exposures could cause health effects. Allergic responses caused by specific

fungi among those specifically sensitized are well understood. However, even for these well-documented responses known to be caused by outdoor fungal exposures, causation by fungi growing indoors rather than entering from outdoors has not been completely certain (Institute of Medicine 2000; Kangchongkittiphon et. al. 2015). However, a recent review found suggestive evidence for associations of some measured indoor fungal exposures with asthma exacerbation among fungally sensitized children, even after adjustment for outdoor fungal concentrations (Kangchongkittiphon et. al. 2015; Pongracic et. al. 2010). Increasing evidence of several kinds now also suggests adverse respiratory effects from indoor D/M exposures even among those not allergically sensitized to fungi. Also, the diseases documented to be associated with D/M include two, respiratory infections and bronchitis, which are not allergic in nature. Together, these different types of evidence suggest that dampness-related exposures may trigger irritant or pro-inflammatory mechanisms as well as the recognized mechanism of traditional immunoglobulin E- (IgE) mediated fungal allergy (e.g., (Weinmayr et. al. 2013).

Non-epidemiologic evidence also supports the plausibility of D/M-related exposures causing respiratory and allergic health effects through non-IgE-mediated allergic, as suggested in the epidemiologic findings mechanisms. Increasing *in vivo* and *in vitro* toxicological evidence, as stated in the WHO (2009) review, demonstrates "the occurrence of diverse inflammatory, cytotoxic, and immunosuppressive responses after exposure to microorganisms isolated from damp buildings, including their spores, metabolites and components (WHO 2009)." Immunosuppressive responses shown in animals exposed to damp-building-associated fungi may explain a link to respiratory infections (Park et. al. 2004). More recently, curdlan (a configuration of beta glucans found generally in fungi), as well as other toxins emitted by damp-building fungi, have been shown to produce irritant and inflammatory effects in animal models (Rand et. al. 2013; Miller et. al. 2010). Also, findings in animal models (Van Dyken et. al. 2011) suggest an innate inflammatory response to chitin, an important fungal polysaccharide. An epidemiologic study has shown that genetic variation in human chitinase (an enzyme targeting chitin) was associated with greatly increased adverse respiratory effects from exposures to airborne fungi (Wu et. al. 2010). Another recent review has summarized the substantial available evidence on the effects of the many toxins produced by fungi found on damp building materials, demonstrating the plausible role of these compounds in adverse, non-allergic health effects among occupants of damp and moldy buildings (Miller and McMullin 2014). Recent identification within normal human lungs of fungal species previously unrecognized there, and identification of secreted proteases that cause asthma in mice, suggests that indoor microbial exposures may be related to unrecognized fungal colonization that influence asthma (Porter et. al. 2011).

Studies using recently developed microbial identification methods based on molecular sequencing techniques suggest an even more complex picture: that microbial exposures of specific kinds, or at specific ages, may have either adverse or beneficial effects on human health. Such studies have not yet identified specific microbial species associated with adverse health effects; however, they have found that early more diverse microbial exposures are associated with reduced future risk of atopy and asthma (Ege et. al. 2011; Dannemiller et. al. 2014), and some bacterial species are associated with reduced illness occurrence (Ege et. al. 2011; Ege et. al. 2012). These new sequence-based methods can much more comprehensively identify microbial species and characterize entire microbial communities regardless of species

culturability; however, these methods are not yet fully quantitative, and can identify some species only to the genus or even higher levels of taxonomy.

A different set of findings relates to moisture produced intentionally in many buildings – on the cooling coils of air-conditioning systems that remove water from incoming warm, moist outdoor air in order to provide cool, dry indoor air. The surfaces of air-conditioning cooling coils, over which all ventilation air flows into a building, are repeatedly saturated by condensation, and have dust particles and microbial aerosols continually deposited on them (Siegel and Walker 2001). A number of diverse findings in different studies, considered together, suggest that unidentified fungi or bacteria in air-conditioning cooling coils, growing in a desiccation-resistant biofilm on the intermittently wetted surfaces, may be at least partially responsible for the nonspecific symptoms sometimes called "sick building syndrome" (Menzies et. al. 2003; Seppänen and Fisk 2002; Simmons et. al. 1999). This evidence comes from studies of offices and automobiles, not homes, but similar exposure and biologic responses may also occur in homes. These findings suggest a need for research on whether home air-conditioning systems are sources of adverse microbial exposures, especially given that air-conditioning use is increasing in the U.S. (U.S. Energy Information Administration 2011) and worldwide.

Assessing D/M: knowledge gaps for actions and policies

Quantified indoor D/M-related exposures do not yet have established associations, much less causal links, with respiratory or allergic health effects. These investigated exposures are almost entirely microbial, but chemical emissions from damp materials are plausibly relevant. Only limited, suggestive evidence is available, for instance, of an association between measured, culturable fungi in indoor air and exacerbation of existing asthma in fungally sensitized children, an association between measured ergosterol in indoor dust and current asthma, and an association of fungal QPCR in dust with new asthma. Thus, specific dampness-related causal agents have not been identified, nor any dose-response relations with health effects established. Quantified microbial measurements are not yet near being useful for setting threshold values to trigger health-protective actions. Still, the most promising findings of this type have not been synthesized and emphasized in order to focus future research.

Qualitative, observed D/M factors, in contrast, have a causal link with asthma exacerbation in children, supported by clear findings from intervention research. These D/M factors also have documented consistent associations with multiple other important respiratory illnesses (e.g., asthma exacerbation in adults, asthma development, allergic rhinitis, eczema, bronchitis, and respiratory infections, plus various upper and lower respiratory symptoms). Toxicological evidence also provides support for a link between dampness-related microbial agents and adverse health effects. Such qualitative factors are thus the best validated assessments to use in health-protective dampness-related actions and policies.

However, qualitative D/M risk factors have generally been studied simply as present or absent and not quantified. Only a small number of studies, using multi-level metrics or indices of observed D/M, have identified dose-response relationships with specific health outcomes. These dose-response relationships strengthen the confidence that observed D/M factors are suitable proxies for underlying causal agents, and thus suitable for use in health-protective actions and policies. The dose-response evidence also provides initial information for the process of deciding

the maximum indoor D/M that is acceptable for health. However, there is apparently no replication across studies showing the same multi-level assessment metrics associated with the same specific health outcomes (or even with different outcomes), to provide validated candidates for use as standardized D/M assessments now. Nor do these studies provide a body of consistent evidence on the magnitude of increased risk at specific levels of the qualitative D/M indicators, to support setting specific maximum acceptable D/M thresholds to protect health.

Identification of excess moisture in a building, regardless of presence of mold, should be a useful assessment for D/M-related health risk. Substantial empirical knowledge exists about ways to identify excess building moisture, among practitioners who investigate and solve building moisture problems. This experience in detecting excess, undesirable building moisture is highly relevant to the goal of assessing unhealthy levels of building D/M, even though this knowledge is related to comparisons of material moisture levels expected vs. observed, rather than to health risks at specific moisture levels.

Quantifying moisture, the key limiting factor for mold growth in buildings, seems a promising assessment approach for D/M-related health risks, and does have some limited positive epidemiologic findings: two studies from the United Kingdom (Williamson et. al. 1997; Venn et. al. 2003), both finding dose-related associations between measured wall moisture and respiratory health effects. However, these findings show elevated health risks even at moisture levels considered relatively dry in North America, and were made in a region with a cold wet climate, poorly heated houses, and exterior walls of brick covered inside with gypsum plaster. Thus the findings may not apply to North American home construction and climates (personal communication, Dr. David Miller). Also, despite its theoretical appeal, using measured building moisture to identify D/M-related health risks has multiple limitations now:

- There are currently no levels of measured moisture documented to be consistently associated with increased health risks;
- Each of the many available makes and models of moisture meter, including pin-less and pin models, may be calibrated differently and produce different readings for the same moisture level;
- Moisture readings may miss elevated moisture in unmeasured wall locations or at times between periodic wetting;
- Moisture meters cannot measure moisture in inaccessible building locations; and
- Moisture content as measured by moisture meters is not equivalent to “water activity” (Aw), the metric of moisture most relevant to the support of microbial growth (Aw, historically not measurable in the field, may now be approximated and monitored over time using newly available instruments).

In fact, observed D/M factors and measured moisture may each provide different kinds of complementary evidence, each with advantages and limitations, on D/M-related health risks in a building. A combined index reflecting both might be more effective than using either element alone. Unfortunately, studies to support such a combined index have not been conducted, although there is ongoing work to develop one (Cho et. al. 2015).

In summary, the best-documented current evidence-based advice on D/M is still that the presence of any D/M factor (i.e., seeing or smelling D/M) indicates an increased health risk and should be

remedied. While this guideline, based on consistent findings, merits use for investigations and decisions about remediation, without waiting for additional evidence, it is non-quantitative and imprecise. It also seems clear that currently available evidence is not sufficient to support specific threshold values of any quantified microbial exposures as triggers for health-protective actions. Thus, that the key current limit to effective D/M-protective policies is not lack of enough etiologic evidence, but lack of detailed evidence on the *relationships* of exposure proxies and health effects to allow specification of acceptable D/M levels.

Assessing D/M: priority research questions for actions and policies

Pre-research questions – The knowledge gaps discussed above suggest many possible research questions. To then select research questions for priority attention requires deciding, implicitly or explicitly, on some "pre-research" questions about goals and assumptions. If a framework of goals and assumptions is first explicitly established, the priority research questions that are selected can be better explained and critiqued. Example pre-research questions, listed in the left column of Table 6, concern the primary goal of the research, the amount and type of evidence needed to justify actions and policies, and the way evidence is used in setting policies.

Specific recommendations related to these example questions, used in the research agenda presented here, are listed in the right column of Table 6. The appropriateness of these *assumptions* about D/M and health has not been explicitly evaluated. For different sets of pre-research goals and assumptions, the priority research questions chosen below should be reevaluated. For instance, the research agenda presented here is based on a decision to pursue a goal of establishing health-protective D/M guidelines, and thus focuses on research needed to facilitate real-world health protection rather than to achieve etiologic explanation. The assumptions made are: that sufficient evidence on the links between building D/M factors and health effects is already available to justify health-protective actions, without current identification of specific causal agents; that future evidence produced on D/M factors and health can improve the precision and usefulness of related indices relatively quickly; and that while identification of causal agents could improve the specificity of health-protective actions prescribed now, this process may take substantially longer. An additional assumption made is that evidence on specific pairings of D/M factors and health effects can be generalized to other such pairings, so that common assessment (and remediation) strategies can be assumed appropriate for all these health effects. By recommending adoption of thresholds for action based on maximum acceptable levels of D/M indices that correspond (based on dose-response relationships) to maximum acceptable increases in associated health effects, this report defines a *type of data* needed from future studies without recommending yet any specific health thresholds.

To expand on one assumption: limited current findings suggest that eventually we will be able to identify specific indoor D/M-related causal agents, measure their exposures in human health studies, and characterize dose-response relations with human health effects. However, to date, it has been much easier to identify proxies for D/M-related exposures that have consistent associations with human health effects. The state of the science suggests that the most immediately promising and useful research would identify more detailed, multi-level

Table 6. Example pre-research questions in assessing unhealthy levels of indoor D/M

Pre-Research Questions	Comments	Recommended Process
1) What is the primary goal of the research?	Example primary goals: • Identify the underlying dampness-related agents that cause dampness-related health effects. • Provide evidence supporting quick, practical health-protective assessment guidelines for indoor D/M.	Recommendation: Create a consensus process to make decisions about goals and assumptions in choosing priority research questions, with broadly multidisciplinary participation.
2) In interpreting research results, how much evidence is needed to support a D/M-related health-protective action or policy?	The necessary amount of evidence depends on the strength of the evidence, the potential benefits from preventing D/M- related health effects, and the costs of actions required by the policies.	Assumption: Sufficient evidence is now available on links between building D/M and health to justify health-protective actions.
2a) Does prescribing health-protective actions and policies on D/M require identification of specific dampness-related causal agents?	The identification of specific causal agents may take an indefinite number of years.	Assumption: Policies and actions can be based on findings using proxies for unidentified causal agents, and need not wait for identification of specific dampness-related causal agents; however, later identification of causal agents can improve the specificity of future health-protective policies and actions.
2b) Can scientific evidence about D/M factors and specific health effects (e.g., asthma exacerbation) be generalized to other health effects?	Etiologic reviews consider only the evidence per specific outcome; e.g., findings on D/M and current asthma are not considered for allergic rhinitis, or even for new asthma or asthma exacerbation.	Assumption: If, for instance, asthma exacerbation in children has a documented causal link to indoor D/M factors, then other health effects (e.g., asthma exacerbation in adults, new asthma, allergic rhinitis, respiratory infections, bronchitis, eczema) that are consistently associated with these D/M factors can for practical reasons also be assumed to have causal links with these factors.
3) How should a maximum acceptable threshold for D/M indicators be set?	For a D/M index with a dose-response association with a health effect, a maximum acceptable threshold can be set at a level corresponding to a maximum acceptable dampness-related increase in the effect.	This report makes no decision as to thresholds for health effects, but this process defines a type of data needed from studies, that otherwise most studies do not produce.

assessments of D/M exposures that have dose-response relations with health effects. Although ultimately, we want to identify specific dampness-related causal agents that are measurable and have defined exposure-response relations with human health effects, such identification is not needed for effective preventive actions now. For health protection, D/M assessments need to be at least acceptable proxies for the underlying dampness-related causal agents of disease.

Priority research questions – Based on pre-research decisions made here, seven priority research questions are listed in Table 7, in the left column. The logic behind many of these research questions is as follows: the links between D/M and health are strong enough to justify health-protective policies; however, because most studies have used dichotomous assessments of D/M factors, there is no basis for choosing specific thresholds of D/M to trigger remedial actions; thus it is urgent to explore the current data (e.g., as in Table 3) to maximize the effectiveness of policy recommendations and also to aim future research in the most promising directions. Lower priority research questions are listed in Table 8.

Assessing D/M: recommended research activities

Recommended priority research activities, corresponding to the listed research questions, are listed in Table 7 in the right column, to guide research that may be completed in an estimated 2-3 years, or, for activity 7, 3-10 years. A set of lower priority research activities, not specified but of substantial interest, would correspond with the lower priority research questions listed in Box 1.

In addition, the following specific *strategies or approaches* are recommended for conducting these research activities:

- For answering pre-research questions, the recommended consensus process, as described in Table 6, should be broadly multidisciplinary; e.g., including epidemiology, exposure assessment/environmental health science, public health medicine, microbiology, building and moisture science, building moisture investigators, health policy, and possibly insurance policy.
- The first recommended research activity is a thorough review and synthesis of existing research findings: on D/M and health relationships, on the key gaps in current knowledge, and on the most promising directions for improved assessments to guide future research.
- Priority research studies should use strong study designs such as prospective or incident case-control studies, performed iteratively using the best available multifactorial environmental assessments. (Controlled intervention studies, the strongest design, are more appropriate for assessing remediation strategies than assessment, although this design can provide strong evidence on causal links.). Studies should:
    - control in design or analysis for potential confounding by factors related to both D/M and health; e.g., socioeconomic status, age of building, renting vs. owning home, season, and ventilation rate. Ventilation rate may need consideration as a strong effect modifier for D/M, as demonstrated by Oie L et al. (1999) and Sun et al. (2011).
    - include multidisciplinary collaboration, as in the pre-research consensus process.
    - in selecting metrics and analyses, aim to produce policy-relevant evidence.
    - consider a focus on exacerbation in severely asthmatic children, development of new asthma in high-risk non-asthmatic children, etc.

Table 7. Proposed priority research questions and research activities for *assessing* unhealthy levels of indoor D/M

Research Questions	Comments	Recommended Research Activity
High priority, short-term research, for completion over the next 2-3 years		
1) What are the best currently reported single or combined *qualitative assessments* of D/M factors that indicate increased health risks (in a dose-related manner if possible) that could be used in health-protective guidelines for indoor D/M?	The current evidence has not been systematically mined for this information. As an example, even the brief summary above (Table 3) of reported dose-response relationships for D/M assessments and health has not been previously reported. Consideration should be given to D/M factors by sight or smell, and might include measured moisture. A more comprehensive search for such findings is needed, plus a careful critique and synthesis of available findings to see what findings are currently usable, singly or combined.	1) Comprehensively review the literature on *qualitative* indoor D/M assessments and health. Focus on identifying the available dichotomous or semi-quantitative multi-level metrics/ indices of D/M that most strongly correlate with a key increased health risk in a dose-related manner (see examples in Table 3), and that might be suitable for inclusion in current health-protective policies on D/M.
2) What are the best currently reported *quantified microbiological measurements* for indicating increased health risks (in a dose-related manner if possible) that could be used in health-protective guidelines for indoor D/M?	The current evidence has not been systematically mined for this information. A current comprehensive search, critique, and synthesis are needed. Microbial measurements that have so far best indicated increased health risks, some in a dose-related manner, include specific fungal or bacterial genera or species, microbial groups such as hydrophilic fungi, bioactive microbial compounds, or compounds such as ergosterol used as proxies for fungal biomass. Consider, each with specific advantages and disadvantages, parallel use of culture-based, QPCR-based, and next-generation sequencing-based measurements for microbial identification.	2) Comprehensively review the literature on *quantitative* indoor microbial measurements and health, and synthesize any dose-response and other relevant findings. Identify metrics, if any, suitable for inclusion in current health-protective policies on D/M. Because highly promising among existing methods, develop improved summary metrics for fungal QPCR data, using existing data with various approaches, and statistically optimize for associations with disease.

Research Questions	Comments	Recommended Research Activity
3) What expanded or combined multi-level D/M *indices* can be constructed, from combinations or expansions of the most strongly health-related D/M (or microbiologic) assessments in current studies, using information easily collected in a building, that have potential for dose-related associations with key health effects that are even stronger than current metrics, and that could be compared in future studies?	New metrics should include at least D/M factors assessed by sight or smell, and might include multi-level metrics of measured moisture and easily measured microbiologic agents. More detailed aspects of D/M factors to consider including are: frequency, locations, and strength of mold odor; surface area of visible mold and of water damage; location of damage, relative to occupant time in specific rooms; moisture content or water activity level of building material surfaces; specific fungal or bacterial genera or species present; specific bioactive microbial compounds. Personal exposure estimation based on room-specific D/M assessments and personal locations/activity may improve dose-response associations in analyses and help define metrics, but personal location/activity data may not be necessary in the metrics ultimately recommended. Based on available evidence, this process is likely to be more productive now for qualitative D/M assessments than for quantified microbial assessments. Next-generation sequencing-based measurements show still unfulfilled promise for comprehensive microbial identification.	3) Develop new semi-quantitative, multi-level D/M assessments with likely stronger dose-response relationships with important disease outcomes than current metrics, for use and comparison in epidemiologic studies of D/M. The goal is to develop metrics that are feasible for widespread use in assessing homes, as practical proxies for true D/M-related causal agents. Create new metrics by combining elements of the strongest metrics identified in (1) and (2), or expanding them by inclusion of other promising metrics.
4) What field strategies are now the most effective in identifying undesirable/ *excessive moisture* in buildings (without requiring documented linkage of these strategies to microbial growth or health effects)?	This information is useful for assessing D/M-related health risks, even if these field strategies have not been directly linked to documenting health effects or microbial growth, because building moisture is a clear risk factor for adverse health effects.	4) Synthesize the empirical experience of building investigators specializing in building moisture problems, to identify relatively simple ways to identify excess building moisture.

Research Questions	Comments	Recommended Research Activity
5) How should building moisture be measured to best indicate health risks? What improved objective measurements of building moisture are possible, to allow more standardized methods across materials, possibly involving moisture meters or water activity sensors, possibly in conjunction with thermographic cameras? Can moisture content measurements be sufficiently standardized for interpretation with respect to the level of health risk or to the potential for growth of specific suspect fungi or groups of fungi, or is Aw the only truly predictive metric? What methods can improve an investigator's ability to detect moisture hidden within building envelopes or other inaccessible locations?	This is important, because building dampness is the critical and initial factor in all D/M problems, yet dampness measurement approaches are poorly developed and standardized. Also, moisture and mold can often be inside walls or otherwise not visible, yet still result in exposures to occupants.	5) Perform laboratory work to better standardize measurement of building moisture for purposes of assessing risk of microbial growth. Include comparisons of different moisture meters and water activity sensors on different materials at different moisture levels. Investigate the potential combination of these sensors with thermographic cameras for identifying building moisture on or within building envelopes. In parallel, develop improved data characterizing the moisture/water activity conditions required for specific microorganisms or microbial groups that are suspected as health risk factors, to facilitate risk characterization by moisture measurements.
6) What is the prevalence and severity of D/M in U.S. housing, and how does it vary in buildings of different design, construction, and location?	This information will allow estimation of the public health burden from existing D/M, establish justification and urgency for policy changes, and help identify higher-risk designs. Inclusion of the specific D/M assessment metrics used in epidemiologic studies in collecting this data would improve the ability to estimate the magnitude of related health risks.	6) Collect cross-sectional survey data from representative U.S. homes on D/M prevalence, severity, and details. Estimate the public health burden from D/M, overall and in relevant subcategories such as by owner-occupied vs. rental, single family vs. multi-family, and by income level, design type, and geographic region. Include D/M assessment metrics best linked to health in epidemiologic studies to improve estimation. Include analyses by building factors to identify high-risk features.

Research Questions	Comments	Recommended Research Activity
7) What are the best research designs to take advantage of periodic water-related disasters in U.S. homes, so that they can be implemented promptly in situations of widespread high-level water damage in homes?	These situations offer valuable opportunities for concentrated increase in knowledge, because of extreme moisture conditions and large numbers of affected homes, but usually cannot be fully utilized because the lag time in orchestrating a complex study prevents data collection till past the optimal period.	7) Design multiple scenarios for home selection and data collection that can interface with rescue efforts, and determine responsible agencies, to accelerate response after water-related disasters.
High priority, medium-term research, for completion over the next 3-10 years		
8) What new multi-level combined indices of building D/M are most strongly correlated, with dose-response, with key D/M-related health effects in occupants?	Use findings from (3) on semi-quantitative D/M indices to create hypothetically promising new indices. Based on current evidence, D/M factors will provide the most promising components; only include quantitative microbiologic measurements if promising and also feasible for broad use.	8) Conduct iterative epidemiologic studies of key relevant disease, using the best previously documented D/M metrics (see (1) and (2) above), using D/M exposure assessments of increasing effectiveness in predicting health effects (conduct this research in parallel with the development of improved D/M assessment methods – see (4) and (5) above). Choose specific diagnostic outcomes such as asthma exacerbation, new asthma, or allergic rhinitis, rather than nonspecific symptoms. Design studies to define multiple levels of excess risk, in order to support decisions about acceptable D/M thresholds. If feasible, include indicators of human susceptibility to D/M. Based on findings, produce guidance to focus iterative future research (see (3) above) on improving indoor D/M and microbial exposure assessment methods.

- Use prospective studies for comparison and validation of assessment strategies.
- Use cross-sectional or prevalence case-control studies for generation of hypotheses or promising new assessment strategies.
- To the extent practical, research should be performed in a coordinated manner so that findings can be benchmarked and compared across studies, to systematically build the body of knowledge needed to support health-protective actions and policies.
- To develop D/M indices that are highly correlated with health effects, use of exposure matrices, as used in occupational health studies may be helpful; e.g., Park et al. (2004) assessed D/M factors in specific locations and combined them with each occupant's time at each location to develop individual semi-quantitative exposure indices.
- Research focused primarily on identifying dampness-related causal agents is not a high priority because of its low likelihood, based on current evidence, for being useful soon in informing actions and policy. However, identification of relevant quantitative microbial assessments is in the long term very useful, so inclusion in studies is appropriate; however, despite the appeal of precise measurements, such research should be considered less likely to be useful soon, compared to simpler D/M assessments.
- Priority research does not include further studies using rough, dichotomous assessments of D/M factors, and cross-sectional or prevalence case-control study designs, especially with simple symptoms outcomes, except where new hypothesis generation is important, such as for new health outcomes.
- Evidence on D/M factors and health should allow estimation of human benefits from reduced D/M, as regulations and guidelines may need to balance expected benefits with the costs of D/M surveillance and remediation.

Box 1. Proposed lower priority research questions (not essential for initial protective policies and actions) in assessing unhealthy levels of indoor D/M, and recommended research

- What are the *dampness-related causal agents* for one or more D/M-related health effects of concern, and what are the quantitative relationships between these agent exposures and health effects? How do specific environmental conditions, especially moisture levels measured as Aw, influence indoor growth of microorganisms, for specific suspect species or for suspect groups such as hydrophilic fungi sharing similar requirements – e.g., minimum water activity or moisture content by material and temperature? (Because specific indoor microorganisms have not yet been linked to health effects, this effort may only suggest as approximate guidelines the maximum acceptable Aw levels not supporting amplification of "suspect" groups of microorganisms.)
- What microorganisms grow on air-conditioning cooling coils, what are their particulate emissions, and do these emissions have adverse health effects on occupants?
- What are the biologic mechanisms of human response to dampness-related agents? What role does specific *allergic sensitization* or genetic susceptibility play in the human response to dampness-related factors or agents?
- Can microbial volatile organic compounds (MVOCs) that cause perception of mold odor (the best current predictor of dampness-related health effects) be identified, quantified, and used to assess dampness-related health risks?

Results – Remediating Unhealthy Levels of Home D/M

Remediating D/M: current knowledge

Almost all of the studies supplying the substantial evidence linking indoor D/M to adverse health effects have been observational, and have not investigated the efficacy of D/M remediation in improving health or preventing adverse effects. Of the limited evidence from field intervention research showing that remediating D/M in homes may reduce asthma exacerbations (Krieger et. al. 2010), by far the strongest is from Kercsmar et al. (2006). Kercsmar et al. (2006) reported that comprehensive and tailored remediation of all identified D/M problems in homes with such problems produced a 90% reduction in severe asthma exacerbations among asthmatic children, compared to asthmatic children in homes without such remediation. Remediation activities used in this study, customized to each home, included repairs that reduced water infiltration, removed water-damaged building materials, and altered (sometimes extensively) heating/ventilation/air-conditioning systems. Remediation also included environmental cleaning. General strategies used in all remediated homes included "cleaning mold from hard surfaces, removing mold exposure pathways, stopping rainwater intrusion, exhausting water vapor from kitchens and bathrooms, and repairing plumbing leaks." Interventions in specific homes as needed included "repair of faulty cold-air return to furnace, elimination of subslab heating duct systems, disconnecting and redirecting downspouts, and reducing moisture in crawlspaces and basements" (Kercsmar et. al. 2006). Costs in the 29 remediated homes averaged approximately $3,500 and ranged from $535 to $6,550 (Kercsmar et. al. 2006).

Typical current evidence-based public health advice for addressing water damage, dampness, visible mold, and mold odor in buildings includes, e.g., as is recommended by the California Department of Public Health, "(a) identification and correction of the *source of water* that may allow microbial growth or contribute to other problems, (b) the rapid drying or removal of *damp materials*, and (c) the cleaning or removal of *mold and moldy materials*, as rapidly and safely as possible, to protect the health and well-being of building occupants, especially children" (California Department of Public Health 2011). This advice, in combination with the empirical knowledge of experts in building moisture, represents the current state of the art for remediating building D/M. Many sources of more detailed recommendations are available; e.g., (U.S. EPA 2013; U.S. EPA 2014; WHO 2009; New York City Department of Health and Mental Hygiene 2008).

The nature, extent, and causes of D/M problems in different buildings, as well as the appropriate remedial strategies, can differ widely. The overall scientific evidence on what specific remediation strategies are necessary and sufficient to protect health is very limited (Sauni et. al. 2013; Krieger et. al. 2010). Current knowledge is based on several sources: (1) the understanding among mycologists that mold control is moisture control; (2) findings from limited field intervention studies; and (3) causal inference from the available epidemiologic research that reducing D/M that is apparent (by sight or smell) in buildings to a level that is not apparent seems likely to result in reduced respiratory and allergic health effects. (Related to this knowledge, substantial practical expertise is available, even if not broadly documented, on how to reduce or eliminate moisture in buildings, which seems likely to reduce D/M-related adverse health effects. This document excludes technical questions on how to identify and eliminate

water incursions or other sources of dampness in buildings; these issues are discussed in numerous other documents, such as those cited in the above paragraph.)

Remediating D/M: knowledge gaps for actions and policies

While substantial practical expertise exists on how to remediate building moisture and mold, current scientific knowledge does not allow us to specify, for a building with evident D/M and thus D/M-associated health risks, the precise nature and extent of D/M remediation needed to eliminate or substantially reduce the D/M-associated health risks. Nor is it yet possible to assess the adequacy of remediation using quantitative assessments of D/M that are clearly linked to health. There is not, for instance, a set of findings documenting a dose-response relationship between increased thoroughness/intensity/expense of D/M repair and degree of health benefits, nor findings demonstrating the greater benefits from specific repairs over others, to support informed decisions. Also lacking are documented strategies for assessing the remaining levels of D/M or microbial contamination after remediation, based on health research, to validate that the desired level of remediation has been accomplished. Observational indices of D/M (see Table 3), although developed for initial assessments of health risks in specific building types, when developed further (as recommended above, in the Assessment section of this report) may be useful in guiding remediation in multiple building types.

Knowledge gaps related to current recommendations for remediating wet or moldy materials in buildings are described in Figure 2, in the context of specific recommended stages of decision making in responding to building D/M. These include questions such as:

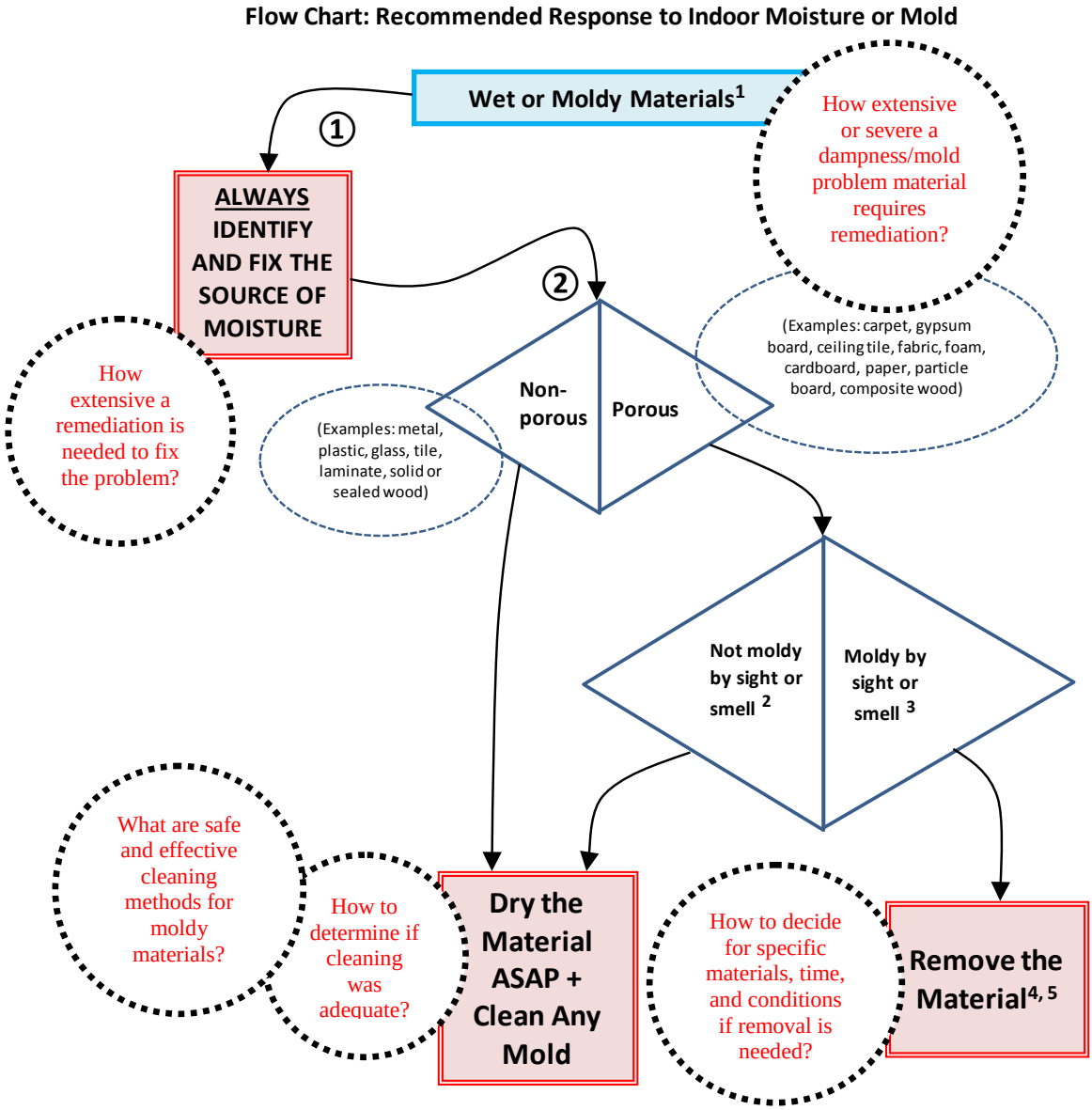
- When remediation for D/M is required, how extensive a remediation is needed to protect health? Can we say how complete the removal of moisture sources must be, and how complete the removal of any mold in or on materials?
- How is it determined if D/M remediation was adequate to protect health? (This links to the questions above on assessment of unhealthy levels of D/M.)
- What is the longest time that porous materials such as carpets or gypsum board can stay wet without requiring replacement? Also, what shorter periods of *repeated* wetting can create a need for material replacement? How do specific materials, age of materials, and indoor temperature and humidity affect these determinations? Can some porous materials be safely cleaned and re-used even after mold growth?
- How does one safely but effectively remove mold from materials? Are there effective and readily available (as for large-scale disasters) alternatives to bleach, use of which is related to adverse respiratory effects?
- How does one determine if a retained dampened material was not moldy or was adequately cleaned of mold? (This links to the questions above on assessment of unhealthy levels of D/M.)

Remediating D/M: priority research questions for actions and policies

Priority research questions in this area are listed in the left column of Table 8.

Remediating D/M– recommended research activities

Suggested priority research activities corresponding to the priority research questions are listed in the right column of Table 8.



[1] Identify by sight or smell. Mold testing not recommended. Assumes clean water, without sewage, oil, chemicals.

[2] Some agencies recommend a maximum wet time of 24-48 hours to keep porous materials, but this is not always correct. Any evident mold on a porous material, from enough prolonged wetting or repeated prior wetting, indicates a need for removal.

[3] Removal of porous materials is needed if mold growth has begun. The time required for mold growth depends on the material, amount of moisture, and environmental conditions such as temperature - growth occurs more quickly in warm, moist conditions.

[4] Porous materials like cloth can sometimes be cleaned thoroughly of mold and re-used; other materials like wall-to-wall carpeting are unlikely to be adequately cleanable, and should be removed.

Figure 2. Flow Chart: Recommended Response to Indoor Moisture or Mold (draft material from Indoor Air Quality Section, California Department of Public Health) with key outstanding questions related to knowledge gaps (in circles)

Table 8. Proposed priority research questions and research activities on *remediating* unhealthy levels of indoor D/M

Research questions	Recommended Research Activities
1) What types of remediation for D/M are necessary, for each case, to eliminate or reduce the resulting health effects (needs to be more specific than a general instruction to correct the source of moisture and dry, clean, or remove damp or moldy materials)? o How should it be determined if a specific porous material needs replacing, in terms of current moisture and moisture history? o What materials, and under what circumstances, can be cleaned and retained, without health risk? o How should it be decided what components in a building (e.g., materials on the outside of the building envelope, those between the outside and inside of the building envelope, or those inside the occupied space) communicate sufficiently with indoor air that indoor-level remediation or removal is necessary?	1) Intervention studies of D/M and health to evaluate different remediation strategies, levels of intensity, and costs, to compare efficacy vs. cost of reducing both D/M and health benefits. • Use a model of strong research designs, of controlled interventions in homes selected for both presence of D/M and of specific disease, intended to produce policy-relevant findings, such as Kercsmar et al. (2006). Studies on development of asthma in at-risk children would be desirable but large and extended; studies on exacerbation of asthma or other existing illness or symptoms could be shorter, smaller, and less costly. These studies will need careful design, if providing different levels of remediation at different times to participating homes with D/M problems, in order to meet ethical requirements for human research. • Including microbiologic measurements in intervention studies of health can help validate causal links for D/M factors, or improve proxies for causal agents. They can also identify causal agents, which, although not a priority for evaluating remediation effectiveness, could help future policies. 2) Simpler and much less expensive intervention studies (no need for control or concern about blinding) could focus entirely on intervention effectiveness in reducing D/M, irrespective of health benefits, based on assumed health benefits of reduced D/M. These studies could be very informative and should provide excellent value for cost.
2) Is there a core of knowledge that D/M remediators should have – e.g., what should be included in training for certification; what level of knowledge should be required to remediate D/M?	3) Combine a review and synthesis of published summaries on recommended approaches for remediating D/M, and a consensus process with experts in D/M remediation
3) What maximum levels of measured moisture (continuous or intermittent) or D/M factors indicate a successful remediation for health protection? (This question is considered under the topic of assessing D/M.)	(See Table 7, research activity 5. Priority research activities aimed at defining unhealthy levels of home D/M will also facilitate research about health-protective remediation of D/M, by providing methods to assess efficacy of D/M.)

4.0 Discussion

The proportion of asthma exacerbation and other respiratory or allergic disease caused by D/M-related agents in homes is unnecessary and potentially preventable. Because the adverse effects of residential D/M have been clearly demonstrated, this problem should now receive the increased governmental and private sector attention it merits, without being mired in controversy.

Having assessment tools that clearly define unhealthy levels of D/M in homes as well as guidelines for necessary and sufficient remediation actions for D/M that are documented as beneficial to health will allow formulation of more effective policies. These policies might be public regulations or codes, whether housing or health codes, assessment or remediation certification requirements, point-of-sale requirements, or non-regulatory tools such as guidelines, standards of care, lease terms, or insurance policy requirements.

Rough proxies for D/M have already shown consistent relationships with adverse health effects. This report suggests research activities aimed at developing more detailed and informative proxies to guide health-protective policies, without waiting for the identification of specific dampness-related causal agents. These proxies for D/M-related causal agents can be used in a health risk management process to allow balancing of costs and benefits, formulation of feasible health-protective policies and guidelines that would inform surveillance to ensure acceptable conditions or to trigger remediation, recommendation of measurable environmental goals for remediation, and validation of effective remediation.

Strengths and limitations

This report provides a focused initial research agenda related to the health effects of residential D/M, based on an apparently novel policy-oriented review of the literature on D/M and health. The research agenda is intended to enhance public and private policies in this area, policy changes that have been impeded by lack of scientific knowledge. The ultimate goal is to help shape a focused research agenda on assessment and remediation of D/M, located within a larger road map that includes other issues such as prevention, all with the goal of reducing the occurrence of dampness-related health effects in homes.

However, this report represents an informal rather than an exhaustive review of available health research, and presents only general recommendations and prioritization. It is intended to provide an initial perspective only, as material for a process of further multidisciplinary review, expansion, and prioritization.

Also, this report focuses only on two of the important components (assessing and remediating unhealthy levels of indoor D/M) within the larger process of developing effective public policies to reduce D/M-related health effects in housing (Fig 1). This broader process would include at least two other high priority research components as input into policies:

- Research on improving primary prevention of home dampness problems, before they occur. This would include identifying the specific features of home design, construction, and

maintenance most strongly related to dampness during the life of a building. Findings would allow identification of buildings at increased risk of D/M problems, and thus facilitate early prevention. More importantly, the results would facilitate changes in codes and other public policies that would help in the creation and maintenance of buildings less likely, over their lifetimes, to develop D/M-related problems and cause consequent health effects.

- Research on policy effectiveness, evaluating the strengths and limitations of current D/M-related public policies such as building, housing, and health codes, or their enforcement, and investigating how to improve the effectiveness of these policies in turning current knowledge into effective health-protective actions. The goal would be to discover and change the design, construction, or maintenance practices that have led to the current widespread occurrence of home dampness. For instance, studies involving proactive surveillance and remediation of D/M in rental housing could assess any advantages of such programs vs. their costs, and if beneficial, develop guidelines for successful programs. Policy research could also evaluate the benefits, costs, and political feasibility of using different policy instruments, such as legal standards or nonbinding guidelines, allowing better informed policy actions.

Overall, prevention (both primary and secondary) of D/M problems in housing that is more effective than what we have today will require new public policies and private actions, motivated and informed by increased knowledge about indoor dampness, mold, and health. This research agenda is a proposed step in that direction.

5.0 Conclusions

Because of the common occurrence of D/M in U.S. homes and the clear link between D/M and adverse respiratory effects, the D/M-related burden on the public health is important but largely preventable. There is limited understanding of how to identify unhealthy levels of D/M in homes or of what strategies or levels of remediation for D/M are necessary, and sufficient, to reduce D/M-related health risks to occupants.

This paper summarizes current knowledge, knowledge gaps, recommended priority research questions, and proposed research activities focused on two aspects of preventing home D/M and the resulting health effects: (1) how to assess and identify unhealthy levels of home D/M problems requiring remediation, and (2) how to effectively remediate D/M problems to protect health. Proposed research is suggested based on a comparison of current scientific knowledge on home D/M and health to knowledge required to support evidence-based, health-protective policies. While available knowledge is sufficient to support policies that call for remediation of residential D/M when they are apparent by sight or smell, this knowledge is not sufficient to provide clear, quantitative thresholds for action or explicit directions on the nature or extent of needed remediation. The research agenda does not include two other important subjects of research needed for optimal prevention of D/M-related health effects in housing: increasing primary prevention through building design, construction, and maintenance, and improving the effectiveness of policies that implement current knowledge into public and private actions.

The suggested research agenda includes, for improved assessment of D/M (Table 7): (1) focused scientific literature reviews to identify the current D/M proxies and microbiologic measurements

most strongly associated with health effects in a dose-response manner, to support current policies and to provide draft D/M metrics for use in epidemiologic studies; (2) epidemiologic studies, prospective or of other strong design, focused on semi-quantitative indices of qualitative D/M factors, conducted iteratively with continued development of improved assessment methods for building D/M; (3) review and synthesis of current empirical knowledge about detecting excess moisture in homes; (4) laboratory studies to improve the usefulness of moisture measurements in assessing building D/M and health; and (5) surveys to estimate the extent and severity of home D/M in the U.S.

The suggested research agenda for improved remediation of D/M includes (Table 8): (1) controlled D/M intervention studies of two kinds, including health effects but with and without microbiologic measurements, and also simpler studies focused just on reducing D/M factors without a health component; and (2) review and synthesis of the ample available empirical knowledge on effective strategies for reducing excess moisture in buildings, without need for evidence linking these strategies to health. Microbiologic measurements are not suggested as a priority current focus for epidemiologic studies, as such measurements are currently less promising for use in health-protective policies than qualitative D/M factors; however, identification of microbiologic measurements with consistent dose-response relations with health effects would be very helpful for health policies. The research needs and suggested research strategies for assessing unhealthy levels of home D/M and for evaluating successfully remediated home D/M have substantial overlap in both suggested study designs and the improved assessment tools needed.

The research agenda suggested here is limited in scope, is preliminary, and rests on a specific set of goals and assumptions. The recommendations are intended to stimulate further multidisciplinary review, input, and expansion, in order to help focus future healthy housing-related research.

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