Sayers, Margery

From: Victor Velculescu <velculescu@jhmi.edu>
Sent: Monday, October 16, 2017 12:24 PM
To: CouncilMail; Kittleman, Allan
Cc: John Tegeris; rick.lober@gmail.com; Feldmark, Jessica
Subject: Testimony from Dr. Velculescu regarding CB60
Attachments: Mulch and Composting Health Effects Velculescu 121414.pptx; Herr et al., Bioaerosols, 2003.pdf; HHS Report on Carcinogens 14th Edition Wood Dust, 2002.pdf; Siddiqui, Clin Infect Dis.-2007-Siddiqui-673-81, 2007.pdf; Butler et al., Mulch pneumonitis, 2013.pdf

Dear Members of the County Council and Executive Kittleman,

I am writing let you know that I would be glad to be available for any questions to health issues related to CB60. I have let Jessica Feldmark know that I would be available on October 11, 2017, the first date offered for a Council Work Session. I will also be available at the next meeting October 23, 2017, and would be glad to make myself available on other occasions. Unfortunately, I am not available on today, Monday October 16 due to my participation at a medical meeting in New York that was scheduled many months ago.

I have seen the video testimony from the Work Session of October 2, 2017 where several erroneous points were raised by Council Member Sigaty, suggesting that the references in my presentation are from occupational risks and therefore are not relevant. This is an incorrect conclusion by Ms. Sigaty. There are indeed many health risks posed by industrial mulch and composting facilities where the bioaerosol pollution of residential outdoor air can indeed be very similar to that of occupational environments. To clarify this issue, please see items below. I am also attaching to this email my presentation from 2014 as well as several recent publications that highlight the health dangers of industrial mulch and composting operations.

1. Wood dust is a carcinogen. This is well-established as has been indicated by many national and international organizations, including the American Cancer Society, WHO, CDC, and the Department of Health and Human Services. Importantly, wood dust is a carcinogen regardless of whether it arises from wood cutting occupations or from composting activities, as indicated in the 14th Report on Carcinogens from the US Department of Health and Human Services. Please see attached document for further information.

2. Mulching and composting have health risks due to infectious agents (fungi, bacteria, endospores). My presentation from 2014 (attached) included many such examples. See slides 3, 4, 5 and 23. Please also see attached example medical references from Butler and colleagues and Siddiqui and colleagues.

3. Composting can lead to toxic and carcinogenic substances. Please see slides 21 and 22.

4. Dust from mulch and composting can lead to inflammatory effects. Please see slide 24.

5. Animal mortality and food waste in composting can contaminate groundwater. Please see slide 25.

6. Composting facilities have health effects on nearby communities. Please see slides 26, 27, and 28 for examples in California, Maryland and Europe of negative outcomes from such facilities on nearby residents. Please also see attached medical reference from Herr et al.

7. Infectious agents from mulch and composting facilities can pose health risks at significant distances. See slides 31 and 32. These studies detected infectious agents at up to 1000 – 2400 feet away from site.

8. Individuals living near composting sites have exposures similar to those in high risk occupations. Please see attached article by Herr et al., describing a study performed in Germany of residents near a large-scale composting site. The authors indicate "Bioaerosol pollution of residential outdoor air can occur in concentrations found in occupational environments." They also indicate "Concentrations of culturable airborne microorganisms, including molds, measured in the residential air during the study at 150 to 320 m from the composting site were 100–1000 times higher than those concentrations generally reported as natural background concentrations."

9. Mulching and composting can contaminate groundwater. Others have testified on the risks associated with this aspect, including risks for neurologic disorders.

Looking forward further discussing any of these points with any of you.

Please include this email and attached documents as part of the testimony for CB60 2017.

Best regards,
Victor

Victor E. Velculescu, M.D., Ph.D.
Professor of Oncology and Pathology
Co-Director of Cancer Biology

Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University School of Medicine
1550 Orleans St., Rm 544, Baltimore, MD 21287
Phone 410.955.7033 FAX 410.502.5742
velculescu@jhmi.edu

Administrative Assistant
Jennifer Dillard
jdillar1@jhmi.edu

Health Hazards of Industrial Wood Waste and Composting

Victor Velculescu, M.D., Ph.D.
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University

Submitted to Howard County Task Force, December 14, 2014

Health Hazards

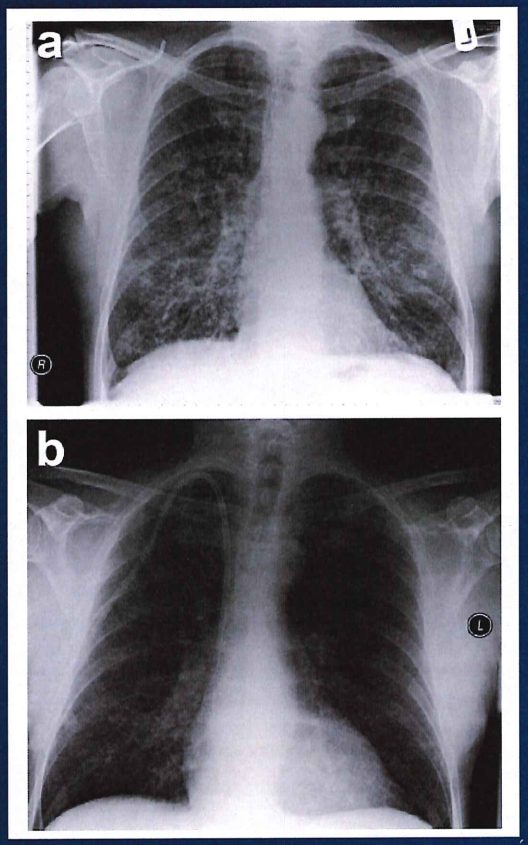
Industrial mulch processing and composting results in increased health risks

- Mulch infectious agents – fungi and bacteria
- Wood dust – allergic and mucosal effects
- Wood dust – cancer
- Composting – volatile compounds, organic dust, infectious agents
- Exposure and risk

Infectious agents example: acute fungal pneumonia

At presentation

2 months later



A 69 year old retired man with no significant medical history. Developed acute pneumonia after spreading tree bark mulch.

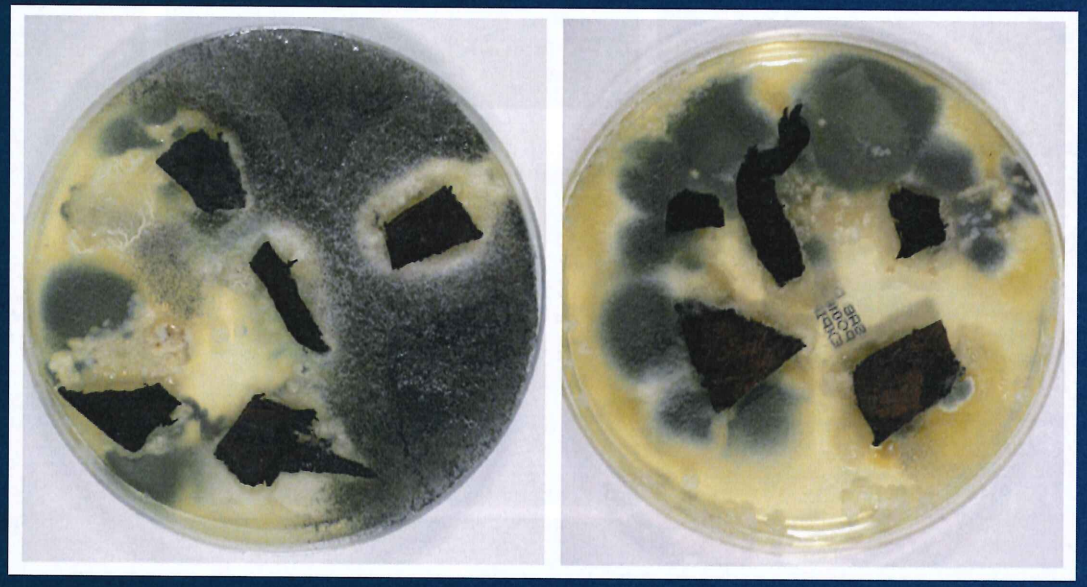
Hospitalized, developed kidney injury and failure. Remained dialysis dependent and housebound.

Died of sepsis 10 months later.

Inhalation of fungal spores from mulch was determined be the likely route of infection.

Medical MycologyCaseReports2(2013)125–127

Infectious agents example: acute fungal pneumonia



Mulch culture showing growth of microogranisms (Aspergillus fumigatus, Rhizopus spp., Sporobolomyces spp. and bacteria)

Medical MycologyCaseReports2(2013)125–127

Studies of mulch related infections in medical literature

1: Ameratunga R, Woon ST, Vyas J, Roberts S. Fulminant mulch pneumonitis in undiagnosed chronic granulomatous disease: a medical emergency. Clin Pediatr (Phila). 2010 Dec;49(12):1143-6. doi: 10.1177/0009922810370057. Epub 2010 Aug 19.

2: Siddiqui S, Anderson VL, Hilligoss DM, Abinun M, Kuijpers TW, Masur H, Witebsky FG, Shea YR, Gallin JI, Malech HL, Holland SM. Fulminant mulch pneumonitis: an emergency presentation of chronic granulomatous disease. Clin Infect Dis. 2007 Sep 15;45(6):673-81. Epub 2007 Aug 8.

3: Veillette M, Cormier Y, Israël-Assayaq E, Meriaux A, Duchaine C. Hypersensitivity pneumonitis in a hardwood processing plant related to heavy mold exposure. J Occup Environ Hyg. 2006 Jun;3(6):301-7.

4: Nagai K, Sukoh N, Yamamoto H, Suzuki A, Inoue M, Watanabe N, Kuroda R, Yamaguchi E. [Pulmonary disease after massive inhalation of Aspergillus niger]. Nihon Kokyuki Gakkai Zasshi. 1998 Jun;36(6):551-5. Japanese.

5: Weber S, Kullman G, Petsonk E, Jones WG, Olenchock S, Sorenson W, Parker, Marcelo-Baciu R, Frazer D, Castranova V. Organic dust exposures from compost handling: case presentation and respiratory exposure assessment. Am J Ind Med. 1993 Oct;24(4):365-74.

6: Johnson CL, Bernstein IL, Gallagher JS, Bonventre PF, Brooks SM. Familial hypersensitivity pneumonitis induced by Bacillus subtilis. Am Rev Respir Dis. 1980 Aug;122(2):339-48. PubMed PMID: 6774642.

Dozens of examples of scientific articles from throughout the world related to infectious agents in mulch.

Particularly important and dangerous for immune compromised individuals.

Recent study found that of patients with fulminant mulch pneumonitis, half of those died of due to infection and underlying kidney disease.

Health Hazards

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- Wood dust – cancer
- Composting – volatile compounds, organic dust, infectious agents
- Exposure and risk

Health Effects of Wood Dust

From Centers for Disease Control and Prevention:

"Exposure to wood dust has long been associated with a variety of adverse health effects, including dermatitis, allergic respiratory effects, mucosal and nonallergic respiratory effects, and cancer. The toxicity data in animals are limited, particularly with regard to exposure to wood dust alone; there are, however, a large number of studies in humans."

1988 CDC OSHA PEL Documentation

Health Effects of Wood Dust

From *Ann Agric Environ Med* 2010, **17**, 29–44.

- **Abstract:** This paper reviews the literature on associations between dry wood dust exposure and non-malignant respiratory diseases … The results support an association between dry wood dust exposure and asthma, asthma symptoms, coughing, bronchitis, and acute and chronic impairment of lung function. In addition, an association between wood dust exposure and rhino-conjunctivitis is seen across the studies."

Dermatitis

- "Dermatitis. There are a large number of case reports, epidemiological studies, and other data on the health effects of wood dust exposure in humans. Dermatitis caused by exposure to wood dusts is common, and can be caused either by chemical irritation, sensitization (allergic reaction), or both of these together. As many as 300 species of trees have been implicated in wood-caused dermatitis."

1988 CDC OSHA PEL Documentation

Asthma

- "Allergic respiratory effects. Allergic respiratory responses are mediated by the immune system, as is also the case with allergic dermatitis. Many authors have reported cases of allergic reactions in workers exposed to wood dust … Asthma is the most common response to wood dust exposure"

1988 CDC OSHA PEL Documentation

Other Lung Effects

- "Mucosal and nonallergic respiratory effects (changes in the structure and function of the nasal mucosa and respiratory tract that are caused by exposure to wood dust). These changes include nasal dryness, irritation, bleeding, and obstruction; coughing, wheezing, and sneezing; sinusitis; and prolonged colds."

1988 CDC OSHA PEL Documentation

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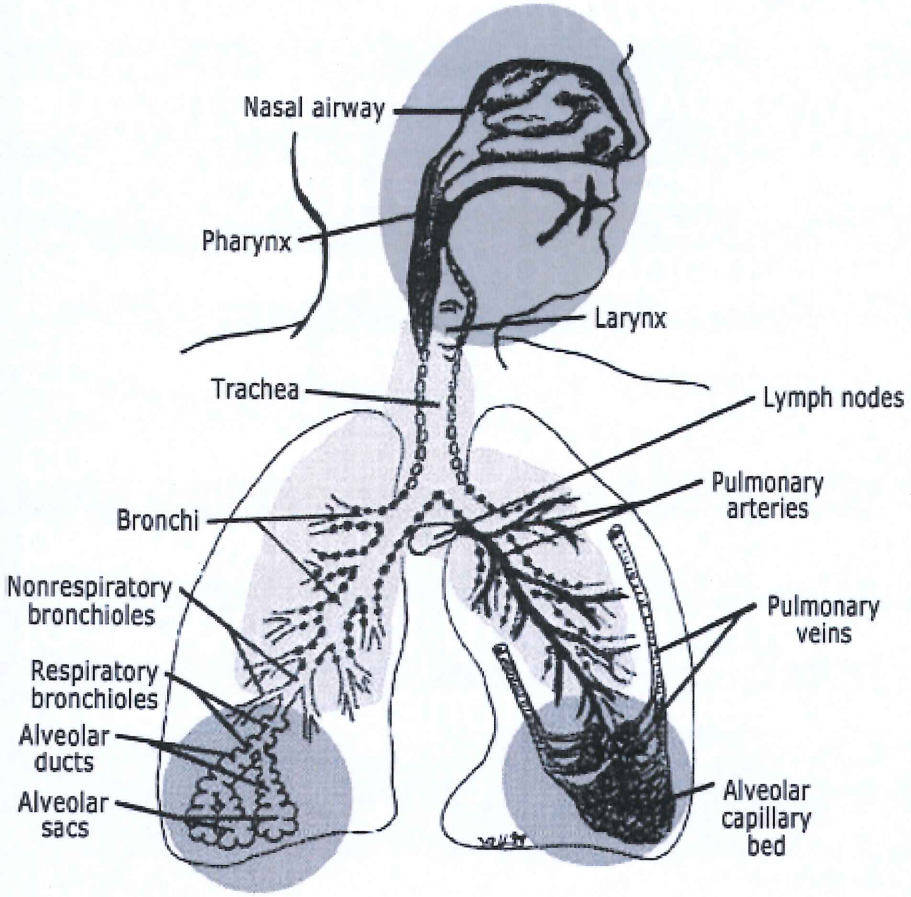
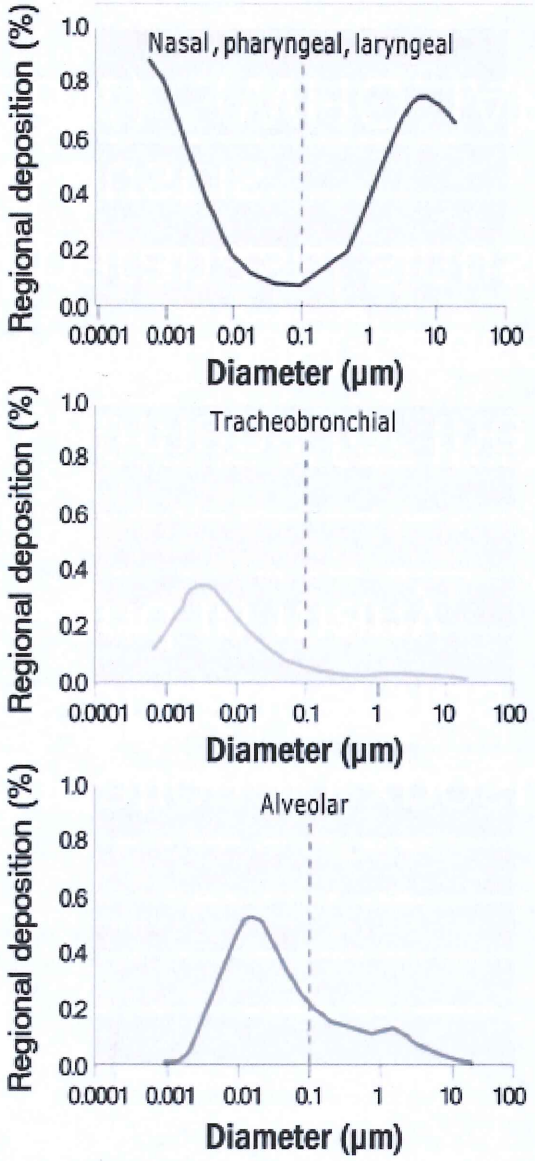
Cancer

- "The association between occupational exposure to wood dust and various forms of cancer has been explored in many studies and in many countries." (CDC)
- "There is *sufficient evidence* in humans for the carcinogenicity of wood dust. Wood dust causes cancer of the nasal cavity and paranasal sinuses and of the nasopharynx. Wood dust is *carcinogenic to humans (Group 1).*" (WHO, IARC)

Fig. 4.1 Deposition of inhaled particles in the human respiratory tract during nasal breathing





From Oberdörster *et al.*, (2005). Drawing courtesy of J Harkema. Reproduced with permission from Environmental Health Perspectives.

Nasal Cancer

- "Summary of evidence for nasal and sinus cavity cancers. The literature clearly demonstrates an association between wood dust exposure and nasal cancer. "
- English studies first identified this link by showing a 10- to 100 times-greater incidence of nasal adenocarcinoma among those exposed to wood dust than in the general population.
- "In the United States, three studies have reported a fourfold risk of nasal cancer or adenocarcinoma … and wood dust exposure."

1988 CDC OSHA PEL Documentation

Lung Cancer

- "Pulmonary cancer. A number of studies investigating the association between wood dust exposure and the development of lung cancer have been conducted."
- Milham (1974/Ex. 1-943) found a significant excess of malignant tumors of the bronchus and lung in workers who exposed to wood dust.

1988 CDC OSHA PEL Documentation

Hodgkin Lymphoma

- "Hodgkin's disease. Milham and Hesser concluded, on the basis of a case-cohort study of 1,549 white males dying of this disease … that there was an association between Hodgkin's disease and exposure to wood dust."
- Other studies concluded that men working in the wood industries in the eastern United States as well as Washington state were at special risk for Hodgkin's disease.

1988 CDC OSHA PEL Documentation

Other Cancers

- "Other cancers. NIOSH (1987a/Ex. 1-1005) concluded that the data on the relationship between occupational exposure to wood dust and the development of cancers other than nasal, Hodgkin's disease, or lung cancers are insufficient and inconclusive."
- Emerging evidence that risks of oral cancer increase with exposure to wood dust.

1988 CDC OSHA PEL Documentation

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Composting

A commonly used method of waste management involving aerobic, biological process of degradation of biodegradable organic matter

Composting Health Effects – VOC's

- Composting generates volatile organic compounds (VOCs)
- VOCs can comprise hundreds of compounds including benzene, toluene, m,p-xylene, o-xylene, styrene, formaldehyde, chloroform, ethylbenzene among others.
- High levels of VOC's observed in many studies at variety of composting sites

Environ. Sci. Techno/. 1995, 29, 896-902
J.L. Domingo, M. Nadal / Environment International 35 (2009) 382–389

Composting Health Effects – VOC's

VOC's comprise substances that are

- Carcinogenic: examples include benzene, a risk factor for leukemia, and formaldehyde, associated with nasal carcinoma
- Toxic: includes many VOC's that may lead to renal, hematological, neurological and hepatic damage as well as mucosal irritation.

J.L. Domingo, M. Nadal / Environment International 35 (2009) 382–389

Composting Health Effects – Biologic Agents

Composting sites due to their contents comprise infectious, allergenic, toxic, and carcinogenic agents including

- Fungi such as Aspergillus fumigatus (A. fumigatus), gram negative bacteria, and parasitic protozoa, all involved in a variety of infectious conditions
- Endotoxins produced by bacteria and fungi, including aflatoxins which are known to be associated with liver cancer

J.L. Domingo, M. Nadal / Environment International 35 (2009) 382–389

Composting Health Effects – Biologic Agents

Composting sites due to their contents comprise infectious, allergenic, toxic, and carcinogenic agents including

- Organic dusts that can lead to pulmonary inflammation (acute inflammation, hypersensitive pneumonitis), occupational asthma, chronic bronchitis, gastrointestinal disturbances, fevers, and irritation of eyes, ear and skin.

J.L. Domingo, M. Nadal / Environment International 35 (2009) 382–389

Composting Health Effects – Animal Mortality and Leachate

- Composting process can lead to increases in solubility of hazardous metals and organic substances in contaminated water (leachate)
- Burial of animal carcasses can lead to significant contamination of soil and groundwater with antimicrobials, steroid hormones, other veterinary pharmaceuticals

Q. Yuan et al. / Science of the Total Environment 456–457 (2013) 246–253

Composting Health Effects – Food Wastes and Pathogens

- "There have been numerous studies on pathogen content in the composting process."
- "In San Jose, California literally hundreds of people were affected by a nearby composting yard. This case illustrates the importance of carefully siting compost facilities with adequate setbacks from residential areas. One study, presented at a BioCycle conference recommended two miles isolation distance from residential and high travel areas."

Cronin, C. Pathogens and Public Health Concerns with Composting
Vermont Department of Environmental Conservation

Local Example – MDE and Recycled Green Industries

- "A Woodbine company that had been processing food scraps into composted materials with commercial applications … has ceased those operations after hearing concerns about pollution from the Maryland Department of the Environment… Food scraps present different environmental concerns than yard waste, the spokesman said. Namely, food contains "nutrients and potential pathogens" not found in yard waste, and are harmful to the environment when washed into surface and ground water, said Jay Apperson, the spokesman, in an email… The letter said water samples taken by the department on or near the company's property "confirm that the operation is generating polluted leachate and storm water and is discharging pollutants without a permit in violation of state law."

Rector, K. Baltimore Sun, Feb 6, 2012

Real World Example of Composting Health Effects on Nearby Residents

- Health effects to a residential area from environmental outdoor pollution hundreds of meters from a composting site (Occup Environ Med 2003;60:336–342)

		Bioaerosol pollution in residential air‡ up to $>10^5$ CFU m^{-3} air		Duration of present residency >5 years	
Reported health complaints§	SS¶	OR**	95% CI††	OR	95% CI
Respiratory tract					
Frequency of colds >5×/year	209	1.94	0.65 to 6.78	**4.72**	**1.19 to 31.83**
Bronchitis	210	**3.02**	**1.35 to 7.06**	**2.91**	**1.29 to 7.03**
Waking up due to coughing	202	**2.70**	**1.23 to 6.10**	**2.51**	**1.19 to 5.53**
Wheezing	207	1.96	0.84 to 4.82	**2.95**	**1.22 to 7.99**
Shortness of breath at rest	203	**3.99**	**1.31 to 15.19**	1.50	0.56 to 4.49
Coughing on rising or during the day‡‡	210	**2.67**	**1.17 to 6.10**	1.51	0.69 to 3.29
Shortness of breath after exertion	205	**4.23**	**1.74 to 11.34**	2.03	0.90 to 4.91
Eyes and general health					
Itching eyes >10×/year	206	1.35	0.61 to 3.05	**2.85**	**1.31 to 6.50**
Smarting eyes >10×/year	205	**2.44**	**1.02 to 6.22**	**2.42**	**1.06 to 5.86**
Nausea or vomiting >5×/year	204	2.65	0.87 to 9.97	**4.10**	**1.28 to 18.44**
Excessive tiredness >5×/year	200	**2.80**	**1.22 to 6.72**	1.83	0.84 to 4.11
Shivering	210	**4.63**	**1.44 to 20.85**	**3.67**	**1.32 to 12.20**
Joint trouble >10×/year	207	1.27	0.54 to 3.07	1.52	0.65 to 3.71
Muscular complaints >10×/year	201	1.17	0.47 to 2.99	1.39	0.55 to 3.86

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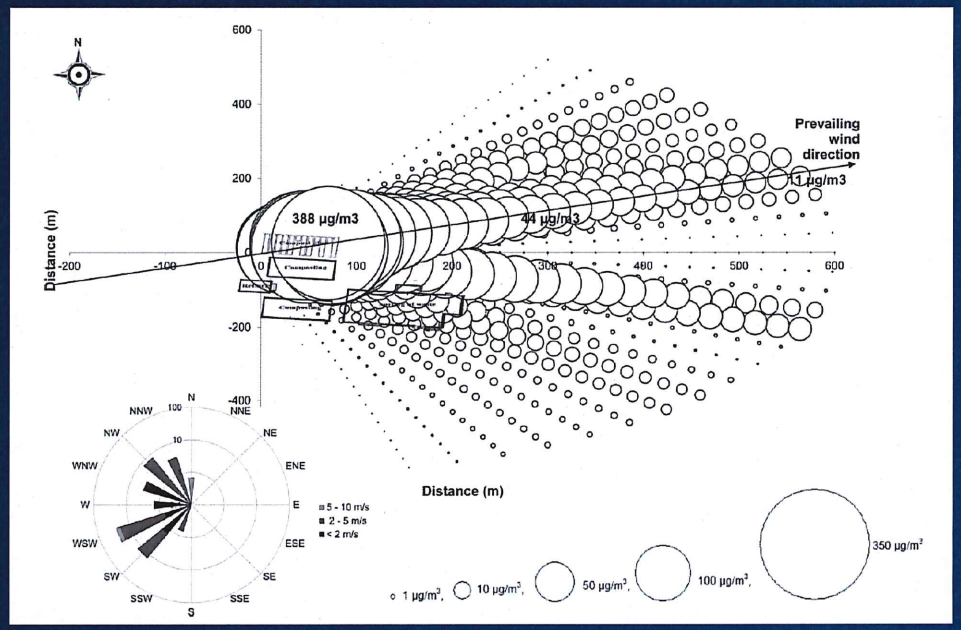
Significant Medical Literature of Effects of Emissions from Waste Facilities

- Chalvatzaki E, Aleksandropoulou V, Glytsos T, Lazaridis M. The effect of dust emissions from open storage piles to particle ambient concentration and human exposure. Waste Manag. 2012 Dec;32(12):2456-68
- Nadal M, Inza I, Schuhmacher M, Figueras MJ, Domingo JL. Health risks of the occupational exposure to microbiological and chemical pollutants in a municipal waste organic fraction treatment plant. Int J Hyg Environ Health. 2009 Nov;212(6):661-9.
- Domingo JL, Nadal M. Domestic waste composting facilities: a review of human health risks. Environ Int. 2009 Feb;35(2):382-9.
- Herr CE, Nieden Az Az, Stilianakis NI, Eikmann TF. Health effects associated with exposure to residential organic dust. Am J Ind Med. 2004 Oct;46(4):381-5.
- Herr CE, zur Nieden A, Stilianakis NI, Gieler U, Eikmann TF. Health effects associated with indoor storage of organic waste. Int Arch Occup Environ Health.
- Herr CE, Zur Nieden A, Jankofsky M, Stilianakis NI, Boedeker RH, Eikmann TF. Effects of bioaerosol polluted outdoor air on airways of residents: a cross sectional study. Occup Environ Med. 2003 May;60(5):336-42.

Dust Emissions and Distance

- Dust emissions from open piles of mulch / organic waste can be measured at distances >500 m (>1500 feet) (Waste Management 32 (2012) 2456–2468)



Microorganisms and VOC's - Dispersion Distance

- High levels of molds, fungi, thermophilic fungi, bacteria and other microorganisms (concentrations of $>10^4$ colony forming units) could be measured >300 m (>1000 feet) in residential air neighboring outdoor organic waste (Am. J. Ind. Med. 46:381–385, 2004)
- Volatile organic compounds can detected at distances of up to 800 meters (Environment International 35 (2009) 382–389) and others

Dispersion of infectious agents – worst case scenario

- Infectious agents have been shown to be dispersed at larger distances. Prominent example includes outbreak of Legionnaires disease in a radius of 6km through release from an elevated water tower
- Dispersion led to 86 infected cases of which 18 (21%) were fatal

J Infect Dis. 2006 Jan 1;193(1):102-11

Summary

- Mulch and composting sites can pose risks for human health due to increased exposure of infectious agents, toxic substances, and VOC's. These include
  - infections due to fungal spores and bacteria
  - Increased risk of dermatitis, allergic respiratory effects, and mucosal and nonallergic respiratory effects
  - Increased risk of cancer, including nasal, lung, and Hodgkin lymphoma
- Exposure risks can occur at significant distances from waste processing area
- Numerous examples of exposure risks have been document in affected populations world-wide

ORIGINAL ARTICLE

Effects of bioaerosol polluted outdoor air on airways of residents: a cross sectional study

C E W Herr, A zur Nieden, M Jankofsky, N I Stilianakis, R-H Boedeker, T F Eikmann

Occup Environ Med 2003;**60**:336–342

Background: Bioaerosol pollution of workplace and home environments mainly affects airways and mucous membranes. The effect of environmental outdoor residential bioaerosol pollution, for example, livestock holdings, farming, and waste disposal plants, is unclear.
Aims: To investigate the perceived health of residents living in areas with measurable outdoor bioaerosol pollution (for example, spores of *Aspergillus fumigatus* and actinomycetes), and effects of accompanying odours.
Methods: In a cross sectional study, double blinded to ongoing microbial measurements, doctors collected 356 questionnaires from residents near a large scale composting site, and from unexposed controls in 1997. Self reported prevalence of health complaints during the past year, doctors' diagnoses, as well as residential odour annoyance were assessed. Microbiological pollution was measured simultaneously in residential outdoor air.
Results: Concentrations of $>10^5$ colony forming units of thermophilic actinomycetes, moulds, and total bacteria/m^3 air were measured 200 m from the site, dropping to near background concentrations within 300 m. Positive adjusted associations were observed for residency within 150–200 m from the site versus unexposed controls for self reported health complaints: "waking up due to coughing", odds ratio (OR) 6.59 (95% confidence interval (CI) 2.57 to 17.73); "coughing on rising or during the day", OR 3.18 (95% CI 1.24 to 8.36); "bronchitis", OR 3.59 (95% CI 1.40 to 9.4); and "excessive tiredness", OR 4.27 (95% CI 1.56 to 12.15). Reports of irritative airway complaints were associated with residency in the highest bioaerosol exposure, 150–200 m (versus residency >400–500 m) from the site, and period of residency more than five years, but not residential odour annoyance. Lifetime prevalence of self reported diseases did not differ with exposure.
Conclusions: Bioaerosol pollution of residential outdoor air can occur in concentrations found in occupational environments. For the first time residents exposed to bioaerosol pollution were shown to report irritative respiratory complaints similar to mucous membrane irritation independently of perceived odours.

See end of article for authors' affiliations

Correspondence to: Dr C Herr, Institute of Hygiene and Environmental Medicine, Friedrichstrasse 16, D-35385 Giessen, Germany; caroline.herr@hygiene.med.uni-giessen.de

Accepted 3 September 2002

Bioaerosols occur ubiquitously as inhalable mixtures of air and microorganisms, parts of microorganisms, or organic substances of microbial and plant origin.[1] In the outdoor air, exposure bioaerosols (for example, containing *Aspergillus fumigatus*) can occur from natural or anthropogenic sources.[2–4]

When evaluating health effects of bioaerosols (organic dusts), their composition, concentration, and measurement methods applied must be considered.[5] Individual susceptibility, for example, atopy, allergic sensitisation, or immunodeficiency, also plays an important role in the risk assessment. Health based threshold levels for microorganisms for outdoor, indoor, or workplace air have not been established.[4] It is, however, known that infectious, allergic, or toxic disturbances triggered by bioaerosols originate mostly in moulds, thermophilic actinomycetes, Gram negative bacteria, and viruses.[3 6–10]

Besides livestock breeding and farming, the increasing number of large scale composting facilities for sewage sludge, and yard and solid waste being established within the scope of modern disposal concepts can release bioaerosols. Health relevant moulds (*Aspergillus fumigatus*) and actinomycetes accumulated in compost material become airborne as vegetative cells or spores through movement of the material.[3 4] Workers on composting sites have higher rates of airway related mucous membrane complaints and diseases. In these workers, specific antibodies against actinomycetes, as well as airway inflammation (or mucous membrane irritation (MMI)) have been reported.[2 11 12] Severe cases of general disease, for example, hypersensitivity pneumonia or severe toxic reactions (toxic pneumonitis or organic dust toxic syndrome (ODTS)) were reported in workers and one private person following direct contact with compost.[3 13–15]

Worldwide several thousand of these often malodorous sites are operating. However, their health effects on nearby residents have not been investigated sufficiently. A study in residents living within 500 m of a site showed no clear evidence of health changes.[16] In a case report, an asthmatic, living 80 m from a composting site (52% of the year in the wind direction), was found to have an allergic bronchopulmonary aspergillosis (ABPA).[17]

There is an urgent need to evaluate pollution due to bioaerosols (organic dusts), which can also occur in indoor air,[18–22] as far as the general public health is concerned. This is particularly important as an increasing fraction of the general population in industrialised countries must be classified as a risk group (for example, atopics) in the context of bioaerosol pollution.[23]

This cross sectional study aimed to relate self reported health to measurable bioaerosol pollution in the residential outdoor air. Prevalence of perceived complaints and self

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CFU, colony forming units; CI, confidence interval; ISAAC, International Study on Allergy and Asthma in Childhood; MMI, mucous membrane irritation; N, north; ND, not detected; NW, northwest; ODTS, organic dust toxic syndrome; OR, odds ratio; WHO, World Health Organisation; SS, sample size; SE, southeast; WNW, west-northwest

reported doctors' diagnoses of residents living very close (150–200 m) to a composting site were compared to those in the same neighbourhood living further away (>400–500 m), and to a corresponding unexposed control group without a residential source of bioaerosols. Measurements of viable airborne microorganisms in residential air were performed during the ongoing epidemiological study and were known neither to interviewers nor to the study subjects at that time. Reports of annoying residential odours were also assessed, as they are known to be of relevance to reported health.[24–26]

METHODS

Assessment of exposure to cultivable microorganisms in the outdoor air of the residential area

The aim of the measurements was to assess location specific "worst case" conditions with regard to released bioaerosols into the neighbourhood. This concerned periods of intense microorganism releasing work activity, previously defined meteorological conditions at the time of measurement, as well as topographical aspects. Because of the ubiquity of the microorganisms under research, especially the thermophilic organisms, comparative quantitative measurements of background concentrations were taken upwind of the site.

The concentrations of three fractions of culturable microorganisms were determined in three repeated measurements. These were collected with filter based samplers (MD 8 Sartorius, Goettingen, Germany, flow rate 8 m^{-3} h^{-1}, collection time 10 min) 1.5 m above ground level, with subsequent indirect plating method after filtration and precipitation on gelatine filters[27 28]:

- Total bacteria (R2A agar (oxoid), 25°C)
- Moulds (dichrorane-glycerine-(DG18)–(oxoid), 25°C)
- Thermophilic and thermotolerant actinomycetes (glycerine-arginine-agar, 50°C).[29]

As results of single microbial measurements are known to vary considerably, results of the three consecutive measurements are given as maximum and minimum concentrations in table 2 and not mean values.

Epidemiological investigation

Study population

A team of doctors, process engineers, microbiologists, and meteorologists selected a composting site which had been in operation for five years and had lead to distress in the neighbouring residents due to odour annoyance and fear of allergies and infection. Considering topographical and meteorological (for example, wind direction) as well as technical aspects (site not completely closed off, processing of yard trimmings and organic waste, a turnover of approximately 12 500 Mg per year), discharge of bioaerosols from the site into the neighbouring residential area was presumed prior to the study. Other sources of bioaerosol exposure (sewage plants, etc) did not exist in the proximity of the residential area. Together with the local health authority, an unexposed control area was selected in the same governmental district. Criteria for the selection were: similarity of population pattern, residential area (size of households, road traffic, petrol stations, and industrial sites) and the lack of sources of microorganisms in the residential outdoor air.

The residential area next to the composting plant was located at a distance from 150 to 500 m downwind. All persons living there (n = 310) and 411 unexposed inhabitants in the control area were invited to participate in the study. Addresses were collected from the municipal registration of address office.

Questionnaires concerning perceived health and odour annoyance

An environmental health questionnaire was used for the assessment of self reported health: complaints and symptoms as well as lifetime prevalence of doctors' diagnoses. The questionnaire was developed with items validated and applied in several national and international studies, for example,

Table 1 Characteristics of 356 participants of the cross sectional study: unexposed controls and residents of a neighbourhood with bioaerosol pollution in outdoor air classified according to the distance between home and emitting composting site

	Study population		Unexposed controls		Residents of a neighbourhood with bioaerosol pollution of outdoor air							
					Total		Classified					
Distance from the emitting site	–		–		150–500 m		150–200 m		>200–400 m		>400–500 m	
Bioaerosol pollution in residential air	–		Not measured		Up to >10^5 CFU* m^{-3}		Up to >10^5 CFU m^{-3}		Up to <10^5 CFU m^{-3}		Near background	
Participants	n=356		n=142		n=214		n=82		n=76		n=56	
	SS†	Yes [%]	SS	Yes [%]	SS	Yes [%]	SS	Yes [%]	SS	Yes [%]	SS	Yes [%]
Female	356	56.7	142	52.8	214	59.3	82	59.8	76	60.5	56	57.1
Age >50 years	356	43.0	142	36.6	214	47.2	82	46.3	76	50.0	56	44.6
Duration of present residency >5 years	350	71.7	137	70.8	213	72.3	82	73.2	75	76.0	56	66.1
Odour annoyance in the residential area	344	59.3	132	25.8	212	80.2	82	95.1	74	75.7	56	64.3
Type of odour annoyance, disgusting	199	7.5	37	0.0	162	9.3	74	5.4	52	17.3	36	5.6
Separate collection of organic household waste	348	55.5	136	75.0	212	42.9	82	32.9	75	45.3	55	54.5
Composting in own garden	350	67.4	137	65.7	213	68.5	82	76.8	75	61.3	56	66.1
Occupation at a composting site	337	0.6	136	0.0	201	1.0	76	1.3	71	1.4	54	0.0
Smoking status (smoker and non-smoker <5 years)	324	26.5	132	25.0	192	27.6	73	17.8	69	39.1	50	26.0
Environmental tobacco smoke (at home/in the workplace)	283	39.6	111	39.6	172	39.5	65	41.5	63	38.1	44	38.6
Use of inhalers at home	343	9.9	140	7.1	203	11.8	78	10.3	73	6.8	52	21.2
Bedroom equipment‡	355	97.5	142	99.3	213	96.2	81	90.1	76	100	56	100
Exposure in the workplace§	349	22.3	136	28.7	213	18.3	82	23.2	75	16.0	56	14.3
Home <50 m from busy street	356	30.6	142	17.6	214	39.3	82	39.0	76	35.5	56	44.6

*CFU, colony forming units.
†SS, sample size.
‡Bedroom furnishings include one of the following: carpet, furs, eiderdown, horsehair or innerspring mattress, furniture made of chipboard.
§Vapours, gases, dusts, heat, cold, dampness.

Table 2 Concentrations of culturable microorganisms [minimum/maximum]* in residential air neighbouring a bioaerosol releasing composting site

Sample points (by distance and direction to composting site†)	Total bacteria [CFU‡ m^{-3} air]		Moulds [CFU m^{-3} air]		Thermophilic actinomycetes [CFU m^{-3} air]	
	Min	Max	Min	Max	Min	Max
Upwind						
500 m SE§	8.4×10^2	1.8×10^3	1.9×10^3	3.6×10^3	[ND]¶	[ND]
Downwind						
200 m NW**	2.2×10^4	5.1×10^5	7.7×10^3	1.3×10^5	2.3×10^4	5.5×10^5
250 m WNW††	3.9×10^4	1.7×10^5	1.3×10^4	4.6×10^4	1.9×10^4	1.1×10^5
300 m N‡‡	4.4×10^3	8.3×10^4	4.3×10^3	1.7×10^4	2.8×10^3	6.0×10^4
320 m NW	6.8×10^3	5.9×10^4	3.9×10^3	1.9×10^4	1.3×10^3	5.0×10^4
550 m N	8.3×10^2	4.3×10^3	2.3×10^3	4.1×10^3	<5	9.9×10^2
Sampling conditions						
Samplers	Filter based MD 8 Sartorius, (Goettingen, Germany), flow rate 8 $m^{-3}h^{-1}$					
Collection time	10 min at 1.5 m above ground level with subsequent indirect plating method after filtration and precipitation on gelatine filters					
Detection limit	40 CFU					
Date and time	07.08.1997; 00:00–02:15§§					

*Minimum (Min) and maximum (Max) values of three repeated measurements. †"Kompostwerk Langes Feld", Kassel, Germany. ‡CFU, colony forming units. §SE, southeast. ¶ND, not detected. **NW, northwest. ††WNW, west-northwest. ‡‡N, north. §§Although there was a cold air flow from the composting site towards the studied neighbouring residential area "worst case" conditions.

ISAAC.[23] It was designed in particular to record health impairments and diseases of the respiratory tract from air pollution.

Prevalence of respiratory (12 items), eye related (two items), and general (eight items) health complaints, as well as current intake of medicine during the past 12 months were recorded (table 1). Subjects were also asked to state lifetime prevalence of diseases found by their own doctors in 18 categories. Interviewing doctors checked allergic conditions and current medicine intake by inspecting documents stating allergies and medicine supply during the study related house call.

Lifestyle factors and individual exposure to microorganisms from household sources (contact with compost, organic waste collection in the home,[30] inhalers, soft furnishings) were determined (see table 1). Further questions concerned the occurrence and quality of annoying odours in the residential area.

Epidemiological survey

The survey was carried out after consultation with the state data protection officer. It took place on all seven days of one week in July 1997, not during school holidays. A press conference, information by mail, and public event had previously taken place. The selected sample was mailed the questionnaire accompanied by additional information stating, for example, that their participation was voluntary. They were then phoned up to three times in order to arrange appointments for the doctor supported medical history interviews. These interviews took place in their homes and lasted for about an hour per person.

Statistical analysis

Using the LOGISTIC procedure of the SAS/STAT software, version 8.0, a logistic regression modelling approach was employed to analyse the health data of the 356 respondents studied. The model associated odds ratios (OR) and the corresponding 95% confidence intervals (CI) were determined. A p value of 0.05 or less was judged relevant. First a core model in which residents living at different distances (150–200 m, >200–400 m, >400–500 m) from the site were compared to unexposed controls living in the residential area without an adjoining compost site. The model included age, odour annoyance, and period of residence in the current home >5 years as fixed covariables. Additional confounders were gender, composting in own garden, collection of organic waste in the home, distance of home from a busy street <50 m, smoking, and exposure to passive smoke.

In a second stage the model was calculated for those 214 residents living near the composting site only. Those living in the two distance groups nearest to the site (150–200 m, >200–400 m) were compared to those living at >400–500 m. Fixed covariables were age, odour annoyance, and period of residence in the current home >5 years.

RESULTS

Exposure to culturable microorganisms in the outdoor air of the residential area

In the outdoor air of the residential area 200 m from the plant, concentrations of up to $>10^5$ CFU m^{-3} air were recorded for total bacteria, moulds, and thermophilic actinomycetes. Even 320 m from the site differences in concentrations of total bacteria and moulds which were 100 times background levels (10^3–10^4 CFU m^{-3} air) were detected. Furthermore, the site characteristic thermophilic actinomycetes which were not found in upwind—background measurements—were still detectable 550 m downwind from the site at a concentration of $<10^3$ CFU m^{-3} air.[27]

These high concentrations of culturable microorganisms close to the plant came down quickly to near background concentrations within 550 m from the plant (table 2). Based on this observation, the exposed population was divided into three groups, dependent on the linear distance of the respective home from the site (150–200 m, >200–400 m, >400–500 m).

Epidemiological investigation

Study population

A total of 356 people took part in the study (see table 1). The response rate in the residential area with bioaerosol pollution was 69%. Selection bias due to low participation rate (35%) in the unexposed group would be characterised by stronger weighing of health concerned subjects perceiving health impairment.

More females and subjects >50 years took part in the exposed group. As stated above an adjustment was made for both parameters in the core model.

In the neighbourhood of the site, residential odour annoyance was reported by 80%, increasing to 95% in residents living 150–200 m from the site. When asked to characterise this odour annoyance, 10% described it as "disgusting". None of the unexposed controls reporting odours from other possible environmental sources stated this kind of odour annoyance. This underlines the specific odour annoyance of the exposed group.

Table 3 Prevalence of reported health complaints in residents in the neighbourhood of a composting site stratified according to the distance between home and composting site respectively, increasing concentration of bioaerosol exposure in residential air and unexposed controls

	Study population	Unexposed controls	Residents in the neighbourhood of a composting site with bioaerosol pollution of outdoor air							
			Total		Classified					
Distance of home from composting site	–	–	150–500 m		150–200 m		>200–400 m		>400–500 m	
Bioaerosol pollution in residential air	–	Not measured	Up to $>10^5$ CFU* m^{-3}		Up to $>10^5$ CFU m^{-3}		Up to $<10^5$ CFU m^{-3}		Near	
Participants	n=356	n=142	n=214		n=82		n=76		n=56	
Reported health complaints†	SS‡	SS	Yes [%]	SS	Yes [%]	SS	Yes [%]	SS	Yes [%]	SS	Yes [%]
Respiratory tract											
Frequency of colds >5×/year	352	142	6.3	210	11.4	81	21.0	73	2.7	56	8.9
Hay fever	355	142	16.2	213	19.7	81	18.5	76	19.7	56	21.4
Sinusitis	354	141	14.2	213	17.4	82	26.8	75	10.7	56	12.5
Bronchitis	355	142	26.8	213	33.3	81	54.3	76	17.1	56	25.0
Pneumonia	348	139	1.4	209	3.3	80	6.3	75	1.3	54	1.9
Shortness of breath at rest	343	137	5.1	206	18.4	82	24.4	68	20.6	56	7.1
Shortness of breath following exertion	344	136	16.2	208	31.3	82	43.9	70	30.0	56	14.3
Waking up with chest tightness	338	135	11.9	203	22.2	79	26.6	69	26.1	55	10.9
Waking up due to shortness of breath	341	136	3.7	205	9.3	82	7.3	67	13.4	56	7.1
Waking up due to coughing	343	138	25.4	205	41.5	82	57.3	67	31.3	56	30.4
Wheezing	349	139	15.8	210	28.1	79	38.0	76	23.7	55	20.0
Cough on rising/during the day§	355	142	19.0	213	35.2	82	47.6	75	28.0	56	26.8
Eyes and general health											
Itching eyes >10×/year	340	131	20.6	209	40.2	80	47.5	74	40.5	55	29.1
Smarting eyes >10×/year	344	136	15.4	208	35.6	80	43.8	74	40.5	54	16.7
Loss of appetite	347	140	5.0	207	10.1	76	10.5	76	10.5	55	9.1
Nausea or vomiting >5×/year	343	136	5.9	207	16.9	81	23.5	73	16.4	53	7.5
Diarrhoea >5× year	349	138	3.6	211	9.5	81	21.0	76	2.6	54	1.9
Excessive tiredness >5×/year	341	138	13.0	203	40.4	76	53.9	76	36.8	51	25.5
Shivering	353	140	13.6	213	19.7	82	29.3	75	20.0	56	5.4
Fever >5×/year	356	142	1.4	214	2.3	82	2.4	76	3.9	56	0.0
Joint trouble >10×/year	346	136	19.1	210	37.1	80	41.3	75	36.0	55	32.7
Muscular complaints >10×/year	339	135	11.1	204	25.0	77	26.0	72	26.4	55	21.8
Current intake of medicine/vitamins	355	142	41.5	213	56.8	82	54.9	76	59.2	55	56.4

*CFU, colony forming units.
†Frequency or occurrence in the past 12 months. If not otherwise stated, rates are for a single occurrence.
‡SS, sample size.
§Criteria of the World Health Organisation for chronic bronchitis.

Regarding exposure to airborne microorganisms from domestic sources, residents near the composting site reported less separate collection of organic household waste. This rate was lowest in those living closest to the site. From this observation, as well as from reports on composting in own gardens, there was no indication of a higher exposure of the residents in the neighbourhood of the site to bioaerosols from domestic waste sources.

Smoking status and exposure to environmental tobacco smoke, occupational exposure, personal use of inhalers, as well bedroom equipment, also gave no indication of a higher burden on the airways of the exposed group. The same applied to the statements on mould or dampness in homes (9% in unexposed controls, 3% in exposed).

Differences were observed for the proximity of the home to a busy street (<50 m), which indicated a higher exposure to car traffic related pollutants close to the site. For this reason an adjustment was made in the logistic regression.

Health effects in a residential area with bioaerosol pollution

Residents living in the neighbourhood of the composting site reported health complaints, medicine intake, and 11 of the 18 self reported illnesses ever diagnosed by a doctor more frequently than unexposed controls without a neighbouring composting site. Stratification showed the highest prevalence of complaints in those living closest to the site who were respectively exposed to the highest concentration of bioaerosols measured. Nevertheless, the exposed group living furthest away from the site at a distance of >400–500 m still reported higher rates of health complaints (but not self perceived diseases) compared to unexposed controls (table 3).

In the core model the unexposed residents without an adjacent composting site were compared with exposed residents in the neighbourhood of the site. For this the exposed group was stratified according to distance between home and composting site, and nine confounders were taken into consideration. Adjusted associations were found between close residency to the site (150–200 m)—highest concentration of airborne microorganisms (up to $>10^5$ CFU m^{-3} residential air)—and three of 12 airway related complaints, as well as excessive tiredness and intake of medicine (table 4). For those living further away from the site (>200–400 m), these associations were not observed.

In this core model, duration of present residency (>5 years), respectively duration of exposure was positively associated with "waking up due to coughing" (OR 2.29; 95% CI 1.13 to 4.79) and "bronchitis" (OR 2.37; 95% CI 1.65 to 5.06) during the past 12 months.

In a second step only those living in the neighbourhood of the composting site were studied. This allowed the effects of the bioaerosols (measured concentrations and duration of exposure) and the possible bias due to the specific, in part disgusting, residential odour annoyance near the composting site to be analysed more precisely. This comparison of the most highly exposed (up to $>10^5$ CFU m^{-3} residential air) with the least exposed (near background concentrations of airborne

Table 4 Health effects* of bioaerosol pollution in residential outdoor air highly exposed (>10^5 CFU† m^{-3} air) in the neighbourhood of a composting site compared to unexposed controls without a neighbouring composting site

	Residents with bioaerosol pollution of up to >10^5 CFU m^{-3} residential air living 150–200 m from the composting site		
Reported health complaints‡	SS§	OR¶	95%CI**
Bronchitis	262	3.59	1.40 to 9.47
Waking up due to coughing	255	6.59	2.57 to 17.73
Coughing on rising or during the day††	263	3.18	1.24 to 8.36
Excessive tiredness	251	4.27	1.56 to 12.15
Current medication intake	263	2.64	1.08 to 6.60

*Only the significant positive associations from table 3 are listed.
†CFU, colony forming units.
‡Frequency of occurrence in the past 12 months; if not otherwise stated, rates are for a single occurrence.
§SS, sample size.
¶OR, adjusted odds ratio comparing the group nearest to the composting site (150–220 m) with the control group in a residential area without a neighbouring composting site adjusted for residential odour annoyance, duration present residency >5 years, composting in own garden, separate collection of organic household waste, distance of home to busy road <50 m, age, gender, smoking, and passive smoke exposure.
**CI, confidence interval.
††Criteria of the World Health Organisation for chronic bronchitis.

Table 5 Health effects* of highest (>10^5 CFU† m^{-3} air) versus near background concentrations of outdoor bioaerosol, pollution, duration of present residency, and odour annoyance in a residential area with a neighbouring composting site

		Bioaerosol pollution in residential air‡ up to >10^5 CFU m^{-3} air		Duration of present residency >5 years		Odour annoyance in the residential area	
Reported health complaints§	SS¶	OR**	95% CI††	OR	95% CI	OR	95% CI
Respiratory tract							
Frequency of colds >5×/year	209	1.94	0.65 to 6.78	**4.72**	**1.19 to 31.83**	3.09	0.50 to 60.14
Bronchitis	210	**3.02**	**1.35 to 7.06**	**2.91**	**1.29 to 7.03**	1.86	0.71 to 5.54
Waking up due to coughing	202	**2.70**	**1.23 to 6.10**	**2.51**	**1.19 to 5.53**	1.95	0.81 to 5.08
Wheezing	207	1.96	0.84 to 4.82	**2.95**	**1.22 to 7.99**	1.97	0.72 to 6.35
Shortness of breath at rest	203	**3.99**	**1.31 to 15.19**	1.50	0.56 to 4.49	1.97	0.59 to 9.02
Coughing on rising or during the day‡‡	210	**2.67**	**1.17 to 6.10**	1.51	0.69 to 3.29	1.51	0.61 to 3.75
Shortness of breath after exertion	205	**4.23**	**1.74 to 11.34**	2.03	0.90 to 4.91	2.15	0.79 to 6.90
Eyes and general health							
Itching eyes >10×/year	206	1.35	0.61 to 3.05	**2.85**	**1.31 to 6.50**	**4.97**	**1.89 to 15.67**
Smarting eyes >10×/year	205	**2.44**	**1.02 to 6.22**	**2.42**	**1.06 to 5.86**	**10.40**	**2.87 to 66.96**
Nausea or vomiting >5×/year	204	2.65	0.87 to 9.97	**4.10**	**1.28 to 18.44**	§§	§§
Excessive tiredness >5×/year	200	**2.80**	**1.22 to 6.72**	1.83	0.84 to 4.11	§§	§§
Shivering	210	**4.63**	**1.44 to 20.85**	**3.67**	**1.32 to 12.20**	§§	§§
Joint trouble >10×/year	207	1.27	0.54 to 3.07	1.52	0.65 to 3.71	**4.30**	**1.55 to 14.17**
Muscular complaints >10×/year	201	1.17	0.47 to 2.99	1.39	0.55 to 3.86	**2.99**	**1.02 to 11.03**

*Only the significantly increased complaints from table 3 are listed and printed in bold type.
†CFU, colony forming units.
‡Distance of home to the emitting site 150–200 m.
§Frequency or occurrence in the past 12 months. If not otherwise stated, rates are for a single occurrence.
¶SS, sample size.
**OR, odds ratio of those living the stated distance from site compared to those living >400 m from the site adjusted for odour annoyance in the residential area, period of residence in the present home >5 years, and age.
††CI, confidence interval.
‡‡Criteria of the World Health Organisation for chronic bronchitis.
§§Due to the small number of subjects of this complaint reliable odds ratio could not be determined.

microorganisms) population of the same neighbourhood was positively associated with eight items of reported health (table 5).

"Shortness of breath" ("following exertion" and "while at rest") was most strongly associated with residential exposure to highest concentrations (>10^5 CFU m^{-3}) bioaerosols. Frequency of perceived bronchitis in the past 12 months and two symptoms associated with cough all had positive adjusted OR above 2.5. Sore eyes as well as diarrhoea, excessive tiredness, and shivering were also positively associated with the close proximity of home to the composting site (table 5).

Duration of present residency (>5 years), defining those individuals exposed to residential bioaerosol since the commencement of operations at the site, was positively associated with an increased frequency of one third of the airway complaints, eye complaints, as well as nausea or vomiting and shivering. Specific odour annoyance did not confound any of the airway related complaints in the neighbourhood of the composting site (table 5).

In this analysis, distance of the home from the site, and duration of residency, as well as residential odour annoyance were not associated with increased reporting of lifetime prevalence of 18 self reported doctor diagnosed illnesses.

DISCUSSION

Concentrations of culturable airborne microorganisms, including moulds, measured in the residential air during the study (table 2) at 150 to 320 m from the composting site were 100–1000 times higher than those concentrations generally reported as natural background concentrations. Background concentrations for total bacteria and moulds are given as <10^3

CFU m^{-3} air and $<10^2$ CFU m^{-3} air for actinomycetes.[2] As a result of this, and particularly because of the detection of site typical actinomycetes, a distance dependent influence of the composting site on the residential air could be demonstrated up to 550 m (table 2). In a study conducted in Islip, New York,[16] the bioaerosol related influence of a large scale composting site on a residential area 500 m away could not be excluded. However, this study has methodological shortcomings as far as exposure measurements and health effects are concerned. In other studies, the bioaerosol pollution due to sites could only be demonstrated up to a distance of 200 m.[4]

The highest concentrations of total bacteria and actinomycetes ($>10^5$ CFU m^{-3} air) measured, were within the range of those reported in occupational studies of composting sites.[2 11] For total bacteria, the measured concentrations of 10^4 or 5×10^3 CFU m^{-3} air also exceeded occupational threshold levels recommended in Denmark and Sweden.[31] Health effects have been observed in the studies on workplace or indoor environment in association with concentration levels recorded here for total bacteria and moulds (*Aspergillus fumigatus*).[11 22]

These microbiological measurements were performed under meteorological conditions which occur on 50% of the days in a year. Desired "worst case" conditions were not achieved completely during these measurements. Considering this the exposure to airborne culturable microorganisms in the residential area could at times have been even higher. The additional health burden from non-culturable microorganisms or allergenic and toxic parts of microorganisms, which also occur in bioaerosols, was not even assessable in the scope of the measurements.[5]

An association could be demonstrated in the present study between residential bioaerosol pollution (<200 m from the plant) and irritative airway complaints. This association was found when comparing with less exposed subjects living in the same neighbourhood further away from the same site (>400–500 m) and also, to a greater extent, when comparing with unexposed controls. Furthermore, an association of these complaints with the duration of bioaerosol exposure (>5 years) could also in part be demonstrated. If at least two irritative mucous membrane symptoms are reported in association with chronic exposure to bioaerosols, this is suggestive of airway inflammation.[9]

Complaints of airway inflammation are to be expected after frequent exposure to microorganisms in the range of concentration of 10^4–10^5 CFU m^{-3} air.[4] These concentrations are similar to those measured 200 m from the site in this study (table 2). Furthermore, due to the meteorological and topographical conditions, this exposure is likely to have existed frequently.

Irritative airway complaints (increased frequency of coughing, shortness of breath, and self diagnosed bronchitis) have already been reported in health studies concerning exposure to microorganisms: At workplaces with handling of garbage and compost, increased frequencies of airway related mucous membrane irritation, coughing, and tracheobronchitis, among others, have been reported[2 11]; similarly, airway symptoms have been reported in residents of mouldy or damp homes.[20–22]

The high OR found in both analyses, comparing highest exposed to unexposed controls as well as least exposed are not considered to be due to unrecognised bias. They are considered to result from high measurable concentrations of airborne microorganisms in residential air (200 m from the site), dropping sharply within 300 m and reaching near background concentrations at 550 m.

It could be shown that perceived odour annoyance, considered to be a strong bias on self reported complaints, had no influence on these irritative airway complaints (table 5). Odour annoyance was only associated with general complaints. This could have been expected on the basis of previous reports.[24–26] Comparable results were found when studying odour annoyed (90%) neighbours of another composting site. Rates of health complaints showed no association (versus controls in a neighbourhood without a composting site) with residency near the composting site (data not shown).

Examiners and study population were blinded to the results of microbiological measurements during the field work as samples for these measurements were obtained during the ongoing survey. Further aspects speak against a reporting bias, based on prejudices regarding the plant: self reported lifetime diagnoses of illnesses were not associated with exposure, although occurrence of some diseases (for example, infections and allergies) had been feared by the residents beforehand. They had stated this during the public event which took place prior to the survey. Furthermore, respondents knew interviewers would not be able to prove or disprove during the house calls whether reported illnesses actually existed.

Additional aspects speak against general over reporting of all health complaints in the neighbourhood of the composting site. Skin irritation (data not shown), occurring when in close occupational contact with waste,[2] was not reported more often, for instance. The same applies for perceived hay fever. It was reported least very close to the site (table 3).

Bioaerosol exposure from other everyday sources or exposure to respiratory irritants also cannot explain the findings of this study, as they were reported the same or less frequently by the group near the site than by the unexposed control group (table 1). Addressing a possible bias due to the low participation rate in the unexposed group, the following should be considered. In a sample with a low participation rate, those more health conscious or health impaired would be more likely to participate in this unexposed sample. This in turn would then lead to higher rates of health complaints in these controls compared to the exposed population, and underestimate the true health effects.

Specific allergic and infectious diseases are reported in subjects exposed to various bioaerosols working at composting sites, indoors, and in the environment.[3 4 13–15 17 19] Severe toxic-irritative reactions (ODTS, pulmonary mycotoxicosis, or toxic pneumonitis), occurring after a single inhalation of very high levels of spores (10^6–10^9 spores m^{-3} air),[3 6 8] and pulmonary haemorrhage[21] have also been described concerning occupational settings and in case reports of indoor environmental exposure. Actinomycetes and mould spores, as well as endotoxins and glucanes,[32] are discussed as their causes. There was no indication in the presented study that the exposure detected in the scope of this study led to any of the above illnesses in the five years since the composting site started operating. However, in this context the limitations of relying on self reported health status have to be taken under consideration.

In the present study, as claimed by others,[4 18] the health related problems of environmental bioaerosols were assessed by measuring microbiological pollution in the residential environment and simultaneously collecting medical histories. Odour annoyance, always associated with bioaerosols, was taken into consideration. To the authors' knowledge it was found for the first time that there can be a demonstrable bioaerosol pollution of the residential environment, which is in part still detectable at a distance of 550 m. This bioaerosol exposure in turn could be associated, as far as concentrations of bioaerosols and duration of exposure were concerned, with symptoms suggestive of airway inflammation also reported at respective workplaces.

Due to methodological shortcomings, cross sectional studies are not able to prove or disprove a causal relationship. Nevertheless it is believed that on the basis of this study irritative airway complaints pointing at MMI-like airway inflammation can be seen as associated with measurable residential bioaerosol pollution.

The health complaints found here in association with residential bioaerosol exposure were not accompanied by increased self reports of diseases diagnosed by a doctor. This

might have been anticipated, as on the one hand diagnosing airway irritation related to environmental exposure is not common by general physicians. On the other hand, higher rates of diseases with clear laboratory findings or organ impairment could not have been expected. Nevertheless, several considerations should be made when considering their relevance as far as public health is concerned. For airway inflammation related to bioaerosol exposure, a toxic or non-specific genesis is hypothesised. It can be accompanied by an increase in bronchial reactivity as a sign of an inflammatory process as well as possibly being the onset of chronic bronchitis.[2 7 9] An effect of the bioaerosol concentration in the residential air with regard to excessive tiredness and shivering (table 5) was also detected in the present study. At workplaces with garbage or compost handling, and in homes containing mould, single general complaints of general disturbances, for example, toxic pneumonitis, including shivering and tiredness, are often observed.[11]

This study forms the basis for further studies using more sophisticated designs (for example, prospective panel study) to study the clinical relevance of these irritative airway symptoms. Clinical parameters, for example, lung function examinations could be included, particularly since connections have been found in the workplace between symptoms of airway inflammation and changes in lung function.[9] Risk groups for airway effects (for example, children) could be particularly looked at. Due to the small sample of children this was not possible in the present study.

Furthermore, mucous membrane lavage could be carried out to document inflammatory changes and evidence of specific antibodies in the sense of exposure manifestation.[2 12] As the amount of time spent outdoors in the residential area is relatively small, and therefore exposure to outdoor air only represents a small part of the day, the possible accumulation in interior rooms of airborne microorganisms from emission sources should be measured in the future.

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Authors' affiliations

C E W Herr, A zur Nieden, M Jankofsky, T F Eikmann, Institute of Hygiene and Environmental Medicine, Medical Centre, Faculty of Medicine, Justus-Liebig-University of Giessen, Germany
N I Stilianakis, European Commission, Joint Research Centre, Via E Fermi 1 T.P. 441, 21020 Ispra (VA), Italy
R-H Boedeker, Institute of Statistics and Informatics, Medical Centre, Faculty of Medicine, Justus-Liebig-University of Giessen, Germany

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Effects of bioaerosol polluted outdoor air on airways of residents: a cross sectional study

C E W Herr, A zur Nieden, M Jankofsky, N I Stilianakis, R-H Boedeker and T F Eikmann

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Wood Dust

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Wood dust is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Many case reports and epidemiological studies (including cohort studies and case-control studies that specifically addressed nasal cancer) have found a strong association between exposure to wood dust and cancer of the nasal cavity. Strong and consistent associations with cancer of the nasal cavity and paranasal sinuses were observed both in studies of people whose occupations were associated with wood-dust exposure and in studies that directly estimated wood-dust exposure. Cancer risks were highest for adenocarcinoma, particularly among European populations. Studies of U.S. populations showed similar significant positive associations between wood-dust exposure and adenocarcinoma of the nasal cavity. A pooled analysis of 12 case-control studies found a very high estimated relative risk of adenocarcinoma (45.5) among men with the greatest exposure, and the risk increased with increasing duration of exposure (Demers *et al.* 1995). The association between wood-dust exposure and elevated risk of nasal cancer (adenocarcinoma) in a large number of independent studies and in many different occupations in many countries strongly supports the conclusion that the increased risk is due to wood-dust exposure, rather than to simultaneous exposure to other substances, such as formaldehyde or wood preservatives (IARC 1995, NTP 2000).

Other types of nasal cancer (squamous-cell carcinoma of the nasal cavity) and cancer at other tissue sites, including cancer of the nasopharynx and larynx and Hodgkin disease, have been associated with exposure to wood dust in several epidemiological studies. However, these associations were not found in all studies, and the overall epidemiological evidence is not strong enough or consistent enough to allow firm conclusions to be drawn about the role of wood-dust exposure in the development of cancer at tissue sites other than the nasal cavity (IARC 1995, NTP 2000).

Studies on Mechanisms of Carcinogenesis

Polar organic solvent extracts of some hardwood dusts were weakly mutagenic in *Salmonella typhimurium,* and two chemicals found in wood, delta-3-carene and quercetin, also were mutagenic in *S. typhimurium. In vivo* exposure of mammals and *in vitro* exposure of mammalian cells to organic solvent extracts of some wood dusts (beech and oak) caused DNA damage, micronucleus formation, and chromosomal aberrations (primarily chromatid breaks). Elevated rates of DNA damage (primarily single-strand breaks and DNA repair) and micronucleus formation were observed in peripheral-blood lymphocytes from people occupationally exposed to wood dust (IARC 1995, NTP 2000).

The roles of specific chemicals found in wood dust (either naturally in the wood or added to it in processing) in causing cancer are not clear. The particulate nature of wood dust also may contribute to wood-dust-associated carcinogenesis, because a high proportion of dust particles generated by woodworking typically are deposited in the nasal cavity. Some studies of people with long-term exposure to wood dust have found decreased mucociliary clearance and enhanced inflammatory reactions in the nasal cavity. Also, cellular changes (metaplasia and dysplasia) observed in the nasal mucosa of woodworkers and of laboratory animals may be precancerous (IARC 1995, NTP 2000).

Cancer Studies in Experimental Animals

The evidence from studies in experimental animals is inadequate to evaluate the carcinogenicity of wood dust. No tumors attributable to beech wood-dust exposure were found in rats exposed by inhalation or intraperitoneal injection. Inhalation exposure to wood dust also did not significantly affect the incidence of tumors caused by simultaneous exposure to other compounds (known to be carcinogenic in humans or experimental animals), including formaldehyde or sidestream cigarette smoke in rats and *N*-nitrosodiethylamine in hamsters. However, each of these studies was limited by such factors as small numbers of animals or exposure groups, short study duration, or inadequate data reporting. In female mice, dermal exposure to a methanol extract of beech wood dust resulted in significant dose-related increases in the incidence of skin tumors (squamous-cell papilloma and carcinoma) and mammary-gland tumors (adenocarcinoma, adenoacanthoma, and mixed tumors) (IARC 1995).

Properties

Wood is an important worldwide renewable natural resource. Forests cover about one third of the earth's total land mass (about 3.4 million square kilometers). An estimated 12,000 species of trees each produce a characteristic type of wood, and the species of trees harvested vary considerably among different countries and even among different regions of a country. However, even in countries with high domestic production of wood, some wood may be imported for specific uses, such as furniture production (IARC 1995).

Most of the 12,000 tree species are broad-leaved deciduous trees, or hardwoods, principally angiosperms. Only about 800 species are pines, firs, and other coniferous trees, or softwoods, principally gymnosperms. The terms "hardwood" and "softwood" refer to the species, and not necessarily the hardness of the wood. Although hardwoods generally are denser than softwoods, the density varies greatly within each group, and the hardness of the two groups overlaps somewhat. The composition of softwood tissue is simpler than that of hardwood, consisting of mainly one type of cells, tracheids. Hardwoods show more detailed differentiation among stabilizing, conducting, and storage tissue. Although most trees harvested worldwide are hardwoods (58% of volume), much of the hardwood is used for fuel. Softwood is the major wood used for industrial purposes (69%); however, the percentage varies from region to region (IARC 1995).

Wood dust is a complex mixture generated when timber is processed, such as when it is chipped, sawed, turned, drilled, or sanded. Its chemical composition depends on the species of tree and consists mainly of cellulose, polyoses, and lignin, plus a large and variable number of substances with lower relative molecular mass. Cellulose is the major component of both softwood and hardwood. Polyoses (hemicelluloses), which consist of five neutral sugar units, are present in larger amounts in hardwood than in softwood. The lignin content of softwood is higher than that of hardwood. The lower-molecular-mass substances significantly affect the properties of wood; these include substances extracted with nonpolar organic solvents (fatty acids, resin acids, waxes, alcohols, terpenes, sterols, steryl esters, and glycerols), substances extracted with polar organic solvents (tannins, flavonoids, quinones, and lignans), and water-soluble substances (carbohydrates, alkaloids, proteins, and inorganic material). Wood dust is also characterized by its moisture content: "dry" wood has a moisture content of less than approximately 15%, and "moist" wood has a higher moisture content. Woodworking operations us-

ing dry wood generate more total dust and a larger quantity of inhalable dust particles than do those using moist wood (IARC 1995).

Use

Wood dust is produced in woodworking industries as a by-product of the manufacture of wood products; it is not usually produced for specific uses. One commercial use for wood dust is in wood composts (Weber *et al.* 1993). "Industrial roundwood" refers to categories of wood not used for fuel, which include sawn wood (54%), pulpwood (21%), poles and pit props (14%), and wood used for other purposes, such as particle board and fiberboard (11%) (IARC 1995).

Production

Wood dust is created when machines or tools are used to cut or shape wood materials. Industries in which large amounts of wood dust are produced include sawmills, dimension mills, furniture industries, cabinetmaking, and carpentry (IARC 1995). In 1990, total estimated production of wood used in U.S. industry was 311.9 million cubic meters of softwood and 115 million cubic meters of hardwood (Demers *et al.* 1997).

Exposure

Exposure to wood dust occurs when individuals use machinery or tools to cut or shape wood. When the dust is inhaled, it is deposited in the nose, throat, and other airways. The amount of dust deposited within the airways depends on the size, shape, and density of the dust particles and the strength (turbulence and velocity) of the airflow. Particles with a diameter larger than 5 μm (inspirable particles) are deposited almost completely in the nose, whereas particles 0.5 to 5 μm in diameter (respirable particles) are deposited in the lower airways (IARC 1981, 1995).

Wood dust usually is measured as the concentration of airborne dust, by particle size distribution, by type of wood, and by other characteristics of wood. Total airborne dust concentration is reported as mass per unit volume (usually milligrams of dust per cubic meter of air). Wood dust generally is collected by a standard gravimetric method, whereby a sampling pump is used to collect a known volume of air through a special membrane filter contained in a plastic cassette. Some sampling studies reported that the particle size distribution varied according to the woodworking operation, with sanding producing smaller particles than sawing, but others found no consistent differences (IARC 1995). The majority of the wood-dust mass was reported to be contributed by particles larger than 10 μm in aerodynamic diameter; however, between 61% and 65% of the particles by count measured between 1 and 5 μm in diameter (IARC 1995).

Exposure to wood dust also occurs through handling of compost containing wood dust. One study measured dust concentrations resulting from handling of compost material consisting of successive layers of chopped leaves, bark, and wood; visible clouds of fine particles were easily generated when the compost material was agitated. The reported background concentration of respirable dust sampled upwind of the compost pile was 0.32 mg/m^3. During loading and unloading of compost, samplers in the breathing zone detected inspirable dust at 0.74 mg/m^3 and respirable dust at 0.42 mg/m^3. Samples collected directly from the visible clouds of particles generated by compost agitation contained inspirable dust at 149 mg/m^3 and respirable dust at 83 mg/m^3 (Weber *et al.* 1993).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that nearly 600,000 workers were exposed to woods (NIOSH 1990). Teschke *et al.* (1999) analyzed 1,632 measurements of personal time-weighted-average airborne wood-dust concentrations in 609 establishments on 634 inspection visits that were reported to the Occupational Safety and Health Administration Integrated Management Information System between 1979 and 1997. Exposures ranged from less than 0.03 to 604 mg/m^3, with an arithmetic mean of 7.93 mg/m^3 and a geometric mean of 1.86 mg/m^3. Exposure levels decreased significantly over time; the unadjusted geometric mean was 4.59 mg/m^3 in 1979 and 0.14 mg/m^3 in 1997. Occupations with high exposure to wood dust included sander in the transportation equipment industry (unadjusted geometric mean = 17.5 mg/m^3), press operator in the wood products industry (12.3 mg/m^3), lathe operator in the furniture industry (7.46 mg/m^3), and sander in the wood cabinet industry (5.83 mg/m^3). High exposures occurred in the chemical, petroleum, rubber, and plastics products industries, in sanding, pattern making, and mill and saw operations. The lowest exposures occurred in industrial pattern-making facilities, paper and paperboard mills, schools and institutional training facilities, and veneer and plywood mills.

Use of hand-held electric sanders has been identified as a particularly dusty process that leads to dust exposure. Wood-dust concentrations vary with type of dust extraction, amount of wood removed, and type of sander (Thorpe and Brown 1994). For electric belt sanders used to sand dowels, total dust concentrations ranged from 0.22 mg/m^3 with external dust extraction to 3.74 mg/m^3 without extraction, and concentrations of respirable dust ranged from 0.003 mg/m^3 with extraction to 0.936 mg/m^3 without extraction. Rotary sanders tested with flat wood samples produced total dust concentrations ranging from 0.002 mg/m^3 with extraction to 0.699 mg/m^3 without extraction; concentrations of respirable dust ranged from 0.001 mg/m^3 with extraction to 0.088 mg/m^3 without extraction. Comparable decreases in dust concentration were observed when dust extraction was used with electrical orbital sanders.

Regulations

Occupational Safety and Health Administration (OSHA)

This legally enforceable PEL was adopted from the 1969 United States Department of Labor regulation *Safety and Health Standards for Federal Supply Contracts* shortly after OSHA was established. The PEL may not reflect the most recent scientific evidence and may not adequately protect worker health.

Permissible exposure limit (PEL) = 15 mg/m^3 total fibers; = 5 mg/m^3 respirable fibers (based on the standard for "particles not otherwise regulated").

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m^3 for western red cedar; = 1 mg/m^3 for all other species.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 mg/m^3.
Listed as a potential occupational carcinogen.

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MAJOR ARTICLE

Fulminant Mulch Pneumonitis: An Emergency Presentation of Chronic Granulomatous Disease

Sophia Siddiqui,[1] Victoria L. Anderson,[3] Diane M. Hilligoss,[2] Mario Abinun,[6] Taco W. Kuijpers,[7] Henry Masur,[4] Frank G. Witebsky,[5] Yvonne R. Shea,[5] John I. Gallin,[2] Henry L. Malech,[2] and Steven M. Holland[3]

Laboratories of [1]Immune Regulation, [2]Host Defenses, and [3]Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, and [4]Department of Critical Care Medicine and [5]Microbiology Service, Department of Laboratory Medicine, Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland; [6]Newcastle General Hospital, Newcastle upon Tyne, United Kingdom; and [7]Emma Children's Hospital, Amsterdam, The Netherlands

(See the article by Bénet at al. on pages 682–6)

Background. Chronic granulomatous disease (CGD) is associated with multiple and recurrent infections. In patients with CGD, invasive pulmonary infection with *Aspergillus* species remains the greatest cause of mortality and is typically insidious in onset. Acute fulminant presentations of fungal pneumonia are catastrophic.

Methods. Case records, radiograph findings, and microbiologic examination findings of patients with CGD who had acute presentations of dyspnea and diffuse pulmonary infiltrates caused by invasive fungal infection were reviewed and excerpted onto a standard format.

Results. From 1991 through 2004, 9 patients who either were known to have CGD or who received a subsequent diagnosis of CGD presented with fever and new onset dyspnea. Eight patients were hypoxic at presentation; bilateral pulmonary infiltrates were noted at presentation in 6 patients and developed within 2 days after initial symptoms in 2 patients. All patients received diagnoses of invasive filamentous fungi; 4 patients had specimens that also grew *Streptomyces* species on culture. All patients had been exposed to aerosolized mulch or organic material 1–10 days prior to the onset of symptoms. Cases did not occur in the winter. Five patients died. Two patients, 14 years of age and 23 years of age, who had no antecedent history of recognized immunodeficiency, were found to have $p47^{phox}$-deficient CGD.

Conclusions. Acute fulminant invasive fungal pneumonia in the absence of exogenous immunosuppression is a medical emergency that is highly associated with CGD. Correct diagnosis has important implications for immediate therapy, genetic counseling, and subsequent prophylaxis.

Chronic granulomatous disease (CGD) of childhood, first described in 1959 [1], is caused by defects in 1 of 4 structural components of the reduced nicotinamide adenide dinucleotide phosphate oxidase enzyme. Mutations in the X-linked $gp91^{phox}$ account for ~70% of cases, and the remainder are autosomal recessive in $p22^{phox}$, $p47^{phox}$, and $p67^{phox}$ [2]. Patients with CGD are prone to develop characteristic bacterial and fungal infections due to pathogens such as *Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia, Nocardia* species, and *Aspergillus* species [2, 3]. In addition, these patients develop steroid-responsive granulomatous complications, including inflammatory bowel disease, urinary tract obstruction, and wound dehiscence, presumably because of abnormal degradation of inflammatory mediators [2, 4, 5].

Unique to CGD among genetic immunodeficiencies is susceptibility to invasive infection with filamentous fungi, especially *Aspergillus* species, which typically occurs in the pulmonary system, is difficult to treat, and is the single greatest cause of mortality associated with CGD [3, 6]. In general, fungal infection in patients with CGD is more indolent than infection due to bacteria [3, 7], and patients rarely experience pulmonary cavitation or hemoptysis because of *Aspergillus* infection. High-level exposure to aerosolized fungi, such as that which can occur during mulching, may lead to an acute fulminant presentation, with fever, dyspnea, and pulmonary infiltrates, and to death. Two such cases of the

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Reprints or correspondence: Dr. Steven M. Holland, Laboratory of Clinical Infectious Diseases, National Institutes of Health, Bldg. 10, CRC B3-4141, MSC 1684, Bethesda, MD 20892-1684 (smh@nih.gov).

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initial presentation of CGD in adolescents and young adults led us to review cases to better characterize this clinical entity.

MATERIALS AND METHODS

The case records of 156 patients with CGD who were followed up according to approved protocols at the National Institutes of Health (NIH; Bethesda, MD) since 1986 were reviewed for acute presentations of fever, dyspnea, diffuse pulmonary infiltrates, and filamentous fungal infection. We also solicited cases from outside the NIH.

Patient 1. A previously healthy 14-year-old boy presented to his local hospital in the fall of 2004 with a 3-day history of fever, sore throat, and shortness of breath. A chest radiograph revealed bilateral infiltrates (figure 1*A*). One week previously, the boy had cleaned gutters containing dead leaves. Despite cefuroxime and azithromycin therapy for community-acquired pneumonia, his hypoxia worsened, leading to intubation and mechanical ventilation on hospital day 4. Meropenem, metronidazole, clarithromycin, and fluconazole were added to his treatment regimen, but respiratory failure progressed; high-dose methylprednisolone therapy was started for possible vasculitis. On hospital day 11, a lung biopsy specimen showed necrotic lung tissue with fungal hyphae and grew *Aspergillus fumigatus.* The dihydrorhodamine test result was consistent with CGD. Voriconazole, caspofungin, and IFN-γ therapy, as well as neutrophil transfusions, were initiated. High-level oxygenation requirements and deterioration of hepatic and renal function led to death 1 month after presentation. Autopsy revealed disseminated fungal infection, granulomatous foci in the lungs and brain with *A. fumigatus,* and extensive vascular invasion and infarction (in the lungs, kidneys, liver, and spleen) due to *Absidia corymbifera.* The patient was subsequently confirmed to have had $p47^{phox}$ deficiency.

Patient 2. A previously healthy 23-year-old female athlete presented to an emergency department in the summer of 2003 with acute onset of dyspnea 1 day after having performed heavy mulching. The initial chest radiograph was read as normal, and the patient was discharged from the hospital (figure 1*B*). Twenty-four hours later, her dyspnea worsened and was accompanied with fever and bilateral infiltrates (figure 2*A*). Antibiotic therapy for community-acquired pneumonia was initiated. The findings of bronchoscopic examination were not diagnostic. Fever and dyspnea progressed to hypoxia, and the patient required intubation and mechanical ventilation. A visually assisted thoracoscopic biopsy was performed on hospital day 8; observation of the specimen revealed intense pyogranulomatous inflammation, with invasive hyphae, and the specimen grew *A. fumigatus* and *Rhizopus* species (figure 3*A–C*). The dihydrorhodamine test result was consistent with $p47^{phox}$-deficient CGD. When the patient was transferred to the NIH (figure 4*A* and *B*), treatment with voriconazole, caspofungin, meropenem, and methylprednisolone led to gradual improvement. Her course was complicated by recurrent bilateral pneumothoraces and exacerbation of pulmonary inflammation upon reduction of prednisone therapy. A second biopsy was performed, and degenerating hyphal elements were seen but did not grow from the biopsy specimens. The patient recovered, with return to normal lung function (figure 4*C* and *D*). She had had several respiratory infections during infancy and an episode of "cat scratch disease," all of which had resolved with

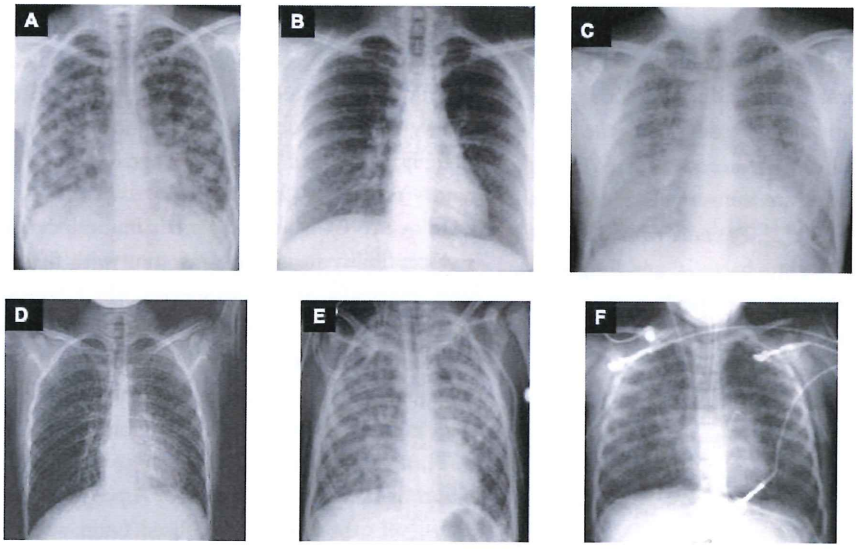

Figure 1. Chest radiographs at presentation for patients 1 *(A),* 2 *(B),* 4 *(C),* 6 *(D),* 7 *(E),* and 9 *(F).* Although the initial film of patient 2 was read as normal, the second films, shown in figure 2, were obtained <24 h later and showed bilateral infiltrates.

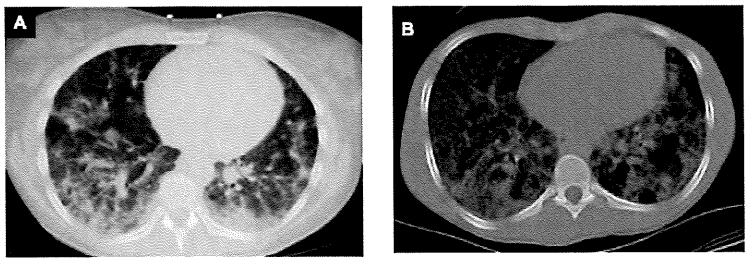

Figure 2. CT of the thorax from patients 2 *(A)* and 5 *(B)* that were obtained during hospitalization, showing bilateral pulmonary infiltrates

oral antibiotic treatment. She and her 25-year-old brother, who had had 2 episodes of "cat scratch disease" and 1 episode of cellulitis, were subsequently confirmed to have $p47^{phox}$ deficiency.

Patient 3. A 20-year-old man with known $gp91^{phox}$ deficiency who was receiving prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) therapy presented in the summer of 2001 with a of 3-day history of fever, cough, and progressive dyspnea. For 3 weeks prior to hospital admission, he had been working in the forest, chipping wood. At hospital admission, he was hypoxic, with bilateral crackles. Despite treatment with amphotericin B, rifampin, and flucloxacillin, the patient required intubation 24 h after hospital admission because of respiratory failure. Sputum and tracheal aspirate cultures grew *A. fumigatus.* Respiratory worsening, with bilateral recurrent pneumothoraces, led to death 10 days after hospital admission. No autopsy was performed.

Patient 4. A 23-year-old man with known $gp91^{phox}$ deficiency who was receiving prophylactic TMP-SMX and itraconazole, as well as prednisone (5 mg every other day), for granulomatous bowel disease, presented to the NIH in the fall of 2001 with a 1-week history of fever, progressive cough, and flu-like symptoms after working in a lawn mower repair shop. His temperature was 39.8°C, and he had tachypnea and bilateral interstitial infiltrates (figure 1*C*). A treatment regimen of levofloxacin, ceftriaxone, TMP-SMX, liposomal amphotericin B, and solumedrol (1 mg/kg daily) was initiated. Percutaneous lung biopsy was performed, and the specimen grew *A. fumigatus, Aspergillus niger, Rhizopus* species, *Penicillium* species, and *Streptomyces thermoviolaceous.* Respiratory failure led to intubation, mechanical ventilation, and bilateral pneumothoraces. The patient died 1 month after presentation. Autopsy revealed extensive abscess formation in the lungs, with abundant hyphal forms consistent with *Aspergillus* species.

Patient 5. A 64-year-old man with known $p47^{phox}$-deficient CGD, insulin-dependent diabetes mellitus, and atherosclerotic coronary artery disease was receiving prophylactic TMP-SMX, itraconazole, and IFN-γ therapy. His initial diagnosis was reported elsewhere [8]. He presented in the fall of 2001 with a 1-day history of dyspnea and cough, oxygen saturation of 91% on room air, with bilateral pulmonary infiltrates (figure 2*B*). One week previously, the man had been mulching trees in his yard. A treatment regimen of intravenous ceftriaxone, TMP-SMX, amphotericin B deoxycholate, and solumedrol (60 mg every 12 h) was initiated. Bronchoscopic examination revealed branching septate hyphae, and specimens grew *A. fumigatus, A. niger,* and *Penicillium* species. Dyspnea and hypoxia led to intubation and mechanical ventilation on hospital day 5. The patient was extubated on day 14, and steroid therapy was gradually tapered. Although his fungal infection resolved, the patient's course was complicated by diabetes, congestive cardiac failure, and recurrent respiratory failure. He died of respiratory failure 1 year after admission to the hospital. No autopsy was performed.

Patient 6. A 16-year-old boy with known $gp91^{phox}$ deficiency who was receiving prophylactic TMP-SMX and IFN-γ therapy presented in the fall of 1999 with fever, cough, dyspnea, and bilateral patchy infiltrates 1 week after riding a tractor while harvesting a field of peppermint (figure 1*D*). On admission to the NIH, a treatment regimen of ceftriaxone, TMP-SMX, amphotericin B deoxycholate, and methylprednisolone (60 mg every 12 h) was initiated. Culture of bronchoalveolar lavage specimens grew *Aspergillus nidulans.* The patient's health gradually improved while receiving therapy, and he was discharged from the NIH after 1 month, with return to normal lung function while receiving itraconazole therapy (200 mg/day) .

Patient 7. An 8-year-old boy with known X-linked CGD who was receiving prophylactic TMP-SMX and IFN-γ therapy presented in the fall of 1999 with fever, cough, rhinorrhea, headache, fatigue, and normal chest radiograph findings 1 week after playing in a moldy garden shed. Therapy with ceftriaxone and gentamicin led to some improvement, but on hospital day 3, the patient became tachypneic and hypoxic, with bilateral infiltrates. Treatment with amphotericin B deoxycholate, vancomycin, TMP-SMX, and azithromycin was initiated. On transfer to the NIH (20 days after presentation), the boy had a temperature of 38.6°C and was tachypneic and hypoxic (figure 1*E*). Therapy was changed to levofloxacin, imipenem, amphotericin B deoxycholate, and prednisone (1 mg/kg daily). An open lung biopsy was performed, and the specimen revealed

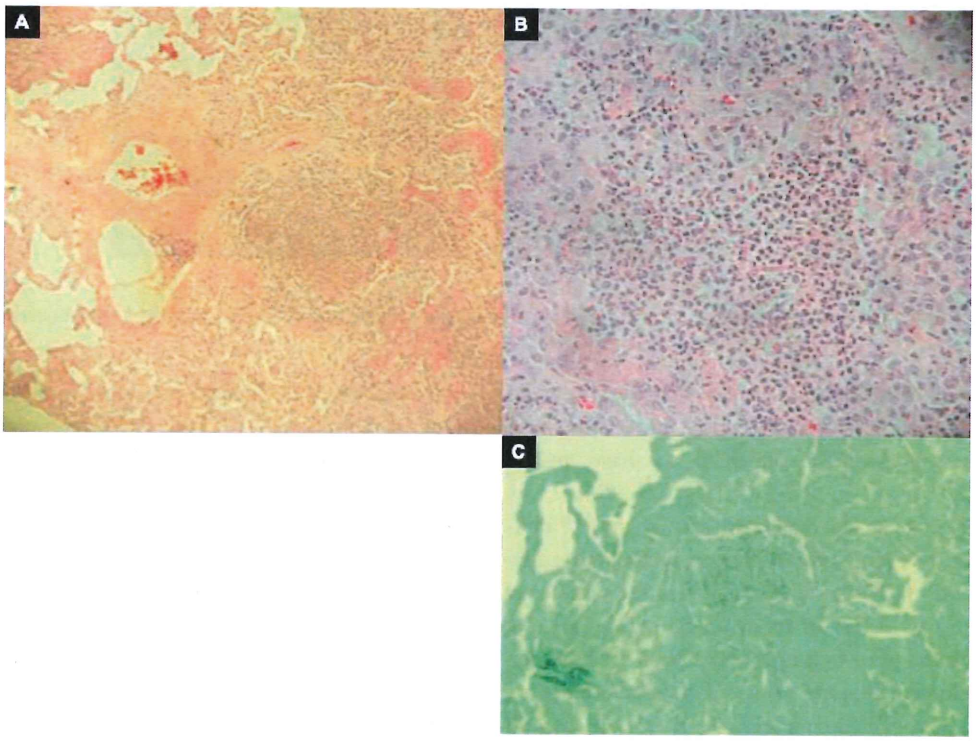

Figure 3. Photomicrographs of the lung biopsy specimen from patient 2 that was obtained on hospital day 8. *A,* Low-power view of lung parenchyma, showing intense pyogranulomatous inflammation with virtually complete effacement of lung architecture (hematoxylin and eosin stain; original magnification, ×100). *B,* Microabscess with visible hyphal structures centrally (hematoxylin and eosin stain; original magnification, ×400). *C,* Gomori-methenamine-silver stain of the section in *B,* showing numerous hyphae.

hyphae consistent with *Aspergillus* species; however, culture of the specimen showed no growth. The patient's health improved gradually, and steroid therapy was tapered. The patient was discharged from the hospital 22 days after NIH admission, with return to normal lung function while receiving amphotericin B deoxycholate therapy.

Patient 8. An 18-year-old man with known $p47^{phox}$-deficient CGD who was receiving TMP-SMX and IFN-γ therapy presented in the summer of 1995 with a 4-day history of fever, cough, dyspnea, nausea, malaise, and fatigue. Six days before hospital admission, he had swept a trailer that was used for hauling mulch. On admission to the NIH, he had a temperature of 38.4° C and was hypoxic, with diffuse bilateral infiltrates. Treatment with ceftriaxone, TMP-SMX, ciprofloxacin, amphotericin B deoxycholate, and methylprednisolone (60 mg daily) was initiated. Culture of bronchoalveolar lavage specimens grew *A. niger, Rhizopus* species, and *Streptomyces* species. Dyspnea and hypoxia worsened on hospital day 3, and granulocyte transfusions were started. The patient's health improved gradually, and he was discharged from the NIH after 1 month of itraconazole therapy (200 mg twice daily), with return to normal lung function.

Patient 9. A 10-year-old boy with a known $gp91^{phox}$ deficiency who was receiving prophylactic TMP-SMX and IFN-γ therapy presented to his pediatrician in the fall of 1991 with fever (temperature, 39.8°C), malaise, and anorexia. After 3 days without improvement, he was admitted to the NIH with fever (temperature, 38.7°C), tachypnea, and diffuse bilateral infiltrates (figure 1*F*). The patient had helped his father spread mulch several days prior to the onset of symptoms. Dyspnea and hypoxia led to intubation and mechanical ventilation. Treatment with ceftazidime, oxacillin, gentamicin, TMP-SMX, amphotericin B deoxycholate, and solumedrol (100 mg every 8 h) was initiated. Culture of bronchoalveolar lavage specimens grew *A. fumigatus, Rhizopus* species, and *Streptomyces* species. A decrease in respiratory function, bilateral pneumothoraces, and shock led to death 1 week after admission to the NIH. Autopsy revealed severe diffuse necrotizing *Aspergillus* pneumonia.

RESULTS

Clinical presentations. The above cases illustrate a temporal relationship between exposure to mold, especially mulch, and presentation with clinical pneumonia in patients with CGD. All patients presented within 10 days after an identifiable ex-

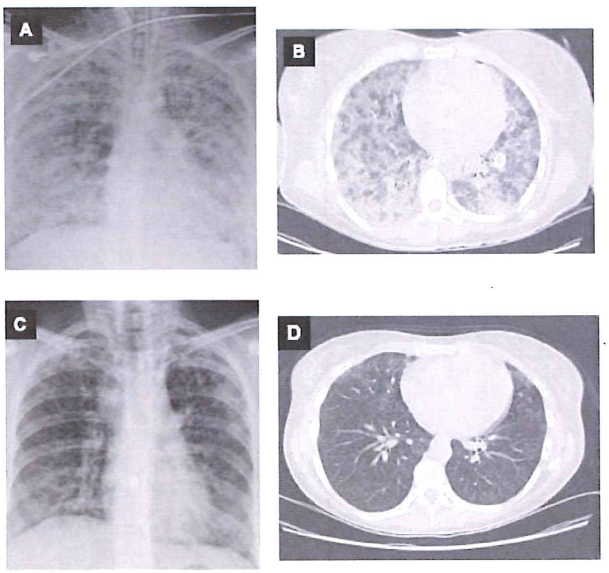

Figure 4. Chest radiographs and CT of patient 2 at transfer to the National Institutes of Health (day 10 of hospitalization; *A* and *B*, respectively) and 2 months after transfer (*C* and *D*, respectively). Note the remarkable resolution of infiltrates and the absence of pneumatoceles, despite the occurrence of pneumothoraces.

posure (table 1) to aerosolized organic material with symptoms of respiratory illness, including fever, flu-like symptoms, and cough. Dyspnea was present in 6 of 8 patients at initial evaluation, and hypoxia developed in all of the patients, except patient 6. Chest radiographs at the time of presentation revealed bilateral infiltrates in all of the patients, except patient 2, who was initially seen 1 day after exposure. By 3 days after the onset of symptoms, all patients had diffuse bilateral infiltrates. Clinical and radiographic progression was rapid. Patients presented with symptoms from May through November; cases were not reported during the early spring or winter.

Microbiologic examination. The diagnosis of fungal pneumonia was made on the basis of examination of bronchoalveolar lavage or lung biopsy specimens. Culture results were positive from at least 1 source in all patients, except patient 7, who had been extensively pretreated; however, examination of biopsy specimens revealed invasive fungal elements consistent with *Aspergillus* species. *A. fumigatus* was isolated from 7 patients, *A. niger* from 2, and *A. nidulans* from 1. Other organisms cultured specimens included *Rhizopus* species, *Penicillium* species, and *Streptomyces* species. The extent to which these organisms contributed to the clinical condition is unclear. Specimens from patient 1 revealed disseminated *Absidia corymbifera;* he had received high-dose steroidal therapy for presumed vasculitis, and this may have predisposed him to invasive infection with *Absidia* species. No routine bacteria were isolated. The rate of fungal coinfection with *Nocardia* species among patients with CGD is ~30% [7], but we recovered no *Nocardia* species from these patients, despite aggressive microbiologic search. However, all patients received antibiotics during their treatment, which would have treated infection due to *Nocardia* species. Environmental mulch specimens were obtained for culture for patients 2 and 9. Results of PFGE of environmental samples associated with patient 2 did not match the *Aspergillus* species found on culture of her lung specimen, possibly reflecting the heterogeneous nature of mulch. Two patients were supposedly receiving itraconazole prophylaxis at the time of presentation, suggesting that high levels of exposure can overcome prophylactic therapies.

Management and outcome. Initial treatment was empirical in all cases. In patients with known CGD, therapy was based on the organisms that were commonly pathogenic for these patients (table 1). Others were treated for community-acquired pneumonia. In patients whose disease progressed, steroid therapy was added, and lung biopsies were performed. For patients 1 and 2, identification of invasive aspergillosis led to the consideration of CGD. Most patients were treated with amphotericin B deoxycholate or a lipid formulation. Voriconazole and caspofungin were added only after biopsies were performed.

Five of the 9 patients died, 4 early in the course of treatment and 1 after a protracted hospitalization. Patients who survived had hospital stays of 4–6 weeks. The time from exposure to presentation and diagnosis did not appear to be linked to survival. Treatment was prolonged and included steroid therapy with a slow taper.

Genetics. Almost one-half of the patients in this series had $p47^{phox}$ deficiency, in contrast to the 25% rate of $p47^{phox}$ deficiency seen in most large series. The late presentation of CGD in patients 1 and 2 after a large exposure likely reflects the overall more-benign course of $p47^{phox}$ deficiency, which is often diagnosed later in life than is X-linked disease [6].

DISCUSSION

Invasive *Aspergillus* infection is a hallmark of compromised phagocyte immunity. Although most cases are extensively described in relation to neutropenia, it occurs in association with many immunocompromised states, as well as in association with emphysema, cavitary lung disorders, and hyper IgE syndrome. Chronic necrotizing pulmonary aspergillosis has been described in a few patients with severe underlying lung disease and low levels of circulating mannose-binding lectin [9]. Among genetic immunodeficiencies, CGD is the only one associated with invasive aspergillus infection in the absence of preexisting lung damage, occurring at a rate of ~0.15 fungal infections per patient-year [10, 11].

There have been rare reports of acute, often fatal, invasive aspergillosis in individuals thought to be immunologically normal [12–14]. Given the lack of other diseases associated with

Table 1. Clinical characteristics of 9 patients with mulch pneumonitis.

Patient	Age, years	Sex	Genotype	Season	Infiltrates	Hypoxia	Exposure	Time from exposure to presentation, days	Duration of hospital stay, days	BAL result	Lung biopsy result	Organisms on culture
1	14	M	$p47^{phox}$	Fall	Bilateral	Yes	Leaves	7	30	NP	Fungal elements	*Aspergillus fumigatus, Absidia corymbifera*
2[a]	23	F	$p47^{phox}$	Summer	No	Yes	Mulch	1	30	Not diagnostic	Fungal elements	*A. fumigatus, Rhizopus* species
3	20	M	$gp91^{phox}$	Summer	NP	Yes	Wood chips	<21	3	NP	NP	*A. fumigatus*
4	23	M	$gp91^{phox}$	Fall	Bilateral	Yes	Mulch	7	10	Negative	Inflammation	*A. fumigatus, Rhizopus* species, *Penicillium* species, *Streptomyces thermoviolaceous*
5	64	M	$p47^{phox}$	Fall	Bilateral	Yes	Mulch	10	354	Branching septate hyphae	NP	*A. fumigatus, Aspergillus niger*
6	16	M	$gp91^{phox}$	Fall	Bilateral	No	Hay	7	35	Negative	NP	*Aspergillus nidulans*
7[a]	8	M	$gp91^{phox}$	Fall	No	Yes	Garden shed	7	43	Negative	Fungal elements	None
8	18	M	$p47^{phox}$	Summer	Bilateral	Yes	Mulch	6	30	Negative	Negative	*A. fumigatus, A. niger, Rhizopus* species, *Streptomyces* species
9	10	M	$gp91^{phox}$	Fall	Bilateral	Yes	Mulch	Unknown	6	Branching septate hyphae	NP	*A. fumigatus, Streptomyces* species

NOTE. At the time of severe clinical illness, all patients had abnormal chest radiograph findings. BAL, bronchoalveolar lavage; NP, not performed.

[a] The findings of the initial chest radiographs of patients 2 and 7 appeared to be normal.

invasive aspergillosis and the similarity of those cases to the cases presented here, we suspect that they might represent undiagnosed CGD.

Environmental exposure to mold is ubiquitous. Conidia develop invasive hyphae, with an incubation period ranging from 2 days to 3 months [15]. The infectious inoculum for *Aspergillus* species is undefined, but in CGD mouse models, it was lower in the $gp91^{phox}$-deficient animals than it was in the $p47^{phox}$-deficient ones [16, 17]. Interestingly, patients 2 and 5, who were both $p47^{phox}$ deficient, had spread mulch several times previously without ill effects.

The initial symptoms of this acute fungal pneumonitis overlap with viral syndromes, community-acquired pneumonia, and hypersensitivity pneumonitides. Failure of adequate therapy directed at common pathogens should lead to consideration of other etiologies, especially when the patient has a history of an immune defect, such as CGD.

All of our patients had large exposures and relatively short incubation periods, emphasizing the importance of obtaining a careful history of the type and degree of recent exposures when confronted with a compatible clinical scenario. Similar clinical characteristics in older individuals should not preclude consideration of the diagnosis, because CGD can present later in life [18].

Radiograph findings obtained early in the course of infection may have been negative, but all of the patients developed a similar diffuse radiographic result 2–10 days after the initial complaint. In contrast, most immunocompromised individuals, especially those with neutropenia, develop nodular or focal *Aspergillus* lesions [17], which are also seen in patients with the typical fungal pneumonia associated with CGD, confirming that this diffuse interstitial presentation after exposure to mulch is clinically and pathophysiologically distinct [3].

The clinical and radiographic pattern seen in association with this syndrome is reminiscent of that seen in association with other syndromes in which there are significant host response components, such as hypersensitivity pneumonitis, which may occur as a consequence of exposure to various environmental pathogens, including bacteria, mycobacteria, fungi, proteins, metals, or chemicals [19]. Farmer's lung and "hot tub lung" are caused by exposure to thermophilic actinomycetes and exposure to *Mycobacterium avium* complex, respectively [20]. They represent inflammation with or without infection, and patients with these syndromes can present with hypoxia, cough, fever, bilateral interstitial infiltrates with necrotizing or nonnecrotizing granulomas, and patchy interstitial pneumonitis [19]. Important to understanding the use of steroid therapy, $gp91^{phox}$-deficient mice who were made to inhale heat-killed aspergillus hyphae developed extensive granulomatous lung disease, whereas normal mice did not [21]. Therefore, at least part of this clinical picture is likely to be caused by the host immune response, even in the absence of invasive fungal infection.

Allergic bronchopulmonary aspergillosis is characterized by elevated anti-*Aspergillus* IgE, eosinophilia, fleeting pulmonary infiltrates, and reactive airways. It has been reported in individuals with CGD [22] and is a differential in this syndrome, but the diagnosis is complex. Antibodies and immediate cutaneous reactivity to *Aspergillus* species are typically demonstrated [19]. Histologic examination may reveal loosely organized granulomas, with prominent interstitial infiltrates and bronchiolitis. Acute presentations or exacerbations may include nodular pulmonary infiltrates, and CT may reveal bronchiectasis. However, allergic bronchopulmonary aspergillosis is not typically associated with invasive disease, and until recently, treatment of the infectious cause was not attempted. Successful use of high-dose steroids for the treatment of allergic bronchopulmonary aspergillosis is a strong argument for the resilience of the normal host defense against *Aspergillus* species, because steroid treatment for prolonged periods is rarely associated with invasive disease.

Invasive aspergillosis is usually diagnosed when clinical suspicion is raised in the appropriate clinical context and appropriate microbiologic data is collected. One of the surrogate markers of fungal infection, galactomannan, is less reliable in patients with CGD than in others [23]. Patients with CGD often receive treatment empirically, and such treatment should incorporate agents effective against relevant pathogens, especially if a specific exposure is known.

Survival for patients with invasive aspergillosis who do not have CGD remains dismal, at 34%–42% [24]. In contrast, overall survival for patients with CGD who are infected with *Aspergillus* species other than *A. nidulans* is considerably higher [3, 6, 11]. Therapy for invasive aspergillosis has changed markedly over the past 10 years, from amphotericin derivatives to the azole derivatives (i.e., itraconazole, voriconazole, and posaconazole) [25, 26] and echinocandins [27–30]. Although the morbidity and mortality among patients with fungal infections who have CGD will likely continue to decrease, overwhelming exposure, such as through mulching, will continue to be problematic. Patients should be cautioned regarding such exposures.

Although CGD is a primary immunodeficiency, steroid therapy successfully controls inflammation [5, 6], particularly in the gastrointestinal and genitourinary tracts. Steroid use has also been reported in individuals with CGD and invasive aspergillosis [31–33]. The defect in inflammatory control is likely to be caused by inadequate degradation of inflammatory mediators, such as LTB4, C5a, and fMLF [4]. Impaired metabolism of inflammatory mediators may play a role in the acute morbidity and mortality associated with invasive aspergillus disease and requires further evaluation in mouse models. Our current practice is to use high-dose steroid treatment (1 mg/kg per day

for 1 week, followed by gradual taper) early in the course of treatment to dampen the acute pulmonary inflammation in patients with CGD who present with pneumonitis after high-level symptomatic mulch exposure.

Acute invasive pulmonary aspergillosis in the absence of known iatrogenic deficiency or AIDS should prompt consideration of CGD, regardless of patient age, in the appropriate clinical context. Early and aggressive therapy, including therapy with antifungals and steroids, is crucial. Acute invasive *Aspergillus* pneumonia following mulch exposure may be pathognomonic for CGD.

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Acute Aspergillus pneumonia associated with mouldy tree bark-chippings, complicated by anti-glomerular basement membrane disease causing permanent renal failure

Louise Butler [a,*], Tomos Brockley [a], David Denning [b], Malcolm Richardson [b], Roger Chisholm [a], Smeeta Sinha [a], Ronan O'Driscoll [a]

[a] Manchester Academic Health Science Centre, University of Manchester, Salford Royal NHS Foundation Trust, Stott Lane, Salford M6 8HD, UK
[b] National Aspergillosis Centre, Education and Research Centre, University Hospital of South Manchester, Southmoor Road, Manchester M23 9LT, UK

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ABSTRACT

A non-immunocompromised man developed acute Aspergillus pneumonia after spreading mouldy tree bark mulch. Despite normal renal function at presentation, he developed rapidly progressive glomerulonephritis with acute kidney injury due to anti-glomerular basement membrane antibodies (anti-GBM) 4 weeks later. He remained dialysis dependent and died of sepsis 10 months later. We hypothesise that he contracted invasive pulmonary Aspergillosis from heavy exposure to fungal spores, leading to epitope exposure in the alveoli with subsequent development of GBM auto-antibodies.

1. Introduction

Goodpasture's Syndrome has been widely described in the medical literature. It is characterised by a rapidly progressive glomerulonephritis due to circulating anti-glomerular basement membrane (anti-GBM) antibodies. The subject of this report developed acute pulmonary Aspergillosis following exposure to fungal spores in mouldy tree bark whilst gardening and this led to Goodpasture's Syndrome. We believe that this is the first presentation of Aspergillosis induced Goodpasture's Syndrome to be reported in the medical literature.

2. Case

A 69 year old retired man with no significant medical history was admitted to hospital with a 5 week history of increasing dyspnoea and intermittent haemoptysis. He had worked in a metal foundry and cardboard works. Antibiotics in the community had not improved his symptoms. He was a lifelong smoker of 30 cigarettes per day.

On admission (day 0), his temperature was 37.2 °C, his pulse was 72, his respiratory rate 22 per minute and his blood pressure was 120/69 mmHg. His oxygen saturation on air was 90%, falling to 84% on walking. Bilateral crackles were present at the lung bases. Chest radiograph on day 0 revealed bilateral patchy infiltrates (Fig. 1a).

Initial blood tests revealed raised inflammatory markers (CRP 225 mg/L and leucocyte count 19.5×10^9/L with a neutrophilia). Creatinine was 70 μmol/L. Initial urine dipstick was unremarkable. He was treated with amoxicillin and clarithromycin for community acquired pneumonia. Spirometry on day+5 was as follows: FEV1 1.69 L (55% predicted); forced vital capacity 2.59 L (65% predicted): FEV1/FVC ratio 65%.

On day+6, a high resolution CT of his thorax revealed widespread fine nodularity, maximal in the midzones and ill-defined peribronchial inflammatory shadowing. There was bronchiectasis (which had improved on a follow-up scan 2 months later) and patchy "tree-in-bud" change, but no radiological features of pulmonary haemorrhage. At bronchoscopy on day+7, endobronchial biopsies showed non-specific inflammatory changes, with no granulomata seen. Transbronchial biopsy was not possible as the patient's oxygen levels fell and so the procedure was abandoned. Serum ANA was weakly

* Corresponding author. *Present address*: University Hospital of South Manchester, Southmoor Road, Wythenshawe, Manchester M23 9LT, UK. Tel.: +44 7748626442.
E-mail address: louiseabutler@hotmail.com (L. Butler).

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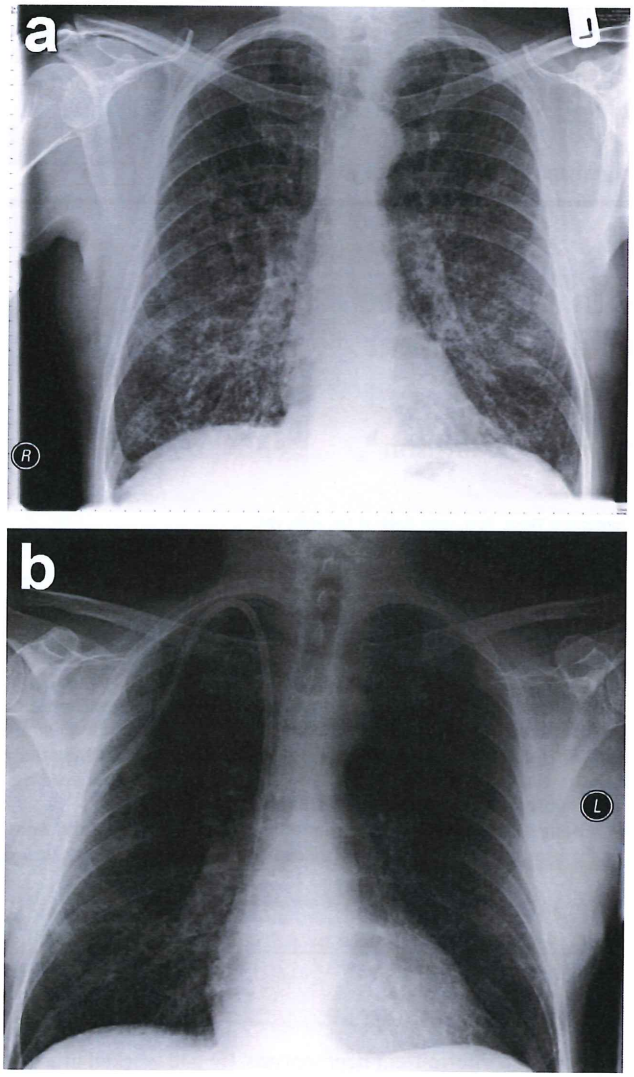

Fig. 1. Chest radiograph at presentation (a) and 2 months later (b).

positive at 1/100 (speckled pattern) with negative ENA and ANCA. Blood levels of IgG and IgA were borderline elevated. Serum IgE was elevated at 1049 ku/L. He had elevated IgG to *Aspergillus fumigatus* of 47 mgA/L (reference range up to 40 mgA/L) but his *A. fumigatus* IgE level was normal. Galactomannan assay was not available at the time of this case report. A diagnosis of acute invasive pulmonary Aspergillosis (IPA) was made and he was discharged home on day+13, on oral Itraconazole, 200 mg twice daily. His discharge creatinine was 80 μmol/L.

At clinic on day+27, his respiratory symptoms had improved substantially following treatment. His oxygen saturation was 95% at rest. He was able to climb 20 steps and the saturation did not fall below 90%. Spirometry was greatly improved at 2.4/3.9 (FEV1 78% predicted, vital capacity 90% predicted, FEV1/FVC ratio 61%). The chest radiograph showed substantial improvement (Fig. 1b). Direct questioning revealed that his symptoms had developed about 2 weeks after spreading eight, 40 L bags of foul smelling mouldy tree bark on the garden. This material was subsequently cultured in the National Aspergillosis Centre and it grew *A. fumigatus*, *Rhizopus* spp., *Sporobolomyces* spp. and bacteria (Fig. 2).

Blood results from clinic showed his renal function had dramatically deteriorated. His urea was 39.6 mmol/L and creatinine was 851 μmol/L. He was readmitted urgently and itraconazole was stopped. Renal ultrasound revealed no urinary tract obstruction.

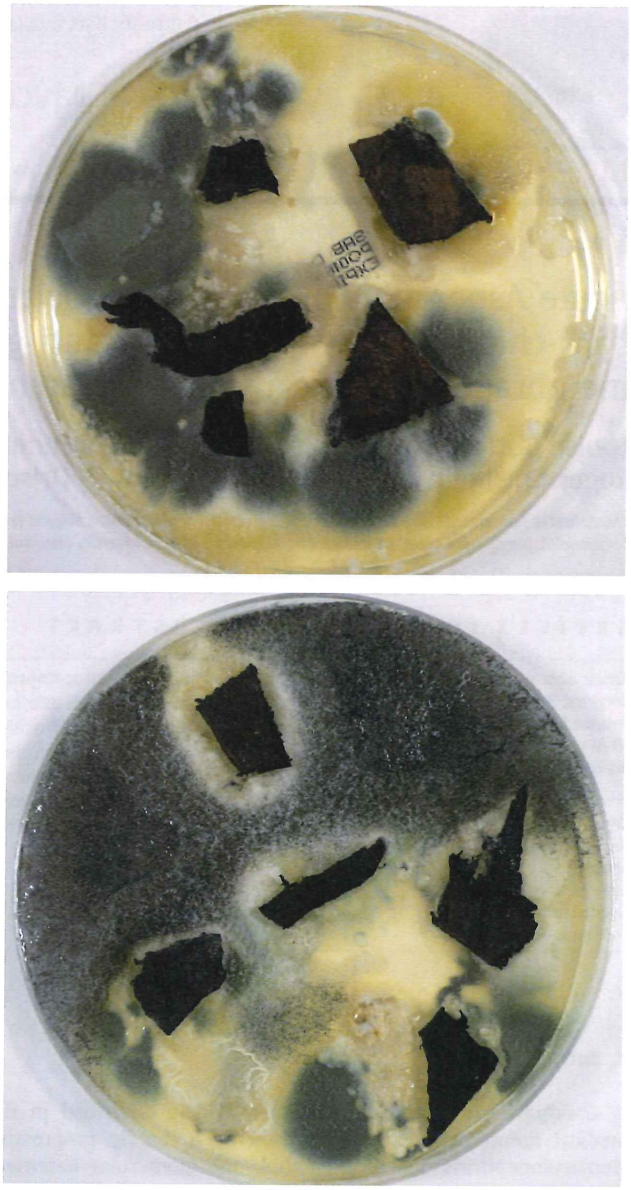

Fig. 2. Tree bark particles on fungal culture plates.

A renal immunology screen showed positive anti-glomerular basement membrane (anti-GBM) antibodies with a titre of 111 U/ml (ELISA assay) (reference range < 15 U/ml). Retrospective analysis of a blood sample from day 3 of his first hospital admission showed an anti-GBM titre of 67 U/ml at that time. Renal biopsy demonstrated necrotising crescentic glomerulonephritis with linear deposition of IgG along the basement membrane, consistent with anti-GBM disease.

On day+28, he was commenced on haemodialysis, pulsed methylprednisolone 500 mg once daily for 3 days, cyclophosphamide 750 mg (once monthly dose) and plasma exchange. Itraconazole was restarted due to the risk of reactivation of Aspergillosis. Despite these measures, he remained anuric. Subsequent anti-GBM antibody titres were significantly lower (20 U/ml 6 weeks post-presentation, 8 U/ml at 8 weeks and < 7 U/ml at 5 months post-presentation). Aspergillus IgG 6 weeks after his acute respiratory presentation had fallen to 7 mgA/L, and after 3 months total IgE was normal. Unfortunately the patient remained frail and

housebound despite haemodialysis and he died from severe sepsis and acute pneumonia 10 months after his first presentation.

3. Discussion

Invasive pulmonary Aspergillosis has specifically been reported in healthy individuals after spreading rotting tree bark whilst gardening [1–3]. In previous cases, massive inhalation of spores was thought to be the likely route of infection [3]. There is diagnostic difficulty in these cases and diagnosis is often made at post-mortem, because blood and sputum cultures have poor sensitivity [1,3]. Serological testing for Aspergillus IgG antibodies can be used in the diagnosis of IPA. In a study of patients developing IPA following bone marrow transplant, an IgG response to acute infection was noted [4]. *A. fumigatus* has been implicated in invasive disease.

Anti-GBM antibody disease is characterised by a rapidly progressive glomerulonephritis due to circulating anti-GBM antibodies. The target of these antibodies is the non-collagenous domain of the α3 chain of Type IV collagen [5]. There is a body of evidence to suggest that certain human leucocyte antigen (HLA) molecules, notably HLA-DR 15 and HLA-DR 4, are associated with the development of anti-GBM disease [6]. Subsequent analysis of our patient's HLA type revealed HLA-DR 17 and DR 4.

Hypothetically certain epitopes that are normally immunologically privileged can become exposed and perceived as foreign, leading to antibody development [7]. *A. fumigatus* conidia bind to type IV collagen (and fibrinogen), a process inhibited by free sialic acid and in particular N-acetylneuraminic acid [8]. Whether the binding of *A. fumigatus* to collagen IV in the lung altered the allergenicity of this major structural protein, allowing auto-antibodies to be formed, remains conjecture. It has been hypothesised that exposure to certain environmental factors may affect the molecular structure of α3NC1 domain, making antibody binding more likely [5].

Development of Goodpasture's syndrome has been reported following exposure to inhaled chemicals, drugs and in association with infectious disease [9]. Hidden epitopes may become exposed during these episodes.

We hypothesise that our patient contracted invasive pulmonary Aspergillosis due to heavy exposure to fungal spores whilst gardening. This led to epitope exposure in the alveoli with subsequent development of GBM auto-antibodies and acute renal failure, in an individual with pre-existing genetic risk factors. We believe that this is the first such presentation in the medical literature.

Conflict of interest

We have no conflicts of interest in the publication of this article, including financial ones to declare.

Acknowledgements

All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication. The results presented in this paper have not been published previously in whole, or part, except in abstract form. The patient himself has since died and gave verbal consent for publication prior to his death. We have now obtained written consent from his wife for this case report to be published.

If our case report is accepted for publication we would wish the colour picture to appear in the printed journal (Fig. 2). We accept the charge for this.

The contributions of the individual authors are as follows. All of the authors were involved in the clinical care of the patient described in the case. Dr. T. Brockley performed the literature searches and drafted the discussion section. Dr. L. Butler drafted the case presentation. Both of the above authors were responsible for editing and revising the article prior to submission. Dr. O'Driscoll, Dr. Sinha, Professor Denning and Professor Richardson were involved in the editing process and also provided intellectual advice of critical importance regarding the proposed disease mechanism. Dr. Chisholm provided radiology advice regarding the patient. In addition, Dr. O'Driscoll initiated the writing of the article and edited each section. He also had final approval of the article prior to submission. Dr. Butler is the main contact correspondent. All authors have reviewed the article for final submission approval.

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