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Review of Quantitative Standards and Guidelines for Fungi in Indoor Air

Carol Y. Rao and Harriet A. Burge
Harvard School of Public Health, Department of Environmental Health, Boston, Massachusetts

John C.S. Chang
U. S. Environmental Protection Agency, Air Pollution Prevention and Control Division, National Risk Management Research Laboratory, Chapel Hill, North Carolina

ABSTRACT

Existing quantitative standards/guidelines for fungi in indoor air issued by governmental agencies are based primarily on baseline data (rather than health effects data), and are either absolute (numerical) or relative (indoor/outdoor comparisons) or a combination of the two. The Russian Federation is the only governmental agency that has binding quantitative regulations for bioaerosols. Recommended guidelines have been proposed or sponsored by North American and European governmental agencies and private professional organizations. A considerable number of frequently cited guidelines have been proposed by individuals based either on baseline data or on personal experience. Quantitative standards/guidelines range from less than 100 CFU/m^3 to greater than 1000 CFU/m^3 (total fungi) as the upper limit for non-contaminated indoor environments.

Major issues with existing quantitative standards and guidelines are the lack of connection to human dose/response data, reliance on short term grab samples analyzed only by culture, and the absence of standardized protocols for data collection, analysis, and interpretation. Urgent research needs include the study of human responses to specific fungal agents, development and widespread use of standard protocols using currently available sampling methodologies, and the development of long term, time-discriminating personal samplers that are inexpensive, easy to use, and amenable to straightforward, relevant analysis.

IMPLICATIONS

Exposure to fungal aerosols clearly can cause human disease. However, methods for assessing exposure remain poorly understood, and approaches for interpreting data are often contradictory. This paper reviews and compares existing quantitative standards and guidelines for indoor airborne fungi, discusses the limitations, and identifies research needs that should contribute to the development of realistic and useful practices regarding these important air pollutants.

INTRODUCTION

Exposure to indoor air contaminated by fungi and their metabolites commonly occurs, and can cause allergic, toxic, and irritant symptoms and diseases.[1-4] However, in spite of these impacts on human health, few studies have focused on the relationship between concentrations of any fungal component and human disease.[5-10] Because of the limited data, standards based on health risk assessments are currently impractical for most fungal agents. The majority of available standards and guidelines for fungi in indoor air focuses on descriptions of clinically-defined diseases and approaches to sampling, remediation, and preventative maintenance without establishing limits for concentrations of fungi in air.[11-15] However, there are a number of published standards and guidelines (S/Gs) that are quantitative and designed to guide in the interpretation of fungal aerosol sampling data. For the purposes of this discussion, a standard is defined as a requirement and a guideline is defined as a recommendation.

Existing quantitative S/Gs fall into two general categories: absolute and relative. Absolute S/Gs specify levels of total or specific fungi in air that are considered acceptable or not acceptable. Some S/Gs are based on the personal experiences of an individual or a group of individuals (e.g., Morey et al.[29], ACGIH[35]). Others are based on baseline data from cross-sectional sampling surveys of representative "normal" environments without reference to specific health effects (e.g., CEC[21]). A range of "normal" levels of airborne fungi for the representative environment is established and levels that exceed this range (or some specific part of the range) are considered "unusual" and possibly indicative of contamination problems. Another absolute approach has been to establish guidelines at or near detection limits for fungi known to have serious health implications (i.e., pathogenic) (e.g., Miller[19]).

Relative standards are based on the relationship between indoor and outdoor levels as represented by simultaneously collected samples. The principle is that lower indoor than outdoor fungal levels indicate an acceptable

indoor environment. Indoor/outdoor ratios are also used to assess the probability of an indoor fungal source. Another relative method is to use rank order assessment where indoor and outdoor fungi are identified by taxa, then ranked according to frequency and compared statistically (i.e., Spearman Rank Order Correlation test) to determine the likelihood that the two populations are identical.

OVERVIEW OF EXISTING QUANTITATIVE STANDARDS AND GUIDELINES

The standards and guidelines with quantitative limits for fungal concentrations in indoor air that are available in the published literature are presented in Tables 1 and 2. The list should be representative of the types of S/Gs that exist. Atypical cases, such as hospitals and clean rooms, are not addressed since these are specialized circumstances and required concentrations could not be achieved by normal building facilities.

Quantitative Standards Issued by Governmental Agencies

Russia has issued the only official quantitative standard concerning fungi in air. In 1993, the State Committee for Hygiene and Epidemiological Surveillance of the Russian Federation revised the "Maximum Allowable Concentrations (MAC) of Harmful Substances"[16] that lists chemical and biological standards for industrial settings. Considering the species of bacteria, yeasts, and other fungi specified, the food processing and pharmaceutical industries appear to be the primary targets for the regulations. Fungal concentration limits are set for individual fungal and bacterial species based on allergenicity in animal models, hazard class, or are otherwise not specified. Limits for some agents are based on metabolite or protein concentrations rather than culturable units.

No other official quantitative standard was found; however, the United States Occupational Safety and Health Administration (OSHA) proposed an Indoor Air Quality Standard in 1994 that would apply to non-industrial workplaces protected under the OSHAct.[17] The proposed standard requires a proactive rather than a reactive program (i.e., extensive preventive maintenance). In the text of the introduction to the standard, relative guidelines are discussed. The promulgation of the standard is pending.

Quantitative Guidelines Issued by Governmental Agencies

Canada Mortgage and Housing Corporation (CMHC), a federal housing agency serving homeowners, the medical community, and the building industry, publishes documents regarding indoor air quality. In 1988, Paracel Laboratories Ltd. prepared a project report, "Determination of Fungal Propagules in Indoor Air," that suggests guidelines for fungi in air, sampling with a Reuter Centrifugal Sampler (Biotest AG, Dreieigh, Germany) with 2% malt extract agar Rose bengal medium.[18] The guidelines are based on a study[19] of 50 Canadian homes where deviations from "normal" levels were determined. The actions required (e.g., remediation or investigation) depend upon the type and concentration of fungal species recovered and on inspection of the inhabited space. Another publication by CMHC cites this guideline.[20]

In 1993, the Commission of the European Communities (CEC) issued "Report #12: Biological Particles in Indoor Environments" that reviews strategy and methodology for investigating house dust mites, dander, fungi, bacteria, and *Legionella* in the indoor air of private houses, non-industrial workplaces, and public buildings (excluding hospitals).[21] Health effects and sampling methods are discussed, although no general sampling strategy is given. Fungal concentration categories were determined using data from assessments of fungal population distributions in residential indoor air from four studies in Europe and Canada[22-25] [using six-stage or N-6 Andersen Samplers (Graseby Andersen, Smyrna, Georgia USA) and malt extract agar or DG-18], not on a health evaluation or any specific health effects. Determination of the categories using the data and interpretation of the levels (i.e., unsafe levels) are not addressed. Comparison with outdoor sampling is also recommended.

A 1989 study by the Dutch Occupational Health Association, "Research Methods in Biological Air Pollution," reports fungal levels that should be considered a threat to the worker's health and when preventative action should be taken. The levels have been cited as a provisional Dutch guideline by researchers.[26] The basis for the guideline is unclear since the original document could not be obtained.

The "United States Occupational Health and Safety Administration (OSHA) Technical Manual" is a public document containing sampling plans and strategies for the agency's workplace inspections.[27] The most recent update (1992) includes a chapter on indoor air quality where air sampling is advised only after medical or clinical reports indicate the existence of workplace related illnesses that are likely to be due to bioaerosols. Identification of predominant taxa along with total fungal counts is suggested. Interpretation of sampling results is based on a paper in which fungal concentrations in air were presumably determined by literature review and personal experience of the cited authors.[28,29] The "OHSA Technical Manual" and the cited authors[28,29] state that results in excess of the suggested concentrations do not necessarily imply unsafe conditions.

The New York City Department of Health has developed guidelines on assessment and remediation of *Stachybotrys atra* in indoor environments based on a 1993 panel discussion.[30] The document addresses health effects, environmental assessment, remediation techniques, and hazard communication. Air sampling is not recommended, but may be required if inspection uncovers possible contamination. Fungal concentrations in air that require action (e.g., remediation or immediate evacuation) are included. The authors did not discuss how the concentrations were chosen.

Table 1. Summary of quantitative standards and guidelines for fungi in air by governmental and private organizations.

Organization/Document/Year	*Recommendations*	*SP* [a]	*Bases*
ACGIH/Guidelines for the Assessment of Bioaerosols[35]/1989	•<100 CFU/m^3 = OK •Indoor/outdoor < 1 = OK if similar taxa •Complaint area/Non-complaint > 10X = unusual	Y	Consensus[b]
ACGIH/Air Sampling Instruments for Evaluation of Atmospheric Contaminants[37]/1995	•<100 CFU/m^3 = low: e.g. cleanrooms and hospitals •100-1000 CFU/m^3 = intermediate: e.g. general indoor and outdoor concentrations •>1000 CFU/m^3 = high: e.g. animal handling areas	Y	Literature Review
AIHA/Biohazards Ref. Manual[38]/1986	•There is no safe level of an uncontained pathogenic organism	N	N/A[c]
AIHA/The Industrial Hygienist's Guide to IAQ Investigations[40]/1993	•Rank order assessment •Indoor/outdoor comparison recommended	N	Citation[d,35]
AIHA/The Practioner's Approach to IAQ Investigations[41]/1989	•Rank order assessment •≥1000 CFU/m^3 = indicates atypical situation •High indoor/outdoor ratio = indoor amplifier present •Cites Miller et al. (1988)[19] (See Table 2)	N/A	Citation[19,29,35]
CEC/Report #12: Biological Particles in Indoor Environment[21]/1993	•For houses: ·>10^4 CFU/m^3 = very high ·<10^4 CFU/m^3 = high ·<10^3 CFU/m^3 = intermediate ·<200 CFU/m^3 = low (<500 CFU/m^3 on DG18 medium) ·<50 CFU/m^3 = very low •For non-industrial indoor: ·>2000 CFU/m^3 = very high ·<2000 CFU/m^3 = high ·<500 CFU/m^3 = intermediate ·<100 CFU/m^3 =low ·<25 CFU/m^3 = very low	Y	Consensus; Survey[22-25]
CMHC/Determination of Fungal Propagules in Indoor Air[18]/1988	•0 CFU/m^3 = no action unless indicated by inspection •≥50 CFU/m^3 if one species = identify source to determine further action •≤150-200 CFU/m^3 if several species = no action unless indicated by inspection •≥200 CFU/m^3 if several species = prudence requires further inspection •≤400-500 CFU/m^3 mainly *Cladosporium* and *Alternaria* = no action unless indicated by inspection •≥500 CFU/m^3 mainly *Cladosporium* and *Alternaria* = determine reason	Y	Citation[18]
CMHC (Disclaimer)/Testing of older houses for microbiological pollutants[20]/1991	•>200 CFU/m^3 variety of species other than *Alternaria* and *Cladosporium* = investigate •>500 CFU/m^3 including *Alternaria* and *Cladosporium* = investigate •Indoor/outdoor comparison recommended when ≤200 CFU/m^3	N	Survey; Citation[18]
Cutter Information Corp./IAQ Update: Biocontaminants in Indoor Environments[46]/1994	•Indoor/outdoor ratios range from < 0.1 to < 1 = OK •Upper limits range from: ·300 CFU/m^3 of common fungi (e.g. *Cladosporium*) ·150 CFU/m^3 of mixed species other than pathogenic or toxigenic species ·200 CFU/m^3 total fungi ·100 CFU/m^3 unless immunocompromised population	Y	Citation[19,35,48,49,52,76]

(continued on next page)

Table 1 *(Continued)* Summary of quantitative standards and guidelines for fungi in air by governmental and private organizations.

Organization/Document/Year	*Recommendations*	*SP*[a]	*Bases*
Healthy Buildings International[43,44]/1994	•≤750 CFU/m^3 total airborne bacteria and fungi = OK if species not infective or allergenic	Y	Survey
IAQ Association Inc./IAQ Standard #95-1 Recommended for Florida[45]/1995	•<300 CFU/m^3 common fungi = OK •<150 CFU/m^3 mixed fungi other than pathogenic or toxigenic = OK	N	Citation[19]
National Health and Welfare, Canada (Disclaimer)/IAQ in Office Buildings: A Technical Guide[31]/1993	•Toxigenic, pathogenic fungi not acceptable in indoor air. •≥50 CFU/m^3 if one species = investigate •≤150 CFU/m^3 if mixture of species = OK •≤500 CFU/m^3 if common tree/leaf fungi = OK in summer	Y	Survey[e]
The Netherlands/Research Methods in Biological Indoor Air Pollution[26]/1989	•>10^4 CFU/m^3 total fungi = threat to health •>500 CFU/m^3 of one species of a potentially pathogenic nature = threat to health	Y	N/A
New York City/Guidelines on Assessment and Remediation of *S. atra* in Indoor Environments[30]/1995	•Indoor/outdoor > 1 = indicates contamination •103-104 CFU/m^3 = immediate evacuation	N	Consensus
Nordic Council/Criteria Documents from the Expert Group[32]/1991	•10-10^4 CFU/m^3 = typical in "sick buildings" and ambient air	N/A	Citation
Russian Federation (Standard)/MAC of Harmful Substances[16]/1993	•Levels from 10^3 cells/m^3 to 10^4 cells/m^3 depending on specific species •Some levels based upon metabolite or protein concentrations	N	Scientific
USOSHA/Proposed IAQ Standard[17]/1994	•Levels of bioaerosols in the indoors would reflect those outdoors •Rank order assessment	N	Consensus
USOSHA/Technical Manual[27]/1992	•≥1000 CFU/m^3 = indicates contamination •≥10^6 fungi/gram of dust = indicates contamination •≥10^5 bacterial or fungi/ml of stagnant water or slime = indicates contamination	Y	Citation[28,29]
WHO/IAQ: Biological Contaminants[42]/1988	•Pathogenic and toxigenic fungi unacceptable in indoor air •>50 CFU/m^3 of one species = investigate •≤150 CFU/m^3 = OK if mixture of species •≤500 CFU/m^3 = OK if *Cladosporium* or other common phylloplane	Y	Citation[13]

[a] Sampling protocol; [b] Agreed upon by group of individuals; [c] Not available; [d] Cited from secondary source (not all sources cited); [e] Based on data from survey

The concentration specified for immediate evacuation is a possible misprint, since the level is quite low (103-104 CFU/m^3). However, we were unable to verify our speculation that the level should be 10^3-10^4 CFU/m^3.

The Nordic Council has issued "Criteria Documents from the Expert Group 1991" that are intended for use by the regulatory authorities in Denmark, Finland, Iceland, Norway, and Sweden as a scientific basis for the setting of

national occupational exposure limits, rather than as actual quantitative proposals.[31] The section on microorganisms is a literature review of dose/response relationships. Cited fungal concentrations describe "normal" or "sick building" indoor environments.

Quantitative Guidelines Sponsored by Governmental Agencies

Some publications regarding biological contamination in indoor air are based on research sponsored by governmental agencies. Disclaimers are often included making clear that provision of financial and other support does not constitute governmental policy. In 1993, the Department of National Health and Welfare of Canada published "Indoor Air Quality in Office Buildings: A Technical Guide" by T. Nathanson.[32] Directed at building maintenance staff, health and safety officials, and consultants, the document addresses general health effects from fungal exposure, inspection protocol and remediation. Rank order assessment, indoor/outdoor comparisons, and limits for fungi in air are included. The fungal concentration limits are based on data from 600 samples collected in 50 federal government buildings with a Reuter

Table 2. Summary of quantitative standards and guidelines for fungi in indoor air by investigators.

Investigator	*Recommendations*	*SP* [a]	*Bases*
Berk et al.[50] 1979	•Exposure to 20 CFU/m^3 to over 700 CFU/m^3 with no ill effects	N/A[b]	Survey[c]
Burge[55] 1990	•If indoor microbial aerosols qualitatively different from outdoors and indoor levels consistently more than double outdoor and exceeding 1000 CFU/m^3 = investigate	Y	Personal experience[d]
Godish[56] 1991	•>1000 CFU/m^3 fungi = high levels; potentially significant contamination •<100 CFU/m^3 = mold-free environment •In between, subject to investigator's owninterpretation •Low recovery cannot confirm low airborne mold spore levels	Y	Personal experience
Holmberg[51] 1984	•<2200 CFU/m^3 = mold-free environment •10,000 to 15,000 CFU/m^3 = surface mold present	N/A	N/A
Lacey et al.[57] 1988	•10^3-10^4 spores/m^3 of total fungi = normal in air	N/A	N/A
Miller et al.[19] 1988	•Some fungi not acceptable in indoor air (toxigenic, pathogenic) •≥50 CFU/m^3 one species = investigate •≤150 CFU/m^3 = OK if mixture of species •≤300 CFU/m^3 = OK if common phylloplane fungi	Y	Survey
Miller et al.[52] 1992	•Indoor mycoflora qualitatively similar to outdoors = OK •Indoor mycoflora quantitatively lower than outdoors = OK	Y	Survey
Morey et al.[29] 1984	•≥1000 CFU/m^3 = investigate •≥10^6 fungi/g dust = investigate •≥10^5 bacteria or fungi/ml stagnant water or slime = investigate •Levels above do not necessarily imply hazard	Y	Literature review; Personal experience
Ohgke et al.[47] 1987	•>100 CFU/m^3 indicates indoor fungal source = further investigation necessary	Y	Survey
Reponen et al.[48] 1990	•>500 CFU/m^3 (winter) = abnormal indoor source •Indoor/outdoor > 1 may indicate abnormal indoor levels in summer •Applies only to urban and suburban subarctic homes	Y	Survey
Reynolds et al.[53] 1990	•>500 CFU/m^3 = abnormal condition •Significant indoor/outdoor differences indicate indoor sources •Speciation and rank ordering recommended	Y	Survey
Solomon et al.[54] 1984	•Domestic interior levels range from 1 - 6000/m^3 •Maximum levels usually < 1600/m^3	N	Survey
Yang et al.[49] 1993	•200 CFU/m^3 total fungi = upper limit •Critical analysis if opportunistic or toxigenic fungi detected	Y	Survey

[a] Sampling protocol; [b] Not available; [c] Based on data from a survey; [d] Based on field experiences of investigator

Centrifugal Sampler over a six-year period. The author does not specify how the limits were derived from the data.

In 1991, Bowser Technical Inc. prepared a report for the Canada Mortgage and Housing Corporation (CMHC) entitled "Testing of Older Houses for Microbiological Pollutants."[20] Citing another CMHC publication[18], fungal concentrations that indicate the need for "further investigation" are recommended. However, based upon its study of 28 homes in Ontario, Canada, indoor/outdoor fungal ratios are suggested as better indicators of microbial activity for houses with fungal densities below the recommended fungal concentration limits because of the variability of outdoor fungal densities. Though a sampling protocol is included, it is not explicitly recommended.

Quantitative Guidelines and Proposals from Professional Organizations

Many professional organizations concerned with the protection of public health have become interested in microorganisms in indoor air. The American Conference of Governmental Industrial Hygienists (ACGIH) Committee on Bioaerosols was one of the first to attempt to establish practical quantitative guidelines for microorganisms in indoor air. At least three different papers have been published, each one consecutively more conservative in recommending upper limits for fungi in indoor air.[33-35] The 1989 publication "Guidelines for the Assessment of Bioaerosols in the Indoor Environment" is primarily an evaluation tool, but does suggest general guidelines for fungi in indoor air. The "1994-1995 ACGIH Threshold Limit Values (TLV) for Chemical Substances and Physical Agents and Biological Exposure Indices" includes an explanation of why a general TLV for a level of culturable bioaerosols is not scientifically supportable.[36] The "8th Edition of the ACGIH Air Sampling Instruments for Evaluation of Atmospheric Contaminants"[37] is a comprehensive guide to the sampling of airborne contaminants in occupational and environmental settings. In the chapter on airborne microorganisms, types of airborne biological particles and suggestions on how to select the most suitable sampling equipment are discussed. A consideration in choosing a specific sampling device is the expected concentration of airborne microorganisms in different situations. The authors did not specify how the expected concentrations were determined.

The American Industrial Hygiene Association (AIHA) has many publications concerning indoor air quality. In 1986, the Biosafety Committee published "Biohazards Reference Manual" primarily for use in laboratory settings. The manual states, "there is no safe level of a noncontained pathogenic organism," though pathogenic is not defined.[38] The committee is also preparing a field sampling manual for biocontaminants.[39] The Technical Committee on Indoor Environmental Quality document, "The Industrial Hygienist's Guide to Indoor Air Quality Investigations,"[40] recommends bioaerosol sampling to verify pathways for exposure to specific microorganisms. In the Technical Committee's "The Practitioner's Approach to Indoor Air Quality Investigations,"[41] rank order assessment, indoor/outdoor ratios, and fungal levels that indicate contamination are included.

Based on a meeting of international experts in 1988, the World Health Organization (WHO) has a published "Indoor Air Quality: Biological Contaminants."[42] The publication focuses on hazard assessment and preventative maintenance and although levels for fungi in air are not explicitly recommended, the Canadian Residential guideline[13] is cited. However, the levels listed could not be found in the original document.

Quantitative Guidelines from Individuals and Private Organizations

Healthy Buildings International, Inc., a private consulting firm, has a standard for use within the organization for levels of microorganisms in indoor air based on data from 5,000-6,000 air samples from commercial buildings worldwide.[43,44] Indoor Air Quality Association, Inc., an organization of professionals interested in indoor air quality issues (e.g., mycologists, attorneys, and HVAC specialists), has published "Indoor Air Quality Standard #95-1 Recommended for Florida"[45] which cites Miller et al.[19] and a World Health Organization seminar as the bases for the standard. In 1994, Cutter Information Corporation published "Indoor Air Quality Update: Biocontaminants in Indoor Environments,"[46] a review of current practices regarding biological contamination where "guidelines for fungi in air that are currently used by most investigators and environmental health experts" are cited and critiqued. Health effects, remediation, and preventative maintenance are included.

Many individuals have published research papers that include recommended fungal levels (Table 2) based on statistical analyses of data collected using defined sampling and analytical protocols. Ohgke et al. (1987)[47] used the median value (100 CFU/m^3) of a data set collected in 11 public buildings as the lower limit for levels suggesting a probable fungal source that should be evaluated. Reponen et al. (1990)[48] sampled 71 noncomplaint subarctic homes, calculated a 95% upper limit (500 CFU/m^3 in winter only) using the geometric mean on a lognormal distribution, and suggested that levels above this upper limit indicate abnormal indoor sources or insufficient ventilation. Yang et al. (1993)[49] based an upper limit guideline (200 CFU/m^3) on 2,000 indoor N-6 Andersen samples collected on malt extract agar where 75% of samples yielded less than 178 CFU/m^3. Other authors have based guidelines on collected data, but do not provide characteristics of the data sets or describe the methods by which the guidelines were derived from the data (Berk et al.,[50] Holmberg,[51] Miller et al.,[19,52] Reynolds et al.,[53] and Solomon et al.[54]). In addition, several investigators specify

guidelines based on indoor/outdoor ratios (Miller et al.,[52] Reponen et al.,[48] and Reynolds et al.[53]) and fungal taxa comparisons (Burge,[55] Miller et al.,[52] Reynolds et al.[53]). Some individuals have based recommended levels on personal experience in evaluating indoor fungal contamination (Burge,[55] Godish,[56] Lacey et al.,[57] Miller et al.,[19] and Morey et al.[29]).

LIMITATIONS OF EXISTING QUANTITATIVE STANDARDS AND GUIDELINES

Human Dose/Response Data

Ideally, standards for fungi in indoor air should be based on the health effects of such exposure. However, basing S/Gs on health effects is difficult at this point in time due to a lack of information on human dose/response relationships for fungi in air. The Russian Federation extrapolates allergenicity in animal models as the basis for some of its standards.[16] Others have attempted to use pathogenicity as a means to determine safe or unsafe levels, where the term pathogen is rarely defined.[19,26,31,38,42,45,46] It is usually inferred that pathogen denotes fungi that can cause infectious disease or produce allergens or toxins.

By this definition, all fungi could be considered pathogenic under some circumstances, since all can produce potential allergens.[58] Levels of fungi and the correlation with allergen levels necessary to cause sensitization or symptoms remain unknown. Host susceptibility (i.e., genetic background) also plays an important part in the development of allergic disease.[59] Existing S/Gs assume that culturable fungi are representative of allergen exposure (which may not be the case) and that "normal" indoor levels (including fungi penetrating from outdoor air) do not represent a health risk.

Many common environmental fungi produce secondary metabolites that are directly toxic to eukaryotic cells.[60,61] The term mycotoxin is commonly used to refer to these compounds. These mycotoxins exert effects (e.g., immunosuppression, carcinogenesis, cytotoxicity, and neurotoxicity) independent of infection or stimulation of antibodies (in contrast to the mycobacterial "mycotoxins"). Most of the known effects of mycotoxin exposure are derived from animal ingestion and inhalation and in vitro studies. Data on the human health effects of chronic, low-level, inhaled mycotoxin exposures are limited and it is not clear that such effects occur in other than highly contaminated (e.g., agricultural) environments.[62-64] Epidemiological studies that associate respiratory exposure to mycotoxins and human disease are lacking since such studies would require more sensitive sample analytical techniques than are currently available for most mycotoxins. The guidelines that have been formulated to protect against exposure to toxigenic fungi have been based on measurements of culturable fungi that are known to produce toxins. This can be misleading since toxin concentration in spores is most likely independent of viability. Also, not all strains of a toxigenic species have the ability to produce mycotoxins in detectable amounts.[65,66] The production of mycotoxins by fungi and accumulation of mycotoxins in fungal spores are dependent upon many factors such as environmental conditions (e.g., substrate, temperature, and humidity), species, and strains of fungi;[4,65-69] therefore, detection of a fungal species known to be toxigenic does not imply mycotoxin exposure. However, until more is known about the potential for serious adverse human health effects of mycotoxin inhalation exposure, conservative approaches are appropriate.

Virulent fungal agents that cause acute respiratory infections (e.g., *Histoplasma capsulatum*) rarely grow indoors (although spores can penetrate from outdoors). Sampling for these agents has not been recommended and sampling-based S/Gs have not been proposed. The development of indoor standards for fungi that can cause human opportunistic infections (e.g., *Aspergillus fumigatus*) is complicated since infection often depends upon host immune status and exposure may also occur outdoors.[70,71]

Relative Standards and Guidelines

Relative standards (i.e., indoor/outdoor and complaint/noncomplaint comparisons) might be appropriate for exposures to agents that are borne on all fungi (i.e., glucans), but are less useful where health effects are associated with specific kinds of fungi. The major advantage of relative standards is that, within limits, different sampling and analysis methods can be used by different investigators as long as methods used indoors and outdoors are identical.

Identification of fungal species, not just fungal genera, is paramount to the proper use of relative standards. Fungal genus-only identification can result in inaccurate characterization of indoor air fungal contamination, since indoor sources of a specific species may be overlooked. Also, not all members of a fungal genus have the same potential to cause human disease.

Seasonal variations must be taken into consideration when interpreting indoor/outdoor fungal concentration ratios, since outdoor fungal levels are strongly influenced by climate and weather.[48,72] For example, when there is snow on the ground, outdoor fungal concentrations in air are usually quite low. Consequently, this will directly affect the penetration of fungal particles into the indoor air and the indoor/outdoor ratio. Therefore, even if the concentration of fungi from indoor sources is constant throughout the year (hypothetically speaking), the extent of indoor fungal contamination (when assessed with indoor/outdoor ratios) will appear to be different due to the seasonal variations of the outdoor fungal concentrations.

Baseline Data

The most common approach to the development of S/Gs has been to accept a set of baseline data from cross-sectional sampling surveys as representing the "normal" indoor air spora and to relate new data to the distribution of the baseline set. This approach essentially describes a "normal"

environment rather than being related to health effects. Standards based on this type of data provide some guidance if the assumption is made that levels that are high relative to a baseline range are more likely to have a significant health impact than those in the lower part of the range. The use of baseline data in establishing S/Gs could allow the pinpointing of unusual exposure situations, provided that methods for data collection are carefully standardized. However, because of geographical variations in fungal populations, the widespread applicability of baseline data-based guidelines outside the geographical boundaries of the initial surveys is debatable.

The major issues associated with the current approach to collection of baseline data and the resulting guidelines pertain to the accurate assessment of fungal exposures that cause adverse health effects. Baseline fungal aerosol data is almost exclusively collected using cultural analysis, in spite of the fact that many of the health effects of concern do not depend on viability of the fungal spores.[73] Although sample collection methods exist that might allow assaying of specific agents, the relevant assays generally do not exist.[37]

Existing guidelines are based on environmental (area), short-term (grab) sampling measurements. Personal exposure assessment is difficult since there are few airborne fungal aerosol sampling devices that can be comfortably attached to clothing and that can measure long-term exposure.[37] Grab samples are problematic in that fungal aerosols vary temporally and spatially, with widely disparate levels possible between two sites in a room and between one minute and the next.[25] Indoor levels are strongly dependent on the kinds of activity occurring in the space, and on the fungal content and rate of penetration of outdoor air.[74,75] These factors often combine to cause internal variability (i.e., variability within buildings) to be higher than the variability between buildings. Accordingly, some measure of variability dependent upon sampling method should be included in a standard. This also implies that accurate exposure assessments cannot be based on the results from a single sample.[24] None of the existing standards or guidelines include specifications for acceptable variability in the method of sample collection.

In addition, no standard sampling and analytical protocols are in common use. Results can vary greatly between the types of sampling equipment, the number and location of samples to be collected for each environment, the volume of air to be sampled (which controls the sensitivity of the devices), the kinds of culture medium, the incubation conditions, the number of colonies that represent an acceptable sample, the counting and identification procedures, and the procedures to be used for data analysis.[37] The existence and use of such standard protocols would allow the accumulation of broadly relevant baseline data by investigators across the world.

SUMMARY OF RESEARCH NEEDS

Research in two areas is essential before reliable health-based quantitative standards and guidelines can be generated. Human dose/response data for a variety of human health effects need to be collected and accurate and reliable methods for fungal exposure assessment need to be developed. The establishment of standardized sampling, analysis and data interpretation protocols would be necessary to achieve these goals. Specific research topics include:

- Characterization of indoor fungal sources: e.g. spatial, temporal, geographical, and seasonal variabilities in fungal populations.
- Development of dose/response data relating chronic and acute airborne fungal exposure to human health effects (including allergic, mycotoxic, irritant and synergistic effects related to complex mixtures).
- Development of accurate and sensitive measures of specific fungal allergens and toxins in air.
- Development of inexpensive, sensitive, precise, and reliable methods for collection and analysis of personal samples.

CONCLUSIONS

Though the focus of this paper has been quantitative standards and guidelines, the majority of standards and guidelines available to the public are qualitative in nature.[11-15] Control of biological contamination and preventative maintenance should always be the first line of defense against the airborne fungal exposure. However, even under ideal preventative maintenance conditions, opportunities for fungal growth and airborne exposure often do occur.

An ideal quantitative standard would be based on scientific evidence of fungal concentrations that cause adverse health effects. More information on the levels and patterns of exposure to fungal effluents (e.g., spores, spore or mycelial fragments, or substrate material containing allergenic or toxic substances, VOC's, etc.) that cause human disease is necessary to provide a solid basis for quantitative standards. Both epidemiological and experimental efforts can contribute to the development of exposure/response relationships for each kind of disease and make clear the kinds and concentrations of agents that must be monitored.

The many different and less-than-ideal microbiological techniques currently available for sampling and analysis of indoor fungal levels and exposures have caused confusion and misconception. Until new techniques are developed, a standardized protocol for sampling and analysis using currently available methods may be an alternative to provide a uniform basis for cross comparison of experimental data.

Of significant value would be the development of new methods for fungal aerosol exposure assessment focusing on simple, inexpensive methods for both sample collection and analysis that can be used by relatively untrained personnel, and that provide time-discriminated personal

exposure data. The development of sampling and analysis methods focusing on the actual agents of disease (allergens, toxins, and virulent cells) rather than indicators such as culturable units or countable spores also has important implications for the development of human dose/response data.

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About the Authors

Carol Y. Rao, M.S., (corresponding author) is a doctoral candidate in the Department of Environmental Health, Harvard School of Public Health, Boston, MA 02115. Harriet A. Burge, Ph.D., is an associate professor in the Department of Environmental Health, Harvard School of Public Health. John C.S. Chang, Ph.D., is a senior engineer affiliated with the Air Pollution Prevention and Control Division, National Risk Management Research Laboratory, U.S. Environmental Protection Agency, MD-54, Research Triangle Park, NC 27711.