EXPRESS STATEMENT*

Flavorings-Related Lung Disease

Revised and reviewed by members of the
SOT Inhalation and Respiratory Specialty Section
in May 2016

Background

In 2000, the National Institute for Occupational and Safety Health (NIOSH), the federal institute that conducts research to prevent work-related injury and illness, investigated workers at a microwave popcorn packaging plant in Jasper, Missouri. Eight former workers at the packaging plant developed illnesses involving fixed airways obstruction on lung function tests. NIOSH also recorded similar findings among current workers and at other plants that use or manufacture flavorings. The obstructive lung disease in affected workers sometimes met clinical criteria for an uncommon lung disease called bronchiolitis obliterans.

Subsequent studies identified obstructive lung disease in other workers exposed to flavoring vapors, including workers in flavoring manufacturing and coffee production. The spectrum of lung function changes now appears to include restrictive as well as obstructive lung disease. The lung disease in workers exposed to flavoring vapors has been called popcorn workers' lung or flavoring-associated lung disease. Symptoms include cough and shortness of breath. Workers also may experience eye, nose, throat, and skin irritation and, in some cases, chemical eye burns that require medical treatment. The disease can be severe and sometimes fatal.

Flavorings are composed of various natural and manmade substances. They may consist of a single substance, but more often, they are a complex mixture of several substances. Most chemicals used in flavorings have not been tested for respiratory toxicity via the inhalation route, and occupational exposure limits have been established for only a small number of these chemicals.

Diacetyl (2,3-butanedione), a 4-carbon-α-dicarbonyl flavoring that produces the flavor of butter in many products, including butter itself, is implicated in the etiology. The severe lung disease seen in workers making a popular snack food and the toxicity of something as common as butter

flavoring have captured public attention. While much remains to be learned, toxicology studies have consistently demonstrated airway toxicity of diacetyl and the closely related α-dicarbonyl flavoring, 2,3-pentanedione. In aggregate, the human studies combined with toxicology studies provide a clear understanding of the potential for respiratory tract injury from these inhaled α-dicarbonyl flavorings. An example of true translational toxicology research, NIOSH has drafted a document containing the criteria for recommended exposure limits for diacetyl and 2,3-pentanedione .

Research

In NIOSH workplace evaluations, case clusters of fixed obstructive lung disease have been documented among workers where butter flavorings are used or produced. Less severe, but demonstrable, airway obstructive disease has been observed in workers exposed to diacetyl with concentration-response relationships between the degree of airway obstruction and the magnitude of diacetyl exposure being apparent. While most attention has focused on workers exposed to volatile chemicals in butter flavorings at microwave popcorn plants, other reports indicate that other flavoring and food manufacturing workers exposed to these flavorings also may be at risk. This includes workers in flavoring manufacturing and coffee production.

In the early 2000s, NIOSH researchers demonstrated that inhaled butter flavoring vapors damaged the epithelium in the large airways of rats acutely exposed to these vapors. This was an important finding because airway epithelial damage in the airways, albeit the small airways, is believed to be a key event in the development of bronchiolitis obliterans in humans. Subsequently, NIOSH researchers demonstrated similar changes in the large airways of rats inhaling diacetyl as a single agent. Moreover, repeated inhalation exposure or exposure of the lungs by an alternate route (instillation) to diacetyl produced lesions in rats reminiscent of bronchiolitis obliterans in humans. Similar lesions are caused by the closely related compound 2,3-pentanedione.

National Institute of Environmental Health Sciences (NIEHS) studies indicated that exposure to diacetyl is harmful to the large as well as small airways of mice. In those studies, mice were exposed to diacetyl at concentrations and durations comparable to historical exposures at microwave popcorn packaging plants. Extensive mathematical modeling studies provide strong evidence that, in humans, significantly greater amounts of inhaled diacetyl penetrate to the small bronchiolar airways than in rodents. This supports the concept that rodent inhalation studies may actually under-predict the small airway risk to humans.

Potential mechanisms of action of diacetyl also are being revealed. Diacetyl is a reactive compound that reacts with specific entities in cellular macromolecules, and its reactivity profile

is such that it may escape many of the cellular pathways that typically offer protection against reactive toxicants. Importantly, the structurally related α-dicarbonyl compounds, 2,3-pentanedione and 2,3-hexanedione, also cause lung injury with their potencies relative to diacetyl correlating with their chemical reactivities. This body of research clearly indicates that volatile reactive α-dicarbonyl compounds, especially diacetyl, are likely key contributors to the pulmonary injury that has been observed in flavoring and food manufacturing workers exposed to sufficient amounts of these vapors.

Gaps in Knowledge

In addition to diacetyl, other vapors present in the workplace environment, including other reactive α-dicarbonyl compounds, may have a direct role in causation of airway disease and/or may modify the response to diacetyl itself. The recent mechanistic studies on α-dicarbonyl compound reactivity and toxicity provide a framework to study and potentially understand the role of other similar vapors in the workplace environment. Thus, there is a critical need to understand the toxicity of these potential substitutes.

There also is a need to more fully understand the mechanism of diacetyl toxicity and to understand the structure-activity relationships responsible for diacetyl toxicity. There is a critical need to better define the effects of long-term, chronic exposure to diacetyl and other volatile reactive α-dicarbonyl compounds. Towards that end, chronic diacetyl inhalation toxicology studies are being conducted by the US National Toxicology Program. Further, it is important to understand how diacetyl vapors are absorbed in the lungs, particularly under workplace conditions. Finally, 2,3-pentanedione inhalation can alter gene expression in the brain, suggesting a need for additional investigation of the neurotoxicity of inhaled dicarbonyl compounds.

Relevant Links and Resources:

The US National Institute for Occupational Safety and Health (NIOSH)

- Topic page on Flavorings-Related Lung Disease: http://www.cdc.gov/niosh/topics/flavorings/
- Draft *Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione*: http://www.cdc.gov/niosh/docket/archive/pdfs/NIOSH-245/DraftDiacetylCriteriaDocument081211.pdf
- Draft publication chapter on Updated Quantitative Risk Assessment Based on Animal Data: http://www.cdc.gov/niosh/docket/review/docket245A/pdfs/245-A-Draft_Chapter6.pdf

- Draft publication chapter on Hazard Prevention and Control of Exposure to Diacetyl and 2,3-Pentanedione: http://www.cdc.gov/niosh/docket/review/docket245A/pdfs/245-A-Draft_Chapter8.pdf
- Guidance on reducing exposures to diacetyl, 2,3-pentanedione and structurally related α-dicarbonyl compounds, *Best Practices: Engineering Controls, Work Practices, and Exposure Monitoring for Occupational Exposures to Diacetyl and 2,3-Pentanedione*: http://www.cdc.gov/niosh/docs/2015-197/pdfs/2015-197.pdf
- 2008 blog post on diacetyl and food flavorings: http://blogs.cdc.gov/niosh-science-blog/2008/11/10/diacetyl/

The Flavor and Extract Manufacturers Association of the United States

- *Respiratory Health and Safety in the Flavor Manufacturing Workplace*, which was updated in 2012: http://www.femaflavor.org/sites/default/files/linked_files/FEMA_2012%20Respiratory%20Health%20and%20Safety.pdf
- The Safety Assessment and Regulatory Authority to Use Flavors-Focus on E-Cigarettes, updated on March 3, 2015: http://www.femaflavor.org/sites/default/files/FEMAGRAS_Ecig_March_3_2015.pdf

The US National Toxicology Program has conducted animal toxicology studies on diacetyl and acetoin, the major volatile components of butter flavoring, and 2,3-pentanedione, a diacetyl substitute.

- Testing status of 2,3-butanedione (diacetyl): http://ntp.niehs.nih.gov/testing/status/agents/ts-m940009.html
- Testing status of acetoin: http://ntp.niehs.nih.gov/testing/status/agents/ts-m990018.html
- Testing status of 2,3-pentanedione: http://ntp.niehs.nih.gov/testing/status/agents/ts-08010.html