TOX IMPACT STATEMENT

Popcorn Workers Lung: The Role of Diacetyl

Approved by SOT Council, May 2018

The Problem

In 2002, a published report described a cluster of irreversible obstructive lung disease cases in non-smoking employees in a single microwave popcorn factory in Missouri. In some individuals, the disease was of sufficient severity to warrant lung transplantation surgery. The disease in these workers had many of the characteristics of bronchiolitis obliterans, a rare and poorly understood condition characterized by inflammation and fibrosis of the small airways. Occupational exposure surveys revealed the presence of numerous airborne volatile organic compounds associated with the flavoring agents in use in the factory, but none were known causes of irreversible obstructive lung disease. The occurrence of this disease in an occupational setting in the 21st century was shocking, especially considering that, at the time, the causative agent was unknown.

Role of Toxicology

Initial inhalation toxicological studies revealed that exposure to butter flavoring vapor mixtures caused airway epithelial injury in rodents. Subsequent studies revealed that inhalation exposure of rodents to a single constituent of butter flavoring vapors, diacetyl, resulted in lung injury similar to that caused by the flavoring vapor mixtures. Diacetyl (2,3-butanedione) is a water-soluble, reactive α-diketone vapor which imparts the taste of butter. It is now known that acute, subchronic, or chronic exposure of rodents to this vapor causes airway epithelial injury and inflammation, albeit with a pattern of injury among the airways which differs from that in the human. Inhalation dosimetric studies revealed that, in the rodent, inhaled diacetyl vapor is absorbed from the inspired airstream very efficiently in the nose and large airways, leading to little penetration of this vapor to the smaller airways. This is not the case in the human respiratory tract, thus explaining the differing patterns of injury between the rodent and human. The human disease can be mimicked in rodents by instillation of diacetyl (in saline vehicle) directly into the lower airways and bypassing the absorption in the large airways. This has provided a novel animal model in which to investigate the pathogenesis of bronchiolitis obliterans.

Mechanistic studies are key to a thorough toxicological evaluation. It is now understood that diacetyl chemical reactivity and toxicity are attributable to the α-diketone structure. The

electrophilic α-diketone moiety is essential for protein binding. Noteworthy is that the chemical reactivity profile of diacetyl allows it to escape the cellular pathways which offer protection against most reactive electrophilic compounds. As might be predicted from this mechanistic understanding, subsequent studies revealed that other α-diketones, specifically 2,3-pentanedione and 2,3-hexanedione, also cause lung injury. Thus, toxicological studies identified a causative agent in butter flavoring vapors, revealed its mechanism of action, and, in addition, indicated that pulmonary toxicity is a characteristic of a class of compounds, not simply diacetyl.

Public Health Impact

Identification of diacetyl as a causative agent indicated that there is a potential risk of developing small airway disease in any occupational setting in which diacetyl is present at sufficient concentrations. In fact, increased prevalence of obstructive lung disease has now been reported in workers employed in multiple occupations, including cookie manufacturing, coffee processing, and baking. With knowledge of the causative agent, it is now possible to estimate exposure levels associated with minimal risk of developing lung injury and to institute appropriate occupational environmental control methodologies to prevent excessive exposures.

Occupational settings are not the only possible source of diacetyl exposure. E-cigarette smoke, for example, contains significant amounts of diacetyl.

The diacetyl-associated health risks would not have been known were it not for extensive toxicological evaluation. Alternate α-diketones have been proposed as substitutes for diacetyl in flavoring vapors. Research indicates that all volatile α-diketones pose a degree of inhalation toxicological risk. Such knowledge can serve to prevent the use of alternative flavoring compounds that carry substantial risk.

As has often been the case, toxicological research has led to the development of novel animal models of human disease. Diacetyl-induced lung disease in the rat provides an experimental model which allows scientists to more clearly understand the pathogenesis of this disease and to develop early biomarkers of disease etiology. This has the potential to lead to the development of better preventive strategies and therapies for this disease, whether or not it is caused by diacetyl. Thus, research on diacetyl-induced lung disease has served to benefit public health in ways far beyond toxicological risk assessment.

References and Resources

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