# DIACETYL

## Overview

Diacetyl is a yellow to green liquid or powder that is found in a variety of foods and beverages. It contributes to beer and wine and has a slick or slippery texture at low levels and a butterscotch flavor at higher levels. It is a natural by-product from the conversion of glucose to ethanol by yeast during fermentation in beer, and it is also found naturally in low concentrations in coffee, vinegar, dairy, honey, and fruits. It is primarily used an artificial food additive found in flours, chocolate, cooking oils, candy, chips, frosting and more. Most notably, it is responsible for the butter aroma and taste in microwave popcorn.

### Just the facts

| Physical Information |
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| Name: Diacetyl |
| Use: Artificial food additive |
| Source: Alcohol Fermentation |
| Recommended daily intake: None |
| Absorption: Ingestion, inhalation |
| Toxicity/symptoms: Respiratory Distress |
| Regulatory facts: |
| Environmental: |
| Recommendations: |

## Diacetyl Structure

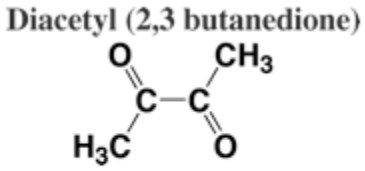


**Figure 1**. 2-Dimensional representation of diacetyl [http://www.thewinemerchantinc.com/educational/WineAcid.html].

## Toxicity and Health Effects

One property of diacetyl that impacts its toxicity is the ease of inhalation of the vapors. Flavoring chemicals in general, including diacetyl can be easily inhaled because they are very volatile substances that readily evaporate from solid or liquid forms into the air, a characteristic that is further amplified by application of heat.

Another property is that diacetyl may inhibit ion transport across respiratory epithelia (Fedan et al. 2006). The most prominent adverse health effect associated with diacetyl exposure is what has been commonly referred to as 'popcorn lung' disease. Specifically, it leads to otherwise rare and irreversible constrictive bronchiolitis obliterations (chronic scarring and severe narrowing of the bronchiole airways) (Hubbs et al. 2008). This inflammation and obstruction, if severe enough, ultimately requires lung transplant to avoid potential suffocation.

The primary symptoms associated with inhalation of diacetyl are persistent dry cough, shortness of breath, wheezing, phlegm production, fatigue, drowsiness, headache, fever, aches, and nausea. The vapors can also irritate the eyes, skin, nose, and throat and generate pain, burning, redness, rash, and soar throat. Many medical analyses can assist in diagnosis, such as a spirometry breathing test or lung biopsy to show fixed airway restriction or complete obstruction; an evaluation of lung volumes or chest X-rays, either of which may show hyperinflation (excessive, trapped air beyond an obstruction); or a high-resolution computerized tomography chest scan, which may reveal air trapping, haziness, or thickened airway walls.

## Exposures and Case Studies

Primary opportunities for exposure to diacetyl exist in occupational settings, where workers in flavoring companies' facilities inhale vapors during food and beverage production processes.; Part of the problem is that the FDA evaluates such flavoring chemicals as generally recognized as safe (GRAS) to be eaten, because they are food additives, but most of these substances have not been specifically tested for respiratory toxicity via inhalation. The first cases in which diacetyl exposure began being associated with the aforementioned adverse health effects appeared in 1985, when investigators from the Centers for Disease Control's (CDC) National Institute for Occupational Safety and Health (NIOSH) discovered two young and otherwise healthy nonsmoking employees that had been diagnosed with severe fixed obstructive pulmonary disease at a bakery flavor production facility in Indiana (that commonly used diacetyl).

Similar cases were reported throughout 2000, 2002 and 2003; in 2000, ten workers from one popcorn plant in Missouri were diagnosed with bronchiolitis obliterations, and the Missouri Department of Health (MDH) notified theOccupational Safety and Health Administration (OSHA) and asked them to inspect the facility. OSHA could not analyze their samples, so NIOSH investigated. Their findings indicated high risk, but the factories that were examined also contained other toxic substances that may have been contributing to the respiratory illnesses, so no definitive conclusions could be drawn yet about diacetyl. Nevertheless, they issued recommendations and precautions, but worker health continued to decline. Next, MDH and NIOSH published an article that described their investigation in 2002 in the CDC's Morbidity and Mortality Weekly Report and concluded "workers exposed to flavorings at microwave popcorn factories are at risk for developing fixed obstructive lung disease."

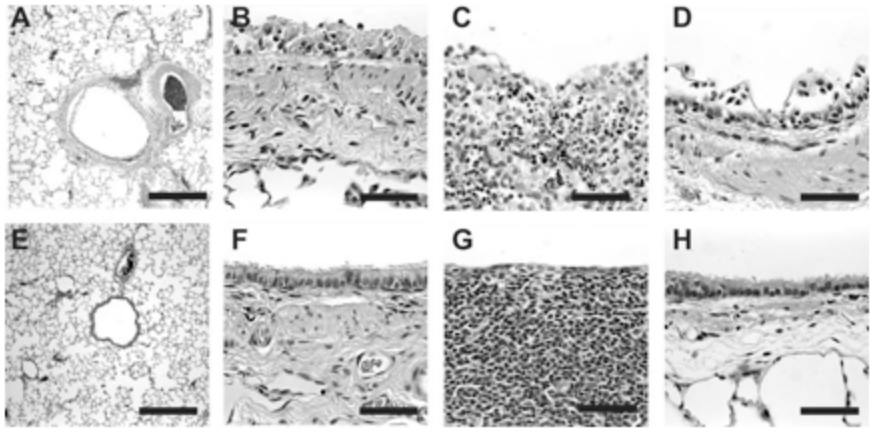


**Figure 5.** "Pulmonary histopathology of rats in the pulsed high exposure group (A–D) and control (E–H) rats. The control sections represent the normal tissue that has been damaged in the exposed group. (A) Necrotic bronchiolar epithelium lifting off the basement membrane of a rat exposed to butter flavoring vapors. (B) Complete necrosis of the bronchiolar epithelium in a rat exposed to butter flavoring vapors. (C) Necrosis extending beneath the epithelium and into bronchus-associated lymphoid tissue of an exposed rat. (D) Necrosis and loss of individual airway epithelial cells in a smaller bronchiole [Hubbs et al. 2002]."

Later in 2002, as a result of reported workers' conditions at popcorn plants, #Hubbs et al., 2002examined the hypothesis that airway injury in rats would result from exposure to diacetyl vapors used in microwave popcorn and other foods. They concluded, "concentrations of butter flavoring vapors that can occur during the manufacture of foods are associated with epithelial injury in the nasal passages and pulmonary airways of rats."

In 2003, the EPA reported that it would complete a project on evaluating the compounds emitted through popping microwave popcorn. Ultimately, it has been shown that diacetyl is just one agent that can cause flavorings-related lung disease:

*"The flavorings industry has estimated that over a thousand flavoring ingredients have the potential to be respiratory hazards due to possible volatility and irritant properties (alpha, beta-unsaturated aldehydes and ketones, aliphatic aldehydes, aliphatic carboxylic acids, aliphatic amines, and aliphatic aromatic thiols and sulfides)."*

These findings soon induced increased legal, political, scientific, and social attention. In 2004, a jury in Missouri awarded $20 million to a former microwave popcorn worker for compensatory personal injury damages against International Flavors and Fragrances, Inc. and its subsidiary, Bush Boake Allen, Inc. The 2006 study by #Kanwal et al. indicated "an apparent widespread risk for occupational lung disease from exposure to butter-flavoring chemicals in this industry." In 2007, the Washington Post reported that California State Assemblywoman Sally Lieber (D) introduced a bill to ban the use of diacetyl. Consequentially, California and OSHA drafted a standard on food flavorings exposure in the workplace. The FDA also faced continual requests to re-examine the categorization that diacetyl was GRAS. Other diacetyl legislation proposals ensued and eventually one was approved:

*"By a vote of 260 to 154, the U.S. House of Representatives on September 26 approved legislation (The Popcorn Workers Lung Disease Prevention Act) that would force OSHA to develop interim (and final) standards limiting worker exposure to the artificial flavoring diacetyl."*

## Scientific Investigation

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It is difficult to say exactly what specific biochemical properties of diacetyl induce the initial adverse physiological responses. As #Hubbs et al., 2002 notes towards the end of the study, *"The vapors emitted from butter flavoring are a complex mixture that produces necrosis that*

*cannot be explained by the known toxicologic properties of any of its components."*

Additionally, they note that although the rat injuries suggest that necrosis could be the initial injury faced by exposed factory workers, there are no published pathology reports on humans for which to compare. However, research has been done in examining what initial physiological responses occur in the respiratory system that lead to the wealth of symptoms and adverse health effects ultimately generated by diacetyl exposure, and there are some proposed mechanisms.

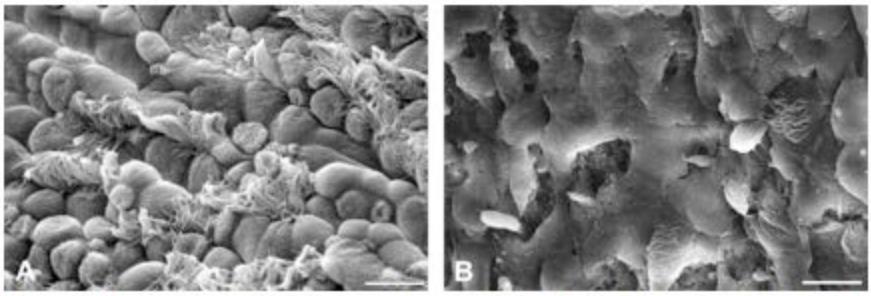


**Figure 6.** "Scanning electron microscopy showing the surface morphology of the tracheal bifurcation of rats exposed to (A) air (control) (B) 294.6 ppm diacetyl as a continuous six-hour exposure. The diacetyl-exposed epithelium is characterized by flattening of cells, loss of microvilli and cilia, and fissure formation [Hubbs et al. 2008]."

In 2008, #Hubbs et al., 2002 expanded on the 2002 study and examined how and why diacetyl exposure causes bronchiolitis obliterations and how damage compares from a maximum concentration of exposure vs. a time-weighted-average exposure. The experiments involved a combination of low, middle, and high exposures that were either continuous or pulsed.

They report that rats in the high-exposure groups experienced consistent changes in the surface morphology of the tracheal bifurcation, as seen in Figure 6, irrespective of continuous vs. pulsed exposure patterns. In all, the experiments specified numerous effects that are eventually responsible for the symptoms associated with diacetyl exposure, such as "cellular degeneration and death in the epithelium lining the nose, larynx, trachea, and intrapulmonary airways" along with "multifocal, mild, necrosuppurative bronchitis" and "minimal suppurative bronchitis" of the lungs (#Hubbs et al. 2008)."With respect to their first hypothesis, the evidence confirms concentration-dependent diacetyl-induced airway epithelial necrosis, which is believed to be the initiating injury for bronchiolitis obliterations; this finding also strengthens the speculation that epithelial necrosis occurs in humans exposed to diacetyl. Thus, the initial targeting of epithelia is sort of a general mechanism of diacetyl that induces adverse health effects. With respect to their second hypothesis, peak diacetyl exposure concentration is not supported to be a greater

hazard than the time-weighted-average.

They also note how the primary epithelial area affected in injured rats differs from that of humans upon exposure, which can be explained by differences in the anatomy of rat and human respiratory tracts. Specifically,
*"The smaller diameter of the rat nasal passages, trachea, and bronchi would be expected to produce increased resistance, decreased air flow, and increased mucosal deposition of vapors when compared with the corresponding structures in the human respiratory tract. This would be expected to shift the site of mucosal absorption of vapors higher up in the respiratory tract of rats as compared to in humans"* (#Hubbs et al. 2008).

This helps to suggest the type of airway that diacetyl targets; it is interesting to note that human bronchioles are similar in cell type and mucous thickness to rat trachea.

In an earlier study from 2006 that was designed to study the effects of diacetyl on guinea pig trachea in vitro, such that the effects of ketone could be studied without interruption of the inflammatory cells that may otherwise locate in airways of in vivo experiments, #Fedan et al. found that diacetyl exposure "alters pharmacological and bioelectric characteristics of large airways...by degrading the protective barrier function of the epithelium...leading to hyperreactivity to mucosally-applied methacholine (a receptor in the nervous system)."

In other words, the diacetyl exposure caused the trachea to contract and relax, depolarizing and damaging the epithelium, potentially increasing membrane permeability and reactivity to methacholine, and potentially inhibiting ion transport across the epithelium (all mechanisms that potentially contribute to toxicity and adverse health). However, as with most in vitro experiments, it is difficult to fully apply these conclusions to flavorings factory worker situations.

## Risk and Risk Management

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Clearly, risk has been demonstrated to flavoring-facility workers, but an interesting aspect all of the cases is to examine the possibility of exposure to the general public via consumption of those products that contain diacetyl (i.e. their diets).  Thus, what are the effects of popping microwave popcorn? It is a more recent and less documented aspect, but on September 5th 2007, the New York Times reported some of the first findings that a consumer unaffiliated with occupational diacetyl exposure may have also developed bronchiolitis obliterations as a result of heavy popcorn consumption. Dr. Cecile Rose, director of the occupational disease clinical

programs at National Jewish Medical and Research Center in Denver, diagnosed the 53-year-old Colorado man after learning that he had consumed at least 2 bags of popcorn daily for more than 10 years.

"When he broke open the bags, after the steam came out, he would often inhale the fragrance because he liked it so much. That's heated diacetyl, which we know from the workers' studies is the highest risk."

Although it is stressed that there is not a definitive causal link, after discovering that measurements of diacetyl in the man's home were similar to levels in microwave popcorn plants, it is difficult not to derive the conclusion. Major popcorn manufacturers such as Weaver Popcorn Co., ConAgra Foods Inc., General Mills Inc., and the American Popcorn Co. have even felt enough pressure to voluntarily remove diacetyl as an ingredient from their products.

Given the wealth of research, risk to human health can be avoided. In the factory, exposure can be limited by having adequate ventilation systems and breathing protection, protective clothing and goggles, and by avoiding ingestion of any food or drink during work. NIOSH also urges employers to substitute less hazardous materials for diacetyl when possible, educate employees sufficiently when it is used and use the lowest necessary temperatures, establish clear labeling clean up procedures, and monitor exposures and worker health status including administering breathing tests such that cases can be reported to state health departments when they occur. Consumers can limit their risk by avoiding excessive amounts of products that contain diacetyl, especially those that undergo heating. Also, with popcorn for example, consumers can open the bags underneath kitchen ventilation systems to capture the fumes, or replace microwave popcorn altogether with homemade stovetop alternatives that lack the artificial flavorings. Considering the anatomy of the respiratory system, both factory workers and consumers should refrain from actions that cause damage to respiratory tracts, such as smoking, because this inhibits the body's ability to effectively capture and eliminate toxic and unwanted substances via inhalation.

Source : http://www.toxipedia.org/display/toxipedia/Diacetyl