

Airway Epithelial Toxicity of the Flavoring Agent 2,3 Pentanedione

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. Medical tests on affected workers revealed an uncommon lung disease called bronchiolitis obliterans. 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 may also 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, a 4-carbon-diketone 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 long captured public attention. An example of true translational toxicology research, the NIOSH research is expected to result in regulatory

changes with the inclusion of diacetyl and diacetyl-related flavorings on this year's agenda for the Occupational Safety and Health Administration (OSHA).

Research

In NIOSH workplace evaluations, case clusters of fixed obstructive lung disease have been documented among workers where flavorings are used or produced. Recent attention has largely focused on workers exposed to volatile chemicals in butter flavorings at microwave popcorn plants, but other reports indicate that other flavoring and food manufacturing workers exposed to various flavorings may be at risk.

In 2002, NIOSH researchers demonstrated that inhaled butter flavoring vapors damaged the airway epithelium. This was an important finding because airway epithelial damage in small airways is believed to cause bronchiolitis obliterans. In 2008, NIOSH researchers demonstrated similar changes in the airways of rats inhaling diacetyl. A 2009 study developed a model that predicated that the deep lung of workers actually received a higher dose than the deep lung of rats at a given ambient concentration of diacetyl. In 2008, the National Institute of Environmental Health Sciences, working in collaboration with researchers at Duke University, completed a study that showed that exposure to diacetyl can be harmful to the nose and airways of mice. Mice were exposed to diacetyl at concentrations and durations comparable to what may be inhaled at some microwave popcorn packaging plants.

Gaps in Knowledge

A general occupational health principle is that, where possible, a compound that is demonstrated to be less toxic should be substituted for a hazardous compound. Unfortunately, there is insufficient toxicity information to fully evaluate the workplace safety of any substitutes for diacetyl in butter flavoring. Thus, there is a critical need to understand the toxicity of these potential substitutes. There is also a need to more fully understand the mechanism of diacetyl toxicity, to understand the structure-activity relationships responsible for diacetyl toxicity and to understand how diacetyl vapors are absorbed in the lungs, particularly under workplace conditions.

Additional Web sites for Information

(<http://www.cdc.gov/niosh/docs/2004-110/>). The Flavor and Extract Manufacturers Association of the United States has provided respiratory safety information and produced a document, Respiratory Health and Safety in the Flavor Manufacturing Workplace.

(<http://www.femaflavor.org/uploadedfiles/FEMA%20Aug%2004.pdf>).

Guidance on communicating the hazard of diacetyl-containing flavorings and diacetyl has been issued by OSHA (<http://www.femaflavor.org/uploadedfiles/OSHA%20Guidance%2007.pdf>) and these flavorings are on their agenda for this year.

The National Toxicology Program initiated animal toxicology studies on diacetyl and acetoin, the major volatile components of butter flavoring and 2,3-pentanedione, a diacetyl substitute (<http://ntp.niehs.nih.gov:8080/index.html?col=010stat>).