11 Research Needs

In this chapter, knowledge gaps pertaining to diacetyl, 2,3-pentanedione and flavoring-induced lung disease are identified. General areas of need include environmental research to better measure and control exposures to flavoring substances, clinical and field studies on the epidemiology of flavoring-induced diseases, research related to personal protective equipment, and toxicological studies concerning the etiology of flavoring-related diseases.

Research is needed to characterize exposures associated with various job tasks in the food production industries and to develop and validate control measures to reduce exposures to potentially harmful substances. This research should address questions such as:

- Can a more sensitive analytical method be developed for 2,3-pentanedione that is comparable to the sensitivity and lower limit of quantification for diacetyl? Can more sensitive analytical methods be developed for other flavoring compounds?
- How does one effectively measure exposure to airborne particulate for diacetyl and other flavoring compounds? Would sampling and analytical methods be influenced by particle size?
- Can a real-time, portable sampling device be developed that will allow for both full-shift and peak exposure measurements for diacetyl and other flavoring agents?
- Is canister sampling with GC-MS analysis comparable to thermal desorption GC-MS for flavoring volatile organic compounds?
- What are appropriate variability estimates for occupational exposures in food production facilities?
- What jobs have peak flavoring exposures that may be pertinent to health risks?
- What are the major food production processes involving flavorings that require engineering controls?
- What are the exposures for the downstream employees in food production processes or workplaces?
- What work practice interventions most effectively reduce employee exposure?

Clinical and field research studies should address such questions as:

- Is the asthma excess in flavoring employees a misdiagnosis of fixed obstruction or part of the range of flavoring-related diseases or their natural history?
- What flavoring or other chemicals are responsible for the increased prevalence in restrictive spirometry seen in one flavoring manufacturing employee population?
- To what extent does the spectrum of diacetyl-related lung disease include restrictive lung disease?
- Because obliterative bronchiolitis can be present pathologically with normal spirometric measures, should exposed employees with exertional shortness of breath be removed from further flavoring exposure or followed more intensively by clinicians until the natural history becomes clear?

- What is the natural history of flavoring-induced illness with continuing exposures, and with cessation of exposure?
- Do biomarkers of flavoring exposure or lung injury exist that could be used in employee screening or diagnosis?
- Are there genetic or epigenetic markers for susceptibility for diacetyl-related respiratory effects?
- Can longitudinal examination of spirometry in flavoring-exposed employees for excessive declines be effective in primary and secondary prevention of lung impairment in flavoring employees? What minimum quality requirements in spirometry equipment, technician performance, interpretation, and physician follow-up are necessary for flavoring-exposed employee medical surveillance to be effective?
- Can the effectiveness of a proposed standard, given the limitations of risk assessment, be substantiated by employee medical surveillance?
- Should flavoring-exposed employees undertake their personal medical surveillance with peak flow meters or portable spirometers?
- Could mortality studies of flavoring employees elucidate other potential flavoring-related risks such as kidney toxicity or burden of respiratory mortality?
- What is the prevalence of increased respiratory morbidity in employees making scented candles, hard candies, snack foods, dairy products, baked goods, e-cigarettes, fragrances, etc.?
- What nonflavoring, volatile chemicals have similar inhalation toxicity for employees in industries already shown to have excess obstructive lung disease in population-based studies such as NHANES or in clusters of obliterative bronchiolitis in specific industries, such as plastic-reinforced glass fibers in boat building or in U.S. soldiers returning from Iraq and Afghanistan?

Research needs have been identified in the area of respirators and other personal protective equipment that will continue to have an important role in employee protection.

- What methodology should be used for respirator selection for mixed chemical environments?
- What gloves should be used in the workplace and how frequently should they be changed?
- What guidance can be provided regarding change-out schedules for organic vapor cartridges used in flavoring production in mixed chemical environments?
- What are the end-of-service indicators for respirators used in mixed environments?

Unanswered questions about the mechanisms of health effects of diacetyl and 2,3-pentanedione, include the following:

- What are the chronic respiratory toxicological and pathophysiological effects of diacetyl inhalation?
- Can a CFD-PBPK model be developed for diacetyl or 2,3-pentanedione absorption during chronic exposure?
- What are the roles of metabolism and adhesion molecules in diacetyl or 2,3-pentanedione toxicity?
- Do biomarkers of flavoring exposure or lung injury exist that could be used in employee screening or diagnosis?
- Are there genetic or epigenetic markers for susceptibility for diacetyl-related respiratory effects?
- What is the role of protein damage in diacetyl or 2,3-pentanedione toxicity?

- What is the role of immunotoxicity in diacetyl or 2,3-pentanedione toxicity?
- What is the relationship between the chemical structure of diacetyl and 2,3-pentanedione and pulmonary toxicity?
- Do nonflavoring volatile workplace chemicals implicated in causing obstructive lung disease have mechanistic similarities to diacetyl or 2,3-pentanedione?
- Can structure-activity relationships be developed that predict the airway toxicity of volatile compounds?
- Do inhalation-related and lung transplant-associated obliterative bronchiolitis share common mechanisms of injury?
- What role do other components of butter flavoring play on diacetyl-induced respiratory tract injury?
- What is the respiratory toxicity of substitutes (or other systems' toxicity) for diacetyl and 2,3-pentanedione?
- What are the pathophysiological mechanisms of acute and chronic diacetyl or 2,3-pentanedione toxicity?
- What characteristics of butter flavoring powder contribute to airway injury?
- Can in vitro models of acute and chronic exposures to flavorings be developed to provide information useful to risk assessment?
- What is the relative respiratory toxicity of flavoring vapors compared to powders?
- Do mixed exposures of alpha-diketone flavorings have different airway epithelial toxicity from single agents in rodents?
- What laboratory tests are the best predictors of flavoring compounds that cause airway injury in humans?
- What is the role of diacetyl and other reactive carbonyl compounds in cigarette smoke (both tobacco cigarettes and e-cigarettes) in contributing to chronic obstructive pulmonary diseases?
- At what steady-state concentration of diacetyl, or above what cumulative exposure to diacetyl, does a fulminant, progressive pathological process initiate as opposed to a regular, constant, relatively lower rate of deterioration (as usually reflected in pulmonary function or structural changes)? Does this accelerated decline continue after cessation of exposure?

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