Prior to initiating the testing of a substance, an NIEHS/NTP staff scientist develops a research concept document. This research concept outlines the general elements for a program of study of the substance to address specific research needs raised in its nomination to the testing program. Additional information about the nomination, review, and selection of substances for study by the NTP is provided from ***Nominations to the NTP Testing Program*** (**http://ntp.niehs.nih.gov/go/nom**).

NTP Concept Document: Mold

Mold present in indoor environments was nominated to the National Toxicology Program (NTP) for toxicological studies. No specific endpoints or health effects were suggested. This nomination reflects a broad public concern regarding the non-infectious adverse health effects of fungal exposures. Recent natural disasters and significant media coverage have heightened awareness of the potential health effects of mold exposure. In its discussions regarding the nomination, the Interagency Committee for Chemical Evaluation and Coordination (ICCEC), acknowledged the difficulties inherent in evaluating indoor mold exposures, including determination of the appropriate test article (whole organism or mycotoxin), selection of the appropriate fungal species and strain for evaluation, toxicological endpoints and testing strategies, and route of exposure. The issue is further complicated by the biology of these organisms, in that there are multiple life stages for these organisms, and the physical (i.e. spores, hyphae) and chemical (mycotoxins, proteolytic enzymes) agents produced may vary with life stage and growing conditions.

In May 2004, an Institute of Medicine (IOM) committee concluded that there is sufficient evidence of an association between mold and other factors related to damp conditions and several respiratory ailments: upper respiratory tract symptoms, cough, wheeze, hypersensitivity pneumonitis in susceptible persons and asthma symptoms in sensitized persons. However, the IOM committee concluded that there was inadequate or insufficient evidence to make conclusions for many other health outcomes, including rheumatologic and other immune diseases, neurological symptoms, cancer and reproductive effects. Notably, the IOM report ("Damp Indoor Spaces and Health") indicated that none of these health outcomes met the definitions for the category of "limited or suggestive evidence of no association". The committee also identified numerous research needs. Along with recommendations for more research in exposure assessment and standardization of definitions (e.g., "dampness"), the committee recommended that animal studies be initiated to evaluate the effects of chronic exposures to mycotoxins via inhalation. However, the NIEHS Nominations Faculty recommended that toxicological studies with the whole organism be considered since it is likely that if noninfectious adverse effects are occurring, they are a result of exposure to multiple biologically active fungal components and not solely to specific fungal mycotoxins. Although many species of fungus can be found in indoor environments, Stachybotrys chartarum (also known as S. atra and S. alternans) was chosen as the representative fungus for toxicological studies largely because it has received considerable attention in the mass media. There is also an extensive body of literature on Stachybotrys, although long-term studies by a relevant route of exposure have not been conducted. The NTP Board of Scientific Counselors and Executive Committee (EC) both endorsed the idea of studying molds but suggested that the NTP should consider studying more common indoor fungi such as

Aspergillus and Penicillium. The final determination reached by the NTP EC was that indoor molds should be studied and emphasis should be placed on methods development for standardized production of organisms and/or specific components, and evaluation of potential toxicants at multiple life stages and under varying growth conditions.

Earlier in 2006, a group of scientists familiar with the challenges in mold toxicology met to discuss the NTP nomination. Although there was consensus that the NTP should conduct toxicity studies with molds, there was not currently sufficient information on what to study or how to study it to move forward at this time. The group suggested that the NTP studies focus on neurotoxicity, reproductive and cardiopulmonary effects, which were data gaps identified in the IOM report on Damp Indoor Spaces and a previous NIEHS workshop. The group recommended several approaches for identifying and prioritizing organisms and endpoints to evaluate.

The project leader presented an overview of the health effects and complexities involved in the design and conduct of mold studies for concept review. The committee explored a number of issues including: how data could be used in regulatory setting; could quantitative dose-response data be generated; would controlled aerosol exposures be possible; and that the lack and toxicological relevance of good HTS screening assay endpoints at present precludes use of this approach to decide on suitable materials for in vivo studies. After extensive discussion the concept review committee made the following recommendations:

1. Explore the feasibility of conducting studies of "real-life" exposure scenarios to mimic the conditions found in damp or water-damaged buildings. These studies would be conducted in multiple strains of rodents to address issues of host susceptibility. As much as possible, try and tie these studies in with ongoing NIEHS efforts evaluating health effects in humans following mold exposures.

2. Convene an expert panel of 15-20 individuals to address the three areas of health effects, biomarkers of exposure and methods of exposure. The purpose of the panel would be to solicit expert input on how to large scale conduct "real-life" exposure rodent studies and the toxicological endpoints to be measured.

The group also suggested that it might be useful to assemble a list of identified fungal products to be nominated for inclusion in HTS studies. These could include, but not be limited to fungal toxins, microbial volatile organic compounds and proteolytic enzymes.

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