

The following Synthesis describes the reports that were individually submitted by each of the external panel members and does not represent consensus advice to the agency

**Reports of Members of the
CDC External Expert Panel on Acute Idiopathic Pulmonary Hemorrhage in Infants:
A Synthesis
December 1999**

Introduction and Background:

During 1993-1994, 10 cases of pulmonary hemorrhage/hemosiderosis in infants were reported in Cleveland, Ohio. In late 1994, investigators from CDC participated along with local public health authorities and clinicians in investigating these cases. Reports of the results and conclusions of these investigations were published in the *MMWR* in December 1994 and in January 1997 (1,2). Three original reports based on this investigation appeared in the peer-reviewed literature in January 1997 (3) and in August and October 1998 (4,5). A second cluster, consisting of seven cases in Chicago during 1992-1994, was reported separately in the *MMWR* in February 1995 (6). Illness in Cleveland was reportedly associated with water damage in case homes, due to flooding and leaks, and with the presence of a toxin-producing mold, *Stachybotrys atra*; these findings were not corroborated in the Chicago investigation, however (2,7). In June 1997, a CDC scientific task force recommended to former CDC Director Dr. David Satcher that important questions remained and that several scientific concerns needed to be addressed. Dr. Satcher directed the Epidemiology Program Office (EPO) to oversee a reassessment of the agency's response to the investigations, including input from outside experts. EPO convened a multi-disciplinary group of senior CDC scientists (CDC internal working group) to study the problem and to develop an agenda for an external panel to review the evidence and make suggestions for further agency activity. Because the issues were complex and required detailed information, it was first necessary for the working group to consolidate and clarify information not readily accessible in the published and unpublished reports and to synthesize the evidence in a report for reference by the external panel.

Following completion of the working group report in June 1999, seven external panel members were selected, representing expertise in epidemiology, general pediatrics, pediatric pulmonology, mycology, and environmental/industrial hygiene. The panel was asked to: 1) review and comment on the working group's report on the methods, findings, and conclusions of the above CDC investigations; 2) review and comment on the similar cases subsequently identified in Cleveland; 3) consider whether and how the current hypotheses should be pursued and whether alternative hypotheses should be considered; and 4) make recommendations regarding CDC's further response to this issue. In addition to the working group report, the panel extensively reviewed the original published and unpublished accounts of the investigations, relevant published literature, and correspondence with the principal investigators. The panel also conducted interviews with some original investigators and with specially invited consultants and met twice as a group, on August 4 and Sept 15, 1999.

The following synthesis represents a distillation of the individual reports submitted by members of

the external panel and does not constitute a separate, independent assessment of the CDC investigations. There was considerable agreement, even unanimity, across the individual reports on the main issues under consideration; in particular, there was uniform concurrence among the panel on the significant points regarding the quality of the scientific evidence and the validity of the conclusions in the CDC investigations, as summarized in the working group report. However, not all panelists specifically commented on all issues or answered all the questions posed in the formal charge to the external panel. To the extent that there were any substantive divergences in opinion (beyond minor differences in degree of emphasis), these will be indicated below; otherwise, one can assume agreement among the panel members who expressed an opinion on the particular issue being summarized.

Panel Conclusions:

Overall, the external panel agreed that the conclusions reached by the investigators regarding association of cases of pulmonary hemorrhage/hemosiderosis with evidence of water damage or exposure to the particular fungus *Stachybotrys atra*, as conveyed in their published reports and through other mechanisms, are not warranted by the scientific evidence produced by the investigations. Panel members considered that the science in the CDC studies underlying these conclusions was “flawed” and that the postulated associations should be considered, at best, not proven. In addition, panel members felt that the published reports contained inadequate discussions of the limitations present in the investigations and the potential biases inherent in the methodology used in the studies. Panel members universally believed that the published record should be corrected to reflect this re-assessment.

More specifically, regarding identification and characterization of cases, the external panel felt that diagnosis of cases was inconsistent and uncertain. This concern applied both to the original cases and to the extended series of Cleveland cases identified since the CDC investigations, but perhaps even more so to the latter. Panel members indicated that no standard or consistent case definition was applied in the identification of cases, and it remains uncertain in the minds of the panel members whether all of the enumerated cases even represent a single clinical entity; it is correspondingly uncertain as to whether it is likely that all have a common etiology.

Additional reservations expressed by panel members regarding identification and characterization of cases included concerns regarding inconsistent sources of cases (e.g., some cases were identified through clinical sources [both retrospectively and prospectively], while others were apparently identified through review of coroner/medical examiner data). Also, there was concern regarding possible confusion or blurring of diagnoses of idiopathic pulmonary hemosiderosis (IPH) and acute idiopathic pulmonary hemorrhage in infants (termed AIPH by the CDC internal working group), which do not appear to be the same disorder.

Regarding characterization and measurement of possible exposures, the panel members felt that this aspect of the equation was also poorly and unreliably characterized. Members concluded

that protocols and procedures for environmental sampling or assessment may not have been applied in a standard or consistent manner; this reservation applied both to sampling for environmental fungi/molds and to definitions for and assessments of household water damage. Some members also expressed more pointed reservations as to whether the environmental sampling methods employed during the investigations were reliable and appropriate – in particular, whether they adequately differentiate between contamination (presence of fungus) and clinically meaningful exposure.

Additional reservations raised by many panel members included significant concerns about possible biases in the sampling procedures. These included apparently non-blinded assessments of case homes, in that the industrial hygienist performing the evaluations innocently became aware of (or inferred) the case vs. control status of some houses being assessed and sampled case houses in a manner that differed from that used in control houses (i.e., obtaining a greater number of samples from case houses); similar concerns were raised about related inconsistencies in the “aggressiveness” of sampling procedures conducted in case homes (e.g., extent to which ventilation ducts were agitated to mobilize dust for sampling). Also, concerns were expressed regarding the interval elapsing between the time of putative clinically significant exposure – whether to *Stachybotrys atra*, other environmental fungi/molds, water damage, or any other possible etiologic agent – and the time of environmental investigation/sampling. Thus, even methodologically sound environmental sampling might not accurately reflect conditions at the time the case infants contracted their respective illnesses. Finally, concern was expressed about the fact that in no instance was any proof obtained to document actual exposure by a case infant to any fungi (i.e., no serologic evidence or recoveries from case infants of organisms from biological specimens such as bronchial lavage fluids), and a theoretical question was raised by at least some panel members to the effect that conidia of *Stachybotrys atra* – the proposed vehicle by which organisms or their associated mycotoxins would be introduced in the alveoli – were too large to be considered respirable in infants.

When the panel members considered all of the above in conjunction, they specifically concluded as follows:

- Regarding the proposed causal connection between cases and *Stachybotrys atra* in particular, or other hydrophilic fungi/molds in general, this hypothesis is not scientifically proven by the CDC investigations; it may not even be strongly supported by the available evidence, both epidemiologic and biologic. Most panelists believed that this hypothesis had some plausibility and merited further investigation should opportunities to do so present themselves; there was, however, divergence in this assessment, and some panel members (notably including the panel’s mycologist) excluded plausibility altogether.
- Regarding the proposed association of cases with household water-damage (presumably as a marker for some unidentified environmental agent or socioeconomic factor), this hypothesis is not scientifically proven by the CDC investigations. Again, most panelists believed that this hypothesis was plausible and merited further investigation should opportunities to do so

present; this possibility was perhaps more strongly supported than was the case regarding association with *Stachybotrys atra* or other molds, but even on this point there remained some divergence of opinion.

Panel Recommendations:

- CDC should continue to pursue investigations of cases of acute idiopathic pulmonary hemorrhage in infants, particularly when clusters of cases can be identified, and should continue to consider possible associations between such cases and household water damage or exposure to environmental hydrophilic fungi/molds, including *Stachybotrys atra*. Other possible etiologic hypotheses should be considered, as well.
- To facilitate the above, CDC should conduct surveillance for individual cases or clusters of cases of acute idiopathic pulmonary hemorrhage in infants. Details regarding recommended approaches to such surveillance (e.g., sentinel vs. regional vs. national systems) varied somewhat among panel members who addressed this point, but there seemed to be some convergence toward a sentinel system (e.g., based on a sample of pediatric pulmonologists) with a possible regional focus in the Midwest, where the index clusters are reported to have occurred.
- To accomplish the above, a consistent standard case definition is needed and should be developed by CDC, perhaps in conjunction with academic experts on this topic (e.g., pediatric pulmonologists). Initial proposals along this line were offered by several panel members. Further, it was recommended that a clear distinction be maintained between the condition of primary interest, acute idiopathic pulmonary hemorrhage in infants, and the broader term idiopathic pulmonary hemosiderosis.
- Standard protocols for investigations, particularly regarding environmental assessments of case (and control) households are needed and should be developed by CDC. As part of such an effort, it may be necessary to develop sampling and laboratory analytic methods – e.g., for sampling and assaying molds and mycotoxins – to better translate the mere detectable presence of organisms in the environment to a clinically meaningful exposure assessment and to better quantify levels of exposure.
- At a minimum, CDC should remain involved in investigating this issue. However, panel members varied widely in opinion regarding the extent of such involvement. Suggestions on this point ranged from simply supporting or conducting surveillance and any follow-up investigations of clusters of cases; to addressing the more general question of effects of environmental fungi on human health; all the way to assuming the lead role in a concerted effort to address this broader issue, which would entail significant investments at CDC in laboratory infrastructure and methods development.
- CDC should make a concerted effort to correct the public record on this issue and should do so on an urgent basis. CDC should publish what could be termed a clarification or reassessment (rather than a retraction) regarding the quality of the evidence supporting the conclusions reached in the CDC investigations, the limitations and potential biases in these studies, and the fact that the proposed associations cannot be considered established. Panel

members generally recommended that such clarifications be disseminated in the MMWR and through communications with the peer-reviewed journals that published the original articles. Finally, panel members felt that, to the extent possible, cooperation and participation in this clarification process should be solicited of the original investigators, but that the clarification should proceed in a most timely manner and without such participation, if necessary.

Additional comments of note:

- The external panel universally praised the work of the CDC work group, in terms of both its thoroughness and scientific rigor and its fairness. Some recommended that the group or its individual members continue to be used as a resource on this general issue.
- The hypothesis that cocaine exposure was etiologically significant found no support among most panelists.

References:

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4. Etzel RA, Montaña E, Sorenson WG, et al. Acute pulmonary hemorrhage in infants associated with exposure to *Stachybotrys atra* and other fungi. *Arch Pediatr Adolesc Med* 1998;152:757-62.
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7. Green C, Etzel R, Conover C, Wylam M. Idiopathic acute pulmonary hemorrhage among infants in the Chicago area (May 14, 1997 draft; unpublished).