SHS exposure may indeed negatively affect the health of patients with COPD.

The finding that indoor $PM_{2.5}$ concentrations had negative respiratory health effects among both smokers and nonsmokers has important implications for future research (3). We also found that SHS exposure had adverse respiratory health effects in both smoking and nonsmoking bartenders (7). Most previous research on the health effects of SHS exposure, however, has excluded smokers. These studies have implicitly assumed that the effects of passive smoking are inconsequential when compared with those of direct personal smoking. SHS exposure can cause very high levels of particulate and other pollution, especially in bars and other workplaces (8). Moreover, studies of outdoor pollution indicate that smokers are actually more susceptible to the respiratory effects of some pollutants (9). In sum, the evidence now indicates that both smokers and nonsmokers should be included in studies of SHS exposure, other pollutants, and respiratory health.

The study by Osman and colleagues provides new data about the impact of NO_2 in COPD (3). NO_2 is another major indoor pollutant produced from combustion, particularly during gas stove or gas heater use. Among adults with asthma, gas stove use or indoor NO_2 exposure has not been consistently associated with more severe respiratory symptoms or pulmonary function impairment (10–13). In the Osman study, there was also no convincing evidence that indoor NO_2 levels negatively affected COPD-related health status. This is an area, however, that requires further study. Because outdoor NO_2 concentrations appear to have negative health effects in COPD, further evaluation of indoor NO_2 effects, especially on pulmonary function, will be needed before NO_2 exposures can definitively be declared safe for patients with COPD (14, 15).

On a global scale, a large burden of obstructive lung disease symptoms is attributable to indoor combustion (16). The burning of biomass fuel for heating and cooking is a major source of indoor pollution in the developing world. Biomass smoke contains high levels of particulate and other pollutants, which are often released into poorly ventilated spaces. Although the evidence is mounting that biomass smoke may be a cause of COPD, its effects on persons with established obstructive lung disease are poorly understood.

Obstructive lung disease appears to predispose to a higher risk of adverse health effects from indoor particulate pollutants, especially SHS. Further research is needed to elucidate the prospective effects of indoor pollutants on adults with COPD, including pulmonary function endpoints. Studies that simultaneously consider a broad range of indoor exposures, including allergens and pollutants, would help to fully characterize the health effects of the indoor environment in COPD. In developing countries, more research is needed to determine the effects of biomass smoke on the development and clinical course of obstructive lung disease.

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Occupational Bronchiolitis Obliterans Masquerading as COPD

Seven years ago, a cluster of severe bronchiolitis obliterans cases among former workers of a small rural microwave popcorn plant precipitated the detective work which identified the hazard of volatiles derived from butter flavoring. In the initial report (1),

diacetyl, a diketone which imparts buttery aroma and flavor to foods, was described as a marker of flavoring exposure. Diacetyl exposure was associated with abnormal lung function, decreased forced expiratory volume in one second (FEV_1), and the mixer job title that was subsequently shown to be highest risk in industry-wide investigation (2). The same severe fixed obstructive syndrome in many flavoring manufacturing workers (3, 4) substantiates the hazard of diacetyl, and biologic plausibility now exists in rodent toxicology studies (5–7).

In the current issue of the *Journal* (pp. 498–504), van Rooy and coauthors (8) make several substantial contributions to the understanding of this newly recognized occupational hazard to flavoring-exposed workers. First, diacetyl manufacture produced at least four cases of severe bronchiolitis obliterans syndrome among 103 process operators in a historical cohort, including the post-study case found in one of the ten nonparticipants. Second, none of the four cases had been recognized as bronchiolitis obliterans or as occupationally related, which is typical of the cases being found throughout both microwave popcorn and flavoring manufacturing industries. To identify flavoring-related bronchiolitis obliterans, physicians need to consider the diagnosis. Third, the risk of flavoring-related pulmonary disease is not a new occurrence, but rather long-standing in industry, in that the first and most severe case occurred in 1970 after two years of employment. As in the microwave popcorn industry, two other cases in this diacetyl manufacturing plant had similar short latency between employment and symptom onset. Identifying excessive decline in pulmonary function before FEV_1 becomes abnormal is particularly difficult over the short periods of time in which flavoring-related bronchiolitis obliterans can develop. Reference limits of longitudinal FEV_1 decline depend on both precision (spirometry quality) and time interval (9, 10). With good quality spirometry, 8% or about 330 ml declines in FEV_1 over 6 to 12 months can be used as a criterion for investigation and follow up (11). The excessive longitudinal FEV_1 declines demonstrated in the two Dutch cases with spirometry data during employment would have been difficult to identify as abnormal early on, when prevention of an irreversible disease was most needed. Fourth, a cross-sectional approach to screening current workers at any point during the plant's existence would have missed the cluster and underestimated disease burden among those ever-employed at the plant. This observation should temper interpretation of low prevalences being found among current workers in flavoring-exposed workforces, since affected workers with severe airways obstruction commonly leave employment. In sum, the evidence marshaled by studying this historical worker cohort is daunting for physicians charged with early identification of this disease in workers with diacetyl and other flavoring component exposures.

van Rooy and colleagues (8) appropriately emphasize the restricted set of exposures in diacetyl manufacture, in contrast to the complex mixture of chemicals in flavoring manufacture. The authors mention that the contribution of acetoin and acetaldehyde to bronchiolitis obliterans syndrome cannot be excluded, but historical acetaldehyde levels were far below the permissible exposure limit of 360 mg/m^3. In the setting of calls for regulation, workers' compensation liability, and third-party litigation against suppliers of flavorings, any uncertainty regarding cause impedes preventive action. For the association between diacetyl and fixed obstructive lung disease, many criteria for causal inference have been fulfilled. (*1*) The strength of association between diacetyl exposure and severe fixed obstruction is about 10-fold in this plant, since FEV_1s less than 40% predicted occur in 0.42% of never-smokers in the age range of these cases (50–72 yr) and in one of 1,000 never-smoking adults. Similar risk ratios have been found in production worker subsets of some flavoring and microwave popcorn facilities. (*2*) Consistency of the association exists in studies of workers in microwave popcorn, flavoring, and diacetyl manufacture. (*3*) The temporal requirement for the exposure to precede the health outcome was met for incident cases in the sentinel microwave popcorn plant, and control of exposure resulted in lowering of risk (4). (*4*) An exposure–response relation exists. (*5*) Biologic plausibility exists in experimental rodent toxicology studies. Thus, the collective evidence for diacetyl causing a respiratory hazard supports action to minimize exposure to diacetyl, even if contributions by other flavoring chemicals exist. The study by van Rooy and coworkers limits the candidates for new regulation to diacetyl and acetoin. Diacetyl is the more reactive, volatile, and concentrated of the two ketones, which often occur in the same work environments, and its control makes good sense as we await animal toxicology studies to evaluate the potential hazard of acetoin and several aldehydes.

Although the hazard of diacetyl is not in question, uncertainties do remain. The spectrum of health effects related to flavorings may be broader than fixed obstruction. Asthma (12), bronchiolitis obliterans with organizing pneumonia (13), granulomatous pneumonitis (4, 14), tracheo- and bronchiomalacia (1, 8), fibrosis (4), and systemic symptoms (1) without obstruction have all been reported in flavoring-exposed workers. Safe levels of exposure are not yet clear, and little demonstration of the effectiveness of workplace intervention exists to date. Our understanding of toxicologic mechanism, genetic predisposition, and early markers of injury are all ripe for investigation. van Rooy and colleagues (8) observe that a diagnosis of chronic obstructive lung disease hinders investigation of occupational etiology. Perhaps bronchiolitis obliterans is a more common finding than we think in those with obstructive disease, including severe asthma with only partial reversibility. The occupational contribution to chronic obstructive lung disease is itself substantial, after taking cigarette smoking into account. The median population-attributable risk for the proportion of chronic bronchitis or chronic obstructive lung disease due to work-related factors is 15% among many recent studies (15). Among never-smokers, the attributable fraction may be as high as 31% (16). Never-smoking patients and young smokers with obstruction may be sentinels for new causes of airways disease that, like flavoring, have been present for decades but await recognition through clusters and epidemiologic study.

The findings and conclusions in this editorial are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Editorial

Notes from the NHLBI Director

National Heart, Lung, and Blood Institute Core Values and Shaping the 2007 Budget

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With fiscal year 2007 well under way, we write to report on the status of our budget for the National Heart, Lung, and Blood Institute (NHLBI). As a result of a Congressional joint resolution, the NHLBI received an allocation of $2,918,808,000, which represents an increase of about one percent over the comparable figure for fiscal year 2006.

The NHLBI has a longstanding and powerful commitment to preserve and enhance investigator-initiated research and to develop and support new investigators. In these difficult times, the Institute's top priorities will be to stay true to these core values. To accomplish this objective, we have developed a number of strategies to assist investigators in launching successful research careers and riding out tough times. Several policies are designed to ease the path to independence for new investigators (http://www.nhlbi.nih.gov/funding/policies/operguid.htm).

- *Investigator-initiated research*. We intend to use about 70 percent of the NHLBI budget for research project grants and to scale back, as necessary, the release of Institute-initiated programs.
- *New investigators*. We are strongly committed to expanding the pipeline of new talent needed to support biomedical research in the future. Since fiscal year 2005, we have been giving new investigators an advantage by increasing the payline for their regular research grant (R01) applications by 5 percentile points and funding their R01s for the full recommended project period. Applicants who fall short of the new-investigator payline by 6 to 10 percentile points are offered an opportunity to address the concerns of the initial review group and receive an expedited administrative review.
- *First-time competing renewals*. Recognizing that the initial competing renewal for a first-time R01 holder often represents a make-or-break career watershed, we offer a more generous payline (5 percentile points higher) for such applications.
- *NIH Pathway to Independence Award (K99/R00)*. To assist new scientists in achieving independent research faculty positions, we have set aside funds to support the new K99/R00 program. In fiscal year 2007, the NHLBI will fund approximately 25 awards.
- *NIH Director's New Innovator Award*. The NHLBI strongly supports the NIH Director's New Innovator Award, established this year to provide funding for new investigators to pursue creative research avenues that have the potential for exceptional impact on biomedical science.
- *NIH Director's Bridge Award*. We recognize that continuity of grant support is a critical issue for established investigators as well. Accordingly, the NHLBI will support the NIH Director's Bridge Award, which is designed to assist new and established grantees whose competing renewal grant applications fall just beyond the payline. The award will provide one year of additional, limited support to enable principal investigators to continue their research while strengthening a resubmission application.

In addition to the measures mentioned above, we are pleased to report that in fiscal year 2007, the NIH Common Fund is receiving a direct allocation from Congress, such that NHLBI monies that would have been committed to NIH Roadmap programs will now be retained by the Institute. This amounts to about $35 million, which will be used to bolster investigator-initiated research and training programs.

We appreciate the expertise and wisdom that the scientific community provided in the development of our newly completed Strategic Plan (http://www.nhlbi.nih.gov/strategicplan/). You will be hearing more from us about the Strategic Plan in the coming months. We anticipate that many of the goals stated within the Strategic Plan will be accomplished through investigator-initiated research. Our commitments to supporting investigator-initiated research and new investigators may require that we scale back to some extent the development of Institute-initiated programs. It will also require that we establish a judicious timetable for implementing our Strategic Plan.

We are grateful for the generous support that the NHLBI has received from the community of investigators it serves, and we look forward to close collaborations with you as we push the frontiers of biomedical science forward. We will continue to do everything in our power to limit the adverse effects of the current budget constraints and preserve the vitality and momentum of the research enterprise. We welcome comments, questions, and concerns and are pleased to hear from readers at any time. We look forward to continuing to work with you as we face our challenges and opportunities together.

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