Comments on "Bioaerosol Lung Damage in a Worker with Repeated Exposure to Fungi in a Water-Damaged Building"

In their case report of a worker with lung damage associated with microbial exposure, Trout et al. (*1*) emphasized the need for further research on markers of exposure to bioaerosols, particularly fungi that produce mycotoxins. The authors presented an interesting pilot serologic investigation for IgG and IgM antibodies to roridin (a macrocyclic trichothecene mycotoxin produced by *Stachybotrys chartarum*) and found no elevation of antibodies in the index case, an individual with repeated exposure to a water-damaged building. The clinical evaluation of the index case did not reveal elevation of IgG or IgE responses to *S. chartarum*, although precipitating antibodies were reportedly positive "only to *Thermoactinomyces vulgaris*."

Although the environmental evaluation and subsequent discussion on bioaerosols focuses on fungi (particularly *S. chartarum*) and mycotoxins, Trout et al. (*1*) did not discuss the role that inhaled bacterial antigens may have played in this individual's illness. This is perplexing, as inhalation exposure to *T. vulgaris* is listed as one of the most frequent causes of hypersensitivity pneumonitis by Cormier (*2*), who was cited by Trout et al. (*1*). Similar to fungi, actinomycetes can grow on building materials in wet and warm places, and spread their spores into the air (*3*).

The pulmonary and immunologic effects of repeated exposure to *T. vulgaris* have been studied in animal models (*4*), and the clinical relevance of elevated and repeated serologic testing of IgG and IgA for *T. vulgaris* has been described after human exposures in agricultural settings (*5*). In a more recent *EHP* Grand Rounds article describing a case of hypersensitivity pneumonitis from residential exposure, the presence of another clinically significant thermophilic bacteria (*Saccharopolyspora rectivirgula*) was documented in a water-damaged home, and precipitating antibodies to this organism were present in the affected individual (*6*).

Although I acknowledge the importance of reducing or preventing exposure to bioaerosols in the indoor environment as well as the need for reliable biomarkers of exposure, limiting the extent of the reported investigation and discussion in this case to fungi and mycotoxins seems unjustified. It would be helpful if Trout et al. (*1*) could further discuss the results of the serologic testing with respect to *T. vulgaris* and if the environmental assessment of bioaerosol exposure included bacterial antigens.

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Bioaerosol Lung Damage: Trout's Response

In his letter referring to our recent paper in *EHP* (*1*), Sudakin points out that hypersensitivity lung diseases have been shown to be associated with exposure to thermophilic actinomycetes such as *Thermoactinomyces vulgaris*. Exposures to these organisms related to lung disease have been reported in both outdoor settings (when handling materials such as compost or decomposing organic matter—the classic example being farmer's lung) and indoor settings (*2*). Regarding the indoor environment, reported exposures to thermophilic organisms that cause documented hypersensitivity lung disease have occurred in situations involving contamination of air-handling systems, primarily heating and/or humidification systems (*3–7*). Thermophilic fungi (thermophiles) grow optimally at temperatures between 35° and 50°C (95°–122°F) or hotter. In contrast, most fungi are considered mesophiles, growing optimally between 15° and 30°C (59°–86°F) (*8*).

Precipitating antibodies indicate exposure to a substance and may provide supporting evidence for a specific etiologic exposure; these tests do not independently prove or disprove a diagnosis of hypersensitivity lung disease (*9*). Although the presence of precipitating antibodies can provide justification for environmental evaluation of exposure to specific antigens (*10*), the results of precipitin testing must be interpreted with knowledge of potential occupational and/or environmental exposures experienced by the patient. One of the limitations of these antibody tests is that a single test that indicates the presence of precipitating antibodies does not provide any information concerning the source of the antigens to which the person was exposed.

The primary problem in the building of concern in our report around the time of the patient's illness (and our evaluation) was large-scale water incursion allowing for massive fungal contamination of building materials in multiple areas of the building. These types of environmental conditions are not conditions in which thermophiles would be expected to grow well. As is commonly found in hotels, each room of the building in question had a dedicated unit ventilator to condition the occupied space. Inspection of selected unit ventilators in the building at the time of our evaluation revealed no obvious reservoirs of microbial growth. In addition, our evaluation, and the illness experienced by the patient in our report, took place during the cooling season when heating units would not routinely be in use.

Given the above and the activities of the patient likely leading to aerosolization of the fungal contamination, there is no reason to believe exposure to thermophilic organisms played a role in this patient's building-related illness. It is unlikely that an environmental evaluation for thermophilic organisms in the areas that were grossly contaminated with fungi would have provided any useful information regarding the illness experienced by the patient discussed in our report. Additional discussion of the potential role of thermophilic organisms in the etiology of hypersensitivity lung diseases in general was beyond the scope of our paper.

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Correction: Exposure Measurement Error in Time–Series Air Pollution Studies

David Mage pointed out an error in the first complete paragraph in the second column of page 423 in our paper "Exposure Measurement Error in Time–Series Studies of Air Pollution: Concepts and Consequences" (*1*). This section contains a brief analysis of the role of pollution originating from indoor and outdoor sources that is incorrect in its derivation but correct in its basic finding that average personal exposure is roughly proportional to ambient concentration. Hence, regression models that use ambient measurements to predict mortality can give different estimates of pollution relative risks than would be obtained if average personal exposure were available. As we show (*1*), however, the corresponding coefficient for personal exposure can be obtained from the coefficient for ambient concentration by a simple rescaling.

Below is a corrected analysis that depends on the following definitions: z_t^* = ambient concentration on day t; I_{it} = concentration from indoor sources for person i on day t; δ_{it} = proportion of pollutant of ambient origin that penetrates indoors for person i on day t; and p_{it} = proportion of time spent outdoors by person i on day t.

The personal exposure for person i on day t is given by

$$x_{it} = p_{it} z_t^* + (1 - p_{it}) \{I_{it} + \delta_{it} z_t^*\} = q_{it} z_t^* + J_{it},$$

where $q_{it} = p_{it} + (1 - p_{it})\delta_{it}$ is the fraction of ambient concentration to which a person is exposed on a given day by either being outdoors or by being indoors and being exposed to ambient pollution which has penetrated indoors; and $J_{it} = (1- p_{it})I_{it}$ is the effective concentration of pollution originating from indoor sources to which person i is exposed on day t.

If we average the equation above across all people in a given region, we have that

$$\bar{x}_t = \bar{q}_t z_t^* + \bar{J}_t.$$

Thus, the average personal exposure is linearly related to the true ambient concentration with slope coefficient $\bar{q}_t$, the average of q_{it} across people. Here $\bar{J}_t$ is the average concentration of pollution from indoor sources to which the population is exposed on day t.

If we further assume that conditional on weather, season and other adjustment variables in the time-series models, $\bar{J}_t$ is roughly independent of the ambient level z_t^*, this equation shows that using ambient concentration z_t^* to predict daily mortality will produce a regression coefficient that differs from what would have been obtained using mean personal exposure $\bar{x}_t$ by a multiplicative factor that is roughly $\bar{q}$, the average of the $\bar{q}_t$s over time. Note that $\bar{q}$ is the fraction of outdoor pollution to which the population is on average exposed, either outdoors or via penetration indoors. There is no further bias introduced by $\bar{J}_t$ because this is an example of Berkson rather than classical measurement error as described above.

In the United States, the average proportion of time spent outdoors tends to be small, so that $\bar{q}_t$ is to first approximation, equal to the average percentage of ambient concentration that penetrates indoors $\bar{\delta}_t$. If nearly all small particles penetrate indoors, then $\bar{\delta}_t \approx 1$ and average personal exposure will equal the ambient level plus the contribution of indoor sources. Again if $\bar{J}_t$ is roughly independent of the ambient level z_t^*, then regressing on ambient levels will give similar results to regressing on average personal exposure for small particles most of which penetrate indoors.

In the original paper, the equation above mistook $\bar{q}_t$ to be the average fraction of total exposure that originates outdoors; the correct analysis here shows that it is the average ambient fraction of ambient pollution concentration to which a person is exposed while outdoors (100%) and indoors (100δ%). In addition, the original article identified $\bar{J}_t$ as the average concentration of particles originating indoors. It is in fact the average of the concentration originating indoors to which persons are exposed and therefore includes a term representing the fraction of time persons spend indoors as well as the pollutant level there.

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Confirmation of Uterotrophic Activity for 4-MBC in the Immature Rat

Schlumpf et al. (*1,2*) reported that the ultraviolet (UV) sunscreen component 3-(4-methylbenzylidine)camphor (4-MBC) is uterotrophic when administered either in diet to immature Long-Evans rats or by whole body immersion of immature hairless hr/hr rats into an oil solution of 4-MBC. Subsequently, Bolt et al. (*3*) questioned the validity of those data and referred to two negative unpublished immature rat uterotrophic assays of 4-MBC (*4,5*).

When the discussion between Bolt et al. (*3*) and Schlumpf et al. (*6*) appeared, we had already studied the uterotrophic activity of 4-MBC in immature rat uterotrophic assays using both oral gavage and subcutaneous injection as the route of administration. The report on these studies has been submitted for publication (*7*). Of particular relevance to the recent discussion (*3,6*), we found 4-MBC to be clearly positive in our standard immature rat uterotrophic assay (*8*). Activity was apparent in the oral study at 500 and 800 mg/kg/day and in the subcutaneous injection study at 500 and 1,000 mg/kg/day. In the oral gavage study (*7*), uterine weights were 22.0 ± 2.5 for controls and 32.5 ± 6.5 and 42.4 ± 6.0 for 500 and 800 mg/kg 4-MBC, respectively (mean ± SD; $p < 0.01$ by analysis of variance and analysis of covariance with terminal body weight).

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