A Comprehensive Review Of Occupational Exposure To Diacetyl In Microwave Popcorn Facilities

JD Roberts
DA Galbraith
BL Finley
San Francisco, CA

ChemRisk®

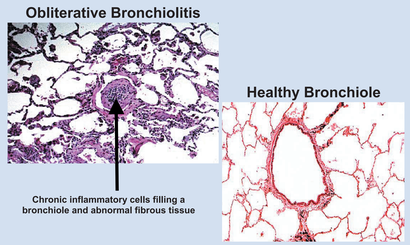
ABSTRACT

In May 2000, eight former employees of a microwave popcorn packaging plant were reportedly diagnosed with a pattern of respiratory symptoms "consistent with" respiratory obliterative bronchiolitis (OB), a severe and sometimes fatal lung disease. It was suggested that the symptoms were a result of exposure to diacetyl, a chemical used in the popcorn butter flavorings. Since that time the National Institute of Occupational Safety and Health (NIOSH) has conducted cross-sectional industrial hygiene and medical investigations in six microwave popcorn facilities. The conclusions offered in the NIOSH reports appear to generally support the belief that respiratory disorders are elevated in certain workers and that diacetyl appears to be a likely candidate for the causative effects. This analysis summarizes the strengths and weaknesses of the existing information and identifies key data gaps. In addition to a detailed analysis of the NIOSH reports, we reviewed the PUBMED and MEDLINE databases for studies that reported animal toxicology and epidemiology results for diacetyl and artificial butter, and known or suspected causes of OB. There exists little toxicology or epidemiology literature for diacetyl, although cases of OB have been noted in agricultural workers and attributed to oxides of nitrogen. There are significant gaps in our knowledge of the effects of diacetyl and definitive conclusions regarding its toxicity to occupationally-exposed workers are difficult to offer.

INTRODUCTION

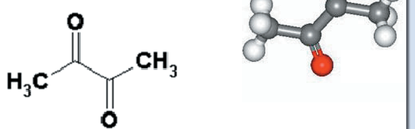
- Diagnoses of obliterative bronchiolitis (OB), a severe and sometimes fatal lung disease (Figure 1), have recently been reported in some employees of facilities that process and package microwave popcorn
- Some investigators have suggested that these cases are likely the result of exposure to diacetyl, a chemical used in the butter flavorings of the microwave popcorn (Figure 2).
- The National Institute of Occupational Safety and Health (NIOSH) has conducted Health Hazard Evaluations (HHE), which have included medical and/or industrial hygiene surveys of several microwave popcorn plant facilities and their workers, and has issued an alert regarding the possible effects of inhaling vapors during the production of butter-flavored microwave popcorn.
- The purpose of this review is to assess the quality of the available information, particularly with respect to specific claims regarding diacetyl exposure and OB, and to identify areas of possible research that would address existing data gaps.

Figure 1 - Obliterative Bronchiolitis



Reference:
http://www.som.tulane.edu/classware/pathology/medical_pathology/New_for_98/Lung_Review/Lung-32.html

Figure 2 - Diacetyl



METHODS

- The PUBMED and MEDLINE databases were reviewed to identify studies that reported
  - Animal toxicology and epidemiology studies involving diacetyl or artificial butter exposures
  - Risk factors for OB (and other respiratory illnesses) that might be present in a popcorn packing facility
- Each of the NIOSH studies was evaluated to assess
  - Representativeness of the industrial hygiene surveys
  - The magnitude of the measured chemical concentrations
  - Whether alternative causes of respiratory disease were assessed
  - The consistency of findings regarding diacetyl exposure and human response
  - The comparisons of respiratory disease incidence in "diacetyl-exposed" popcorn workers vs. unexposed populations

RESULTS

Animal Inhalation Toxicology Data
There is a single published inhalation study involving butter flavoring; two published studies, one unpublished conference presentation and a privately-funded study involving pure diacetyl were identified.

Artificial Butter

Hubbs et al. (2002) exposed rats for six hours at either a constant or pulsed rate to heated (55o C) butter flavoring vapors with the following reported diacetyl concentrations: 203 ppm (constant), 285 ppm (constant), 352 ppm (constant) and 371 (range of 72-940) ppm (pulsed). The rats were euthanized the day after exposure initiation (approximately 18 hours after completion of exposure).

- There were no inflammatory or destructive changes observed in the lungs of any rats in the lowest exposure group (203 ppm); however all rats in the higher exposure groups experienced adverse lung effects and one post-exposure death was observed in each of the higher exposure groups.
- Although it appears that a control group was used, there is no discussion of the effects, if any, that this group experienced or if the control group was exposed to heated air or vapors.

Diacetyl

In 1993, BASF (a manufacturer of diacetyl) conducted an acute inhalation study in which three groups of ten rats were exposed for four hours to 2.25, 5.2 and 23.9 ppm diacetyl in whole body inhalation systems that were supplied through a heated vaporizer (temperature of the heated vapor was not provided). After the exposure period the animals were observed for 14 days.

- None of the rats in the 2.25 ppm group died; all the rats in the 5.2 and 23.9 ppm group died
- "Dragging respiration" and respiratory sounds were observed initially in the 2.25 ppm group, but no clinical signs were detected after day six.
- There was no mention of a control group

Hubbs et al. (2004) presented the results of a study at the annual Society of Toxicology meeting wherein rats were exposed for 6 hours to pure, heated diacetyl vapors at 100, 200, and 300 ppm. The rats were euthanized the next day.

- Necrosis of the nasal and tracheal epithelium occurred at 200 and 300 ppm, but such effects were not observed at 100 ppm. It was also reported that "Diacetyl did not produce significant changes in the lung" at any concentration.
- These results appear to be inconsistent with the BASF study, where most of the rats died one day after exposure to 5.2 ppm. This might be due to the fact that the diacetyl concentrations in the BASF exposure chambers were estimated, not measured. The results also appear to be inconsistent with the Hubbs 2002 study, in which lung effects were observed (in all rats) with artificial butter containing 285 ppm diacetyl; this might suggest that diacetyl was not the cause of the lung effects observed in the Hubbs et al (2002) study. Indeed, as recently noted by OSHA:

> ***"These studies [Hubbs et al.] demonstrated that butter flavoring vapors are capable of causing severe airway injury in laboratory animals, but the causal relationship between diacetyl exposure and development of bronchiolitis obliterans has not been firmly established."***
>
> ***Source: http://www.osha.gov/SLTC/flavoringlung/diacetyl.html***

- As with the Hubbs et al 2002 study, there is no detail provided regarding the exposures, if any, experienced by the control group.

RESULTS CONTINUED

In 2006, Fedan et al. conducted an in vitro study on the effects of diacetyl on the epithelium of guinea pig isolated airway preparations and the effects of diacetyl on reactivity to bronchoactive agents. With perfused trachea preparations, diacetyl was added to the intraluminal (mucosal) surface of the trachea in order to evaluate epithelial barrier function.

- Findings suggested that diacetyl exposure compromised epithelial barrier function
- Results of the study "indicated]" that diacetyl alters the pharmacological and bioelectric characteristics of large airways"

Potential Alternative Risk Factors for Respiratory Disease in Popcorn Packing Plants
The following substances are either known or suspected risk factors for OB or other respiratory diseases:

- Grain dusts (organic dust toxic syndrome)
- Corn endotoxins (inflammatory response)
- Grain fumigants and pesticides (respiratory failure)
- Corn tannins (OB)
- Nitrogen oxides in corn silage (OB)

It is reasonable to expect that some or all of these compounds might be present at a popcorn packing facility. However, as noted below, at a majority of the facilities investigated by NIOSH thus far very little to no information has been collected regarding the potential presence of these compounds.

National Institute of Occupational Safety - Health Hazard Evaluations
Over the last several years, NIOSH has compiled a number of HHE reports for popcorn manufacturing facilities in several Midwestern states. These have included:

1) B.K. Heuermann Popcorn in Phillips, Nebraska (final letter report issued in May, 2003)
2) Nebraska Popcorn in Clearwater, Nebraska (final letter report issued in July, 2003)
3) Agrilink Foods Popcorn Plant in Ridgway, Illinois (final report issued in October, 2003)
4) American Pop Corn Company in Sioux City, Iowa (final report issued in July, 2004)
5) ConAgra Snack Foods in Marion, Ohio (final report issued in December, 2004)
6) Gilster-Mary Lee Corporation (the index plant) in Jasper, Missouri (final report issued in January, 2006)

To our knowledge, the NIOSH data represent the only available analyses addressing industrial hygiene data and respiratory health effects for popcorn facilities. In general, each investigation consisted of personal and area sampling for specific analytes (typically respirable dusts, diacetyl and other volatile organic compounds (VOCs) in different areas of the facility (usually including the mixing room and the packaging line) and evaluations of lung function (e.g., self-reported symptoms and spirometry measurements) in workers in these different areas. Summarizing some of the key findings from these studies:

Industrial Hygiene Surveys

Measured levels of diacetyl in all areas of all facilities were generally low (2 ppm or less); the primary exception was the mean level of 32.27 ppm measured in the mixing room of the Gilster plant in November 2000 (Figure 3). Airborne respirable and total dust levels were also generally very low, as were analyses for other VOCs. Analyses for respiratory risk factors other than butter flavoring (e.g., nitrogen oxides and endotoxins) were conducted only at the Gilster-Mary Lee plant; hence while airborne diacetyl levels in popcorn packing plants have been

Figure 3 - Popcorn Plant Mixing Room

Large mixing tank holds heated oil and butter flavoring mixture. 5-gallon buckets used to manually transfer concentrated butter flavoring from the smaller heated tanks to the large mixing tank.

Reference:
http://www.cdc.gov/niosh/docs/2004-110/#n

RESULTS CONTINUED

Personal Exposure Histories

At the Gilster-Mary Lee plant, 57% of the workers reported having had exposures outside the popcorn packing plant to other possible causes of lung disease: farming (40%), grain dust (32%), irritant gases (14%), and nitrogen oxides (8%). It does not appear that this information was collected in subsequent investigations of the other facilities.

Diacetyl Exposure-Response Relationships

The data collected to date make it difficult to assess the strength of the relationship between diacetyl exposure and worker response. For example, of the former eight workers at the Gilster-Mary Lee plant who were reported to have symptoms "consistent with" OB, only four worked in the mixing room (where mean diacetyl levels exceeded 30 ppm), the other four worked in the packaging area where mean measured diacetyl levels were less than 2 ppm. Further, it was reported that none of the packagers had ever worked in the mixing room. Kreiss et al (2002) presented a figure which indicates a statistically significant relationship between cumulative diacetyl exposure and the degree of airway obstruction in 21 individuals with respiratory obstruction at the Gilster-Mary Lee plant (Figure 4). However, the paper offered no description as to how this figure or the underlying dose calculations were derived. There are also other confounders, such as the presence of other VOCs. For example, acetoin is known to cause adverse respiratory effects, is present in many butter flavorings (Boylstein et al 2006), and has been measured in high concentrations in some of the NIOSH HHEs (up to 273 ppm in the Gilster facility).

Figure 4 - Kreiss et al. (2002)

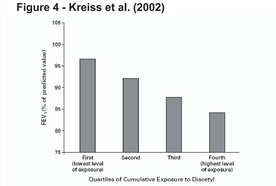


Figure 2. Mean Forced Expiratory Volume in One Second (FEV$_1$) Value, According to Cumulative Exposure to Diacetyl in the Popcorn Plant in November 2000.
Cumulative exposure to diacetyl ranged from 0 to 128 ppm-year. The cutoff points for the four quartiles of cumulative exposure were 0.05, 4.5, and 11 ppm-yr.

Statistical Comparisons to "Background Incidence" of Respiratory Effects

Two general categories of respiratory effects were evaluated at each plant: self-reported symptoms (e.g. coughing, wheezing, shortness of breath etc.) collected via questionnaires and forced expiratory volume (FEV) measurements obtained via spirometry tests. The health effects data were generally interpreted via comparisons of incidence rates (self-reported symptoms and decreased FEV) in the exposed workers via comparisons with 1) age- and smoking-adjusted "background" rates reported in the National Health and Nutritional Examination Survey (NHANES) and, in some cases 2) "internal reference groups" consisting of relatively unexposed workers. While some of these comparisons involve tests for statistical significance, many do not. Those instances where tests for significance were conducted can be summarized as follows:

- *Comparisons of rates of self-reported symptoms and measured spirometric responses in facility-wide workers vs. the NHANES data.*
  - Statistical comparisons were conducted for the Agrilink facility (age groups 17-39 years, 40-69 years, and all ages combined) and the American Popcorn facility (age groups of < 40, > 40 years, and all ages combined) facilities.
  - At both facilities, there was no statistically significant increase in any of the numerous self-reported symptoms (coughing, wheezing, asthma, shortness of breath) or abnormal spirometry (specifically, spirometric measurements by NIOSH investigators) in any age group when all workers combined were compared to the age- and smoking-adjusted NHANES data.
- *Comparisons of rates of self-reported symptoms and measured spirometric responses in "exposed workers" only vs. the NHANES data.*
  - This is arguably a more sensitive analysis than a "facility-wide" comparison because relatively non-exposed individuals (such as office staff) are excluded.
  - Tests for increased risk of self-reported symptoms and measured obstructive or restrictive effects in exposed workers were conducted for the American Popcorn facility and ConAgra facility (slurry room and QA workers).
  - At the American Popcorn facility, there was no statistically significant increase in any of the five self-reported symptoms in age groups comprised of <40 years, >40 years, and all ages combined. At the ConAgra plant, there was a statistically significant increase in "wheezing" and "asthma" in the < 40 year age group; no other symptoms (shortness of breath, chronic cough, chronic bronchitis) were increased in the age comprised of <40 years, > 40 years, or all ages combined.

RESULTS CONTINUED

  - Rates of respiratory restriction and obstruction in the ConAgra and American Popcorn exposed workers were not statistically significantly increased in any age group (no such analysis was conducted for any other facility).
- *Comparisons of rates of self-reported symptoms and measured spirometric responses in "exposed" workers" vs. internal reference groups.*
  - Statistical comparisons of self-reported symptoms in exposed workers vs. internal reference groups were conducted at the Gilster facility only.
  - Twenty-nine different statistical tests for "trends" were evaluated by comparing symptom prevalence in office workers vs. maintenance workers vs. packagers/mixers. It was reported that 9 of the trend tests were significant (night sweats, chills, skin irritation, et al) and 20 were not (chest tightness, wheezing, bronchitis, et al).
  - Increased risks of abnormal spirometry were conducted for the American Popcorn plant only. The Executive Summary of the HHE for this facility states that there was a "statistically significant association" between abnormal spirometry in plant workers vs. "unexposed" individuals such as office workers (odds ratio of 6.5, 95% confidence interval of 1.9-22.4); however, no details concerning this analysis are offered in the report itself.

In short, a vast majority of the statistical analyses presented in the NIOSH HHEs demonstrated that microwave popcorn workers, even those that worked in presumably "high exposure" occupations such as mixing, did not have increased rates of self-reported respiratory symptoms or abnormal spirometry relative to the NHANES data or internal reference groups. Hence, thus far there does not appear to be a consistent pattern of increased respiratory dysfunction in "butter exposed" workers in the NIOSH HHEs. However, it must be noted that tests for statistical significance were not conducted for many of the symptoms at most of the facilities.

Diacetyl and Butter Flavorings Published Literature
In addition to the NIOSH HHEs, there are 7 published studies that provide additional statistical interpretations of the worker health/industrial hygiene data, all of which have been co-authored by NIOSH investigators: (Kreiss K 2002; Akpinar-Elci M 2004; Akpinar-Elci M 2005; Kullman G 2005; Akpinar-Elci M 2006; Boylstein R 2006; Kanwal R 2006). In some cases, as in Kanwal et al 2006, the data from the various facilities are aggregated. As with the individual HHEs, most of the statistical analyses in the published papers indicate that "butter exposed" workers did not have increased rates of self-reported respiratory symptoms or abnormal spirometry relative to the NHANES data or internal reference groups.

CONCLUSIONS

While it is possible that elevated exposures to artificial butter may have been related to the incidence of respiratory disorders in some popcorn workers, the data collected to date do not appear to be sufficiently robust to draw any firm general conclusions. We believe that the following future information-gathering and research endeavors should be considered:

- Animal exposures (with diacetyl and artificial butter) that simulate normal workplace conditions, with well-defined controls
- Release of the NIOSH HHE data to the public domain so that it can be interpreted by other scientists
- More thorough (and transparent) estimates of short-term and cumulative doses of diacetyl and other suspected chemicals, as well as other risk factors for different occupations in the packing plants
- Better understanding of the non-occupational exposures to "off-site" risk factors (e.g., as in the Gilster study)
- Epidemiological surveys of workers in diacetyl and butter flavor manufacturing settings, in addition to more thorough statistical review of respiratory disease rates in "exposed" workers compared to background incidence rates

DISCLOSURE

Both Drs. Galbraith and Finley have been designated as experts on behalf of defendants in litigation related to alleged worker exposure to diacetyl and artificial butter.

REFERENCES

Available upon request.