



**Case Report**

## Diacetyl and Bronchiolitis Obliterans: Review of Patient Histories and Assessment of the Strength of Evidence for a Causal Relationship

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### Abstract

#### Background

Workers in industries that manufacture, distribute, and use food flavorings (with an emphasis on diacetyl) have been reported to be at increased risk of developing a form of bronchiolitis obliterans, known as Constrictive Bronchiolitis (CB). However, exposure-based pathophysiological mechanisms for this disease have not yet been discovered through animal testing, and epidemiological evidence to date does not confirm a clear causative link between food flavoring exposure and risk for bronchiolitis obliterans.

#### Methods

The occupational and medical histories of 12 patients claimed to have sustained permanent lung disease from occupational exposures to flavoring compounds were reviewed and assessed. Diagnostic procedures and responses to therapy are discussed and compared to opinions provided by physicians acting as subject matter experts in litigation proceedings.

#### Results

In all 12 cases, evidence indicated that the available clinical, radiologic, and pathologic data did not support a diagnosis of con-

strictive bronchiolitis. My observations were generally in agreement with the findings of treating physicians, but conflicted with reports from consultants hired by plaintiff attorneys.

#### Conclusion

Based on my findings and the lack of consistency in the toxicological and epidemiological literature, I believe that a more robust methodology formed by experts in pathology, pulmonary medicine, occupational medicine, radiology, and industrial hygiene should be developed, that will more carefully assess a possible causative relationship between constrictive bronchiolitis obliterans and inhalation exposures to diacetyl and other food flavorings.

**Keywords:** 2,3-butanedione; Bronchiolitis obliterans; Constrictive bronchiolitis; Diacetyl; Flavorings; Occupational exposure limits; Occupational lung disease; Popcorn lung

### Background

Over the last decade, an increased awareness has developed regarding the potential dangers of worker exposures to airborne flavorings chemicals. These exposures have been associated with an increased risk of developing Occupational Lung Disease (OLD). The potential association between occupational exposures to the food flavoring chemical diacetyl, often used in formulations of butter flavoring, and reports of several cases of fixed obstructive lung disease in microwave popcorn manufacturing environments, was first described in 2002 [1,2]. Subsequently, a causal relationship between flavorings exposures and OLD was suggested to exist more broadly in other workplaces in which food flavorings, particularly butter flavorings, are manufactured or used [3,4]. Such settings have included bakeries, movie theater concessions, breweries, wineries, restaurant kitchens, and even the homes of consumers preparing microwave popcorn [5].

The National Institute for Occupational Safety and Health (NIOSH), a branch of the Centers for Disease Control (CDC), has followed the problem of flavorings-related lung injury closely since 2002, preparing numerous Health Hazard Evaluation (HHE) reports for facilities in which flavorings agents were used [6]. NIOSH has conducted or overseen many toxicology studies, testing various animal species exposed to diacetyl, butter flavoring, and other related chemicals. It has also advised physicians and other healthcare providers as to the recognition, reporting, and response to possible flavorings-related lung disease [3,7].

Most reports of lung conditions associated with flavorings exposures have focused on a subtype of bronchiolitis obliterans, known as Constrictive Bronchiolitis (CB). Historically, CB has been a relatively rare condition in the general population, associated with connective tissue diseases, such as rheumatoid arthritis or scleroderma [8], inflammatory bowel disease [9], or seen as a post-infectious complication from infectious agents such as respiratory syncytial virus, adenovirus, or mycoplasma pneumonia [10].

CB has most commonly been described in post-lung transplant populations, representing a form of lung allograft dysfunction, and has been recognized as the principal factor limiting long-term survival

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of lung transplant patients and their allografts. Approximately 50% of patients will experience obliterative bronchiolitis within five years of their lung transplant [11], leading to a pathologic picture of progressive fibrotic replacement of the terminal airways in the affected lungs [12]. The unfortunately high incidence of CB in transplant populations led to the creation of a diagnosis known as “Bronchiolitis Obliterans Syndrome”, or BOS, defined as follows:

“Definition of BOS: We use the term bronchiolitis obliterans syndrome to connote graft deterioration secondary to persistent airflow obstruction... BOS does not necessarily require histologic confirmation; in contrast, the term bronchiolitis obliterans is used for a histologically proven diagnosis” [13].

It is important to emphasize, however, that BOS was intended to only apply to patient populations who have had lung (and in some cases, bone marrow) transplantations; it was not designed for the rest of the population [14]. For these post-transplant populations known to be at high risk for CB, who are generally on a variety of powerful immunosuppressant agents, the aim was to allow for noninvasive studies to establish the diagnosis, such as CT scanning and tests of pulmonary function, omitting the need for a pathologic diagnosis, which would have traditionally required an invasive procedure, such as transbronchial biopsy, open lung biopsy or a VATS (Video-Assisted Thoracoscopic Surgery) procedure, to provide confirmation of CB.

The aim of my assessment was to examine the occupational histories, clinical presentations, radiologic studies, and laboratory findings of individuals exposed to food flavorings who presented with claims of CB, in order to evaluate a possible causal link between chemical exposure and respiratory tract injury. As the evolution of lung disease can be affected by multiple factors, it was also of interest to determine whether identifying a diagnosis of CB or other lung conditions might be complicated by the presence of confounding influences.

Although the persons discussed in this review have given up their rights for confidentiality as a result of their involvement in litigation proceedings, their names will not be disclosed.

## Case Summaries

The patients discussed in this investigation were reported to have developed CB from occupational exposures to various flavorings chemicals. Twelve cases are described from an estimated total of approximately 50-100 cases in the United States between 2004 and 2010 that allegedly developed CB as a result of occupational exposures to food flavorings compounds, such as diacetyl (Table 1).

### Case 1

Case 1 worked for Comstock Fruits, a division of Birds-Eye Foods, from 1987 until 2000. He was a general laborer, performing janitorial functions and operating machines that filled and packed bags of microwave popcorn. After leaving employment at Birds-Eye, Case 1 learned that many of the workers at his former job had been complaining of breathing problems. He discovered that some of them were filing lawsuits against his former employer, and he obtained the names of a few attorneys who had experience in “popcorn lung” litigation.

In April, 2003, at the age of 45, Case 1 went to see his primary care physician on the advice of his new attorney, and told his doctor that he had been experiencing shortness of breath and chest pressure for the last five to six years. His treatment records noted, however, that since 1999, he had been seen for the following medical issues: abdominal pains related to his gallbladder, nicotine addiction and “tobacco abuse,” an infection after a tongue piercing, hypothyroidism, diarrhea, hemorrhoids, herpes infection, back pain after falling at work, left wrist sprain after another fall at work, and an episode of bronchitis.

| Patient | Job Description  | Treating Physician Diagnosis  | Open Lung Biopsy Pathologic Diagnosis   | Plaintiff Expert Diagnosis  |
|---------|--|---|---|---|
| 1       | Machine operator, janitor  | No clear disease  | No tissue obtained  | Bronchiolitis obliterans “syndrome”                               |
| 2       | Machine operator, line worker, bagger  | Chest pain, ruled out for myocardial infarction; no cardiopulmonary disease | No tissue obtained  | Skin depigmentation, caused by flavorings exposures               |
| 3       | Packer, line worker, warehouse worker  | Emphysema, COPD, chronic nicotine abuse                                     | Emphysema, smoking-induced respiratory bronchiolitis                                | Bronchiolitis obliterans “syndrome”                               |
| 4       | Mixer, cook  | Interstitial pulmonary fibrosis   | Chronic hypersensitivity pneumonitis  | Hypersensitivity pneumonitis, bronchiolitis obliterans “syndrome” |
| 5       | Clerk, inventory analyst, computer network technician                              | Interstitial pulmonary fibrosis   | Idiopathic pulmonary fibrosis, nonspecific interstitial pneumonitis                 | Bronchiolitis obliterans “syndrome”                               |
| 6       | Production helper, forklift operator   | Hypersensitivity pneumonitis, severe asthma                                 | Chronic hypersensitivity pneumonitis or diffuse panbronchiolitis                    | Bronchiolitis obliterans  |
| 7       | Equipment assembler, quality control   | Interstitial pulmonary fibrosis, bronchiectasis                             | Chronic interstitial pneumonia, interstitial pulmonary fibrosis                     | Bronchiolitis obliterans “syndrome”                               |
| 8       | Flavorings compounder  | Hypersensitivity pneumonitis  | Hypersensitivity pneumonitis  | Bronchiolitis obliterans  |
| 9       | Products inspector, compounder, production supervisor                              | Severe asthma   | Acute and chronic inflammation*   | Bronchiolitis obliterans  |
| 10      | Assistant compounder, general laborer  | Recurrent bronchitis, bronchiectasis  | Benign lung tissue with “nonspecific interstitial thickening*”                      | Bronchiolitis obliterans  |
| 11      | Owner, flavorings compounder, product manager                                      | Chronic bronchitis, COPD, cor pulmonale                                     | Asthma, COPD, severe emphysema  | Bronchiolitis obliterans  |
| 12      | Loading, janitorial duties, mixer of coffee beans and flavorings, machine operator | Allergic rhinitis, bronchitis, environmental allergies                      | “Chronic and subacute small airways injury” consistent with many different diseases | “Obstructive bronchiolitis”                                       |

**Table 1:** \*Tissue obtained from transbronchial lung biopsy, not open lung biopsy.

Multiple lung examinations over the years were described as “clear throughout”, and over the period of time in which Case 1 recalled having shortness of breath and chest pressure, no such complaints were ever recorded by his doctors, nor was he ever treated with any respiratory medications until after 2003, when he obtained legal counsel. Case 1 was referred for a pulmonary evaluation, but he did not follow through with the referral, explaining to his doctor that he had “lost trust” with him for some reason. His doctor noted in his final chart note that he learned that Case 1 had hired at least two attorneys for his claimed breathing problems, and had another attorney representing him for a back injury at work. His doctor decided to dismiss Case 1 from his practice, because of Case 1’s mistrust of his care for him. No mention of exposure data for diacetyl or other food flavorings in Case 1’s workplace was noted in the medical records.

Case 1’s smoking history was variably described by his doctors, from 32 to 50 pack years. Case 1 was prescribed various medications to help him quit smoking that he could not tolerate, but did eventually stop smoking in November, 2002.

Case 1 selected a new primary doctor in May, 2003, and complained that other people had been exposed to poor air quality at the popcorn plant at which he had previously worked, and that he was told they had bronchiolitis obliterans. Arterial blood gas and pulmonary function studies performed at that time were described as normal. He was referred by his new physician to another pulmonary doctor for more testing.

Case 1 saw the pulmonologist in June, 2003, stating that his job at the popcorn factory was to run a machine that filled microwave bags with popcorn, butter, and salt. In his current job, he worked in a factory, but was not exposed to fumes, dust, or chemicals. On exam, his lungs were clear with no abnormal breath sounds. The pulmonary physician decided to order complete pulmonary function studies and a chest CT scan.

Case 1’s high resolution CT scan on June 16, 2003 was reported to show no acute cardiopulmonary disease and his lung doctor commented that his lungs looked completely normal. After reviewing these studies, the pulmonary consultant examined Case 1 again on July 21, 2003, and again found him to have clear lungs and a normal exam. He discussed doing a bronchoscopy and possible lung biopsy. Case 1 called his pulmonologist back a month later, stating that he didn’t need to follow up with him on advice from his lawyer. The lung doctor decided he would try to follow up Case 1 with another CT scan in three or four months, but could not decide on a definite diagnosis in the case. Case 1’s chest CT scan on October 20, 2003 again showed no abnormalities. A follow up visit on February 25, 2004 revealed another completely normal lung exam. Case 1’s pulmonologist could not figure out why Case 1 might be having shortness of breath, noting normal oxygen saturation testing and a consistently normal physical exam. He wanted to see Case 1 again in five months, but Case 1 called in June, 2004 to say that his family doctor would take care of all his medical issues from that point on.

Case 1 chose a different family doctor on May 20, 2004, and told him that he was a non-smoker, and was on long term disability from his work for what he described as “bulging discs” in his back. He noted having difficulty breathing, and that he had seen a lung doctor on his own for this complaint. Later visits in July and September, 2004 noted dermatitis and hypothyroidism, but no respiratory testing or radiologic studies were ordered.

Several months later, Case 1 was referred by yet another primary care doctor for a pulmonary consultation on March 1, 2005. This evaluation took place shortly after an industrial accident in January, 2005 at a different chemical company, where he had been exposed to high concentrations of the industrial chemicals isovaleraldehyde and acetaldehyde, chemicals that are known respiratory irritants [15,16]. After that accident, Case 1 reportedly felt pain and tightness in his chest, and underwent pulmonary function testing on the day of the accident. The pulmonologist observed that one of his lung volumes, the FEV1, had dropped from his prior value of 3.96 to 3.82 L (both values substantially greater than what was measured in his testing in June, 2003).

Case 1 claimed that he had no previous history of asthma or obstructive lung disease and had never smoked. He said he worked more than 20 years at Comstock Fruits, and had received regular pulmonary function testing since 1991. Case 1 denied having any other episodes of heavy exposures to chemicals, and noted that he wore a full face respirator at work and was careful to avoid any work exposures to any irritants. Lungs were clear on exam. As a result of Case 1’s heavy exposure in January, 2005, the physician felt Case 1 was at risk for developing future lung disease, but planned to obtain more PFTs and another high resolution CT scan. This physician seems to have been completely unaware of Case 1’s prior claims of occupational chemical exposures at Birds-Eye, did not have results from earlier CT scans and PFTs, and was unaware of Case 1’s prior pulmonary evaluations.

Case 1 and his attorney hired a medical expert who asserted that Case 1’s lung injury arose from workplace exposures to popcorn flavorings. The expert was told that Case 1 had worked at the Birds-Eye popcorn factory from 1990 until 2003, where he ran machines, performed janitorial services, and cleaned tanks. For the first time, Case 1 described himself as an “off and on” flavorings mixer. The relative frequency of Case 1’s various tasks was not described. He reported that he started smoking at the age of “30 to 35,” up to a ½ pack a day for 14 years. He also stated that during his employment, he took several gallons of butter flavoring home from the plant for frying chicken and other cooking. He believed using the company’s butter flavoring in this way caused his son’s asthma and worsened his own breathing problems.

Case 1’s medical consultant examined him, and again found that his lungs were clear with no abnormal breath sounds. Pulmonary function testing and another CT scan were ordered. The consultant believed that the best explanation for Case 1’s mild drop in his pulmonary function test findings was his prior workplace exposures at the popcorn plant. He concluded that Case 1 had “bronchiolitis obliterans syndrome”, but did not provide any factual basis to support this belief, nor did he provide a description of the clinical aspects of BOS. No biopsy to confirm this diagnosis was entertained, and no discussion of Case 1’s January, 2005 industrial accident was offered. Case 1’s case against Birds-Eye’s historic manufacturers/suppliers was eventually settled for an undisclosed amount in November, 2010.

## Case 2

Case 2 worked at a hat factory from 1972 to 1981, followed by work at an automobile plant from 1981 to 1996. In 1996 at the age of 42, she started working at the Agrilink Foods Popcorn Plant in Ridgway, IL. After working for a few months, she was laid off, but was rehired in September, 1997. She then worked at the plant until

2002. She had various jobs during her tenure, including bagger, general laborer, machine operator, and line worker.

Case 2 visited her healthcare providers for a number of complaints, including lower back pain, occasional upper respiratory infections, hair loss, hemorrhoids, and oral ulcerations. She was a nonsmoker, but was briefly admitted for an episode of chest pain, and ruled out for a myocardial infarction. Her treating doctors never ordered CT scans of her chest, nor pulmonary function studies, nor did they advise her to obtain a lung biopsy, as she had never provided any history of significant lung disease, nor reported any complaints of shortness of breath or reduced exercise tolerance.

Case 2 filed suit against the diacetyl manufacturers who had been suppliers to Agrilink foods during her employment, claiming that she had experienced unspecified respiratory problems since 2002. Case 2's attorney hired a medical expert, who reviewed her medical records and performed a history and physical exam. Pulmonary function studies showed Case 2 to have greater than normal lung volumes for her age, height, and gender, with a Forced Vital Capacity (FVC) that was 128% of predicted, and a Forced Expiratory Volume in one second (FEV1) that was 120% of predicted. The consultant concluded that Case 2 did not have pulmonary disease, but felt instead that she had extensive vitiligo, or patchy skin depigmentation. He believed that Case 2's skin condition had been caused by historical exposure to diacetyl, despite offering no explanation as to how this result could take place medically, nor providing any published references from the medical literature in which any physician had ever described an association of vitiligo with diacetyl exposure. Nonetheless, he stated his opinions were expressed "to a reasonable degree of medical certainty".

Case 2's case was settled in November, 2010.

### Case 3

Case 3 worked at the Agrilink Foods Popcorn Plant in Ridgway, IL from October, 1989 to January, 2003 as a packer, line worker, and warehouse worker. In her lawsuit against flavorings manufacturers, Case 3 stated that she first started having breathing problems two years before the plant closed in 2003. She was a long-term cigarette smoker, starting at age 20 and continuing until age 57 in 1995, at about a pack per day.

A pulmonary consultation was obtained in early 2003. Spirometry testing showed a "mild obstructive ventilator impairment," not responsive to bronchodilators, and a reduced diffusing capacity. The treating pulmonary doctor concluded that Case 3 probably had mild COPD, primarily emphysema, related to her long history of smoking. Her lung volumes in January, 2003 were within the normal range, with an FVC 106% of predicted, and an FEV1 86% of predicted. Her pulmonary doctor thought it was possible that exposures in the workplace could have had some effect, but believed that her abnormal pulmonary function could just as easily have been explained by her smoking history. A high resolution CT scan of her chest showed no signs of air trapping, including expiratory views. No bronchiectasis or ground glass changes were noted, and the only finding noted was some "quite mild" thickening of tissue within the pulmonary lobules, possibly representing a mild hypersensitivity pneumonitis. No changes typically found in cases of constrictive bronchiolitis were described.

Case 3 saw another lung specialist for breathing problems in February, 2003. This doctor felt that Case 3 could have either COPD or bronchiolitis from chemical exposures, but concluded that she required a lung biopsy in order to determine the correct diagnosis. Case 3 underwent a lung biopsy later that month, with tissue sampling from two different lobes, and the specimens were sent to the Armed Forces Institute of Pathology for analysis. Case 3 was found to have emphysema and mild bronchiolar fibrosis, consistent with respiratory bronchiolitis, or lung injuries caused by long term cigarette smoking. No lesions typical of constrictive bronchiolitis were seen.

Case 3 was placed on bronchodilators and inhaled steroids, which seemed to improve her symptoms of exertional shortness of breath. Over the next several years she remained stable, with pulmonary function testing showing a forced vital capacity ranging between 96% and 112% of expected for her age and gender, and an FEV1 between 75% and 88% of expected. She was stated to have been compliant with using steroid and bronchodilator inhalers, continued to do well clinically, and, during her pulmonary clinic visits, was repeatedly diagnosed with stable COPD and emphysema.

At the request of her attorney, Case 3 had another evaluation by a doctor selected by her counsel on July 24, 2006. Despite her generally unremarkable tests of pulmonary function, her stable clinical picture, and her biopsy-proven lung disease that was directly connected to her long term cigarette smoking, this doctor diagnosed Case 3 with "bronchiolitis obliterans syndrome," and claimed that her clinical findings were "more likely due to occupational exposure." Although the pathologist who read Case 3's lung biopsy report confirmed the prior diagnosis of respiratory bronchiolitis, this new doctor claimed that the biopsy demonstrated changes also of bronchiolitis obliterans, but did not identify what changes he was referring to. The consultant did not mention in his report if he looked at the biopsy slides in question, or whether his conclusion was merely a reinterpretation of the findings described by the pathologist in 2003, leading him to arrive at a completely different diagnosis.

Case 3's case was settled in November, 2010.

### Case 4

Case 4 worked for a candy manufacturing plant for almost 30 years. During this time, he was primarily responsible for mixing and heating various ingredients to make hard candies that were cooled and then packaged by others at the plant. He and other coworkers were also tasked with cleaning out the 150 pound kettles in which the candy was heated about once a week, using caustic cleaning solutions containing 35-40% sodium hydroxide, a very powerful basic solution. This cleaning process took about four hours to complete, and was associated with coughing fits experienced by Case 4 that seemed to resolve by the time he got home from work.

Case 4 never smoked, but lived with his wife, who smoked throughout their marriage starting in about 1974. In early 2001, Case 4 presented to his family doctor with complaints of a persistent cough. After he failed to improve following a course of antibiotics, a chest x-ray was obtained, showing signs of diffuse bilateral interstitial lung disease. Over a period of several months, he was treated with inhaled steroids and bronchodilators, which seemed to help his symptoms. In early 2002, he was diagnosed with "allergic rhinitis and allergic bronchitis." A repeat chest film showed worsening interstitial

infiltrates involving his upper lung fields, as well as the right middle and lower lobes. A CT scan of the chest on February 13, 2002 showed signs of emphysema with patchy interstitial fibrotic changes in both lungs, more prominent in the right lower lung. Case 4 had sustained a gunshot wound to the right chest in 1973, following a dispute with his first wife and her boyfriend, and there were retained bullet fragments in the right lung fields, clearly visible on his subsequent radiologic studies. A pulmonary consultation was obtained, which concluded a diagnosis of “diffuse interstitial lung disease” with signs of emphysematous changes. Other laboratory studies suggested that allergies may have contributed, and the pulmonologist recommended a lung biopsy and a comprehensive immunologic workup.

A lung biopsy from Case 4’s right lung was performed on February 14, 2002, described as “interstitial fibrosis with chronic and granulomatous inflammation,” with additional findings of emphysema and “honeycomb changes.” The pathologist concluded that the tissue findings were most suggestive of hypersensitivity pneumonitis, or possibly sarcoidosis. The tissue was also sent to the Mayo Clinic for a second opinion, which felt that the biopsy represented “...a most difficult case without a clear solution.” The differential diagnosis was felt to include an atypical infection, an autoimmune disease process (Sjogren’s disease), or an unusual presentation of sarcoidosis. Emphasis was placed on the small granulomas and giant cells that were seen in the biopsy tissue, findings typically seen in persons with hypersensitivity pneumonitis.

Case 4 continued to be prescribed bronchodilator and steroid inhalers, with an active diagnosis from his treating lung doctor during 2002 of “pulmonary fibrosis of unknown etiology.” Case 4 filed a Worker’s Compensation claim on January 16, 2003 at the age of 60, indicating that he believed that “...he became ill from inhaling a cleaning agent used to clean the cookers”, which he had used over the past 25-26 years at the plant. An Independent Medical Evaluation (IME) was obtained, which concluded that Case 4 most likely had hypersensitivity pneumonitis, based on the two very similar pathology opinions regarding his lung biopsy. If his hypersensitivity pneumonitis was work-related, neither the cause of that injury nor its source was felt to be apparent. The IME concluded that he could not be any more specific regarding a cause for Case 4’s lung disease.

Case 4 filed suit against the flavorings manufacturers that supplied the candy company where he worked for almost 30 years. Case 4’s new attorneys hired an occupational physician to evaluate him, which was completed on January 11, 2005. This physician confirmed Case 4’s history of using a caustic cleaning solution every week at work, and indicated that this material was “...very irritating and it aggravated his lung condition”, causing coughing fits while using the cleaner. After reviewing Case 4’s medical records and biopsy reports, the consultant concluded that Case 4 had hypersensitivity pneumonitis with fibrosis and bullae formation, and named diacetyl as a possible contributor to Case 4’s lung disease.

About 18 months later, the occupational physician completed a reevaluation of Case 4, noting that his health was about the same, still using oxygen at 2 liters/minute, had not required any interim hospitalizations, and had not undergone any additional major diagnostic procedures since his first evaluation. He again reviewed Case 4’s biopsy reports from 2002, as well as his recent testing of pulmonary function and clinic visits. The physician went on to conclude that Case 4 now

had “bronchiolitis obliterans syndrome” instead of hypersensitivity pneumonitis, for reasons that were not explained. However, both his original January, 2005 diagnosis of HP and the July, 2006 diagnosis of bronchiolitis obliterans syndrome were made “...to a reasonable degree of medical certainty.”

Case 4 settled his litigation for an undisclosed amount in late 2007.

### Case 5

Case 5 started working at Tastemaker, a flavorings manufacturing company in Ohio, in 1993. He was initially employed as an operations clerk, and then the following year became an “inventory control analyst”, a position he recalled holding for four years. The company was acquired by Givaudan-Roure in 1997, and Case 5 stayed on with the new company. From 1998 to 2001 he was a network technician and personal computer/help desk analyst at the company, prior to having his job outsourced to another company. He believed he was exposed to chemicals on the production floor once or twice a week as an inventory control analyst, but was never engaged in the production or manipulation of these chemicals directly. He admitted to being a user of smokeless tobacco for 20 years, and recalled a history of allergies and exertional dyspnea since 1983. Prior to working at Tastemaker, Case 5 owned his own desktop publishing company from 1991 to 1992, and after leaving Givaudan in 2001, he worked at Manpower as a “support analyst” for a year, then as a computer consultant for Procter and Gamble from 2002 to 2005. He then was hired by Trasy as a technical support analyst for the Sara Lee Corporation until 2008, and then by Sarcom as a “service technician.” All of these positions appear to have generally involved computer network maintenance, help desk staffing, and other information technology-related tasks. None of these jobs were stated to have involved any exposures to chemicals as a primary operator.

In early 2006, at the age of 47, Case 5 started complaining of increasing shortness of breath, and was initially thought to have bronchitis. Although he initially responded to breathing treatments, his condition did not ever get back to his baseline, and he was sent for additional testing. Pulmonary function testing on March 6, 2006 showed him to have signs of moderate restrictive lung disease. A chest x-ray that day showed an “ill-defined infiltrate,” and a subsequent CT scan demonstrated “extensive changes of pulmonary fibrosis,” with signs of honeycombing and ground glass changes. Case 5 provided a history of having received prior chest and abdominal radiation treatments, but further details were not discussed. His findings were concerning for possible lymphoma or sarcoid, or possibly metastatic cancer to the lungs. A bronchoscopy was done a month later, with findings of normal airway anatomy, and lung bronchial washings and biopsy specimens were submitted and found to be non diagnostic.

A VATS procedure was performed on May 11, 2006; operative findings described Case 5’s lungs as appearing “grossly nodular.” Three wedge biopsies were performed, and were felt to be consistent either with Nonspecific Interstitial Pneumonitis (NSIP) or Idiopathic Pulmonary Fibrosis (IPF), with findings of diffuse interstitial fibrosis with emphysema. The specimens were forwarded to the Mayo Clinic for a second opinion, which concluded that the most compelling diagnosis was IPF.

Over the next several months, Case 5’s condition continued to deteriorate. He was placed on home oxygen and heavy doses of oral

steroids in an attempt to slow the progression of his lung disease. Case 5 filed suit in July, 2008 against Tastemaker and Givaudan, his former employers from 1993-2001, as well as several other manufacturers and distributors of flavorings, claiming that his lung disease was caused by his exposures to chemicals in the workplace. His attorney asked an occupational physician to perform an independent evaluation. At the time of his evaluation, this consulting doctor did not have Case 5's medical records, but on the basis of his physical exam, and on Case 5's history of working at a flavorings company (even though he was employed as a computer and inventory analyst, and not someone who actually had regular significant contact with flavorings and other chemicals), the consulting doctor concluded that Case 5's lung disease was "...caused by flavorings while working at the Givaudan facility in Cincinnati, Ohio." Furthermore, this physician felt that Case 5's most likely diagnosis was bronchiolitis obliterans syndrome, despite Case 5 having:

- Open lung biopsy findings that were strongly compelling for UIP/IPF, including a second opinion from the Mayo Clinic, which concluded that IPF was the most likely diagnosis.
- CT scan findings of honeycomb changes in the lung, a descriptive finding not at all associated with constrictive bronchiolitis, but highly consistent with NSIP or IPF.
- Pulmonary function testing repeatedly showing moderate to severe restrictive changes and no evidence of obstructive lung disease (Restrictive lung disease is typical for NSIP and IPF and not characteristic for constrictive bronchiolitis, for which fixed obstruction is the typical finding on pulmonary function tests).

As an aside, diacetyl and/or butter flavoring exposures have never been associated with developing either IPF or NSIP in the occupational or general medical literature, to my knowledge. Case 5's litigation was eventually settled.

## Case 6

Case 6 worked at Carmi Flavors as a production helper and forklift driver from February to July, 2006. He described his job as "a little of everything," preparing various flavor recipes, packaging, and loading finished product, delivering products to local companies, and cleaning the pots used to make flavorings. Cal/OSHA visited the Carmi facility in April, 2006, and NIOSH performed a comprehensive evaluation of the plant in July, 2006. On a questionnaire that Case 6 filled out for NIOSH, he noted that he remembered using diacetyl as an ingredient only once, in March, 2006. He recalled starting to feel breathing problems in June, 2006 when other workers were using powdered diacetyl.

Prior to working at Carmi, Case 6 worked as an assistant production worker in a meat packing facility. Before that, he was jailed in Iowa for three years after being convicted of robbery. He had at least two other prior felony convictions, (one for armed robbery, and another for burglary), and had worked mostly in shipping and receiving for various companies over the years. Case 6 also had a history of drug abuse, and admitted to using intravenous and inhaled forms of cocaine or crack in his teenage years and early twenties, and continued to intermittently use inhaled forms of cocaine. He was a former smoker, but denied currently using cigarettes.

During his NIOSH evaluation on July 24, 2006, Case 6 had a breathing test that showed severe obstructive lung disease. It was recommended that he seek further medical evaluation to determine the nature of his lung problems and to receive treatment if indicated. A CT scan of his chest was performed on July 29, 2006 to "rule out interstitial lung disease." The study found no evidence of interstitial lung changes, and no significant abnormalities, other than scattered mildly enlarged lymph nodes, were described. A pulmonary evaluation was obtained the next day, indicating that Case 6 had severe "asthma and/or bronchitis of unclear etiology." Pulmonary function testing again demonstrated severe obstructive lung disease with a significant response to bronchodilators (both the FEV1 and FVC improved by over 30%).

Soon thereafter, Case 6 was evaluated by the transplant program at the University of Southern California. As part of his transplant evaluation, Case 6 underwent a psychosocial assessment, which reported that Case 6 was a heavy drinker from age 12 to 30, and that in his teens and early twenties, he had used just about every illegal drug, including heroin and methamphetamines. Case 6 did not appear to be mentally prepared for a lung transplant, and it was not clear to the examiner that his lung disease was related to chemical exposures in the workplace.

On August 11, 2006, at the age of 38, Case 6 underwent a lung biopsy. The final biopsy report noted the presence of a "fibronecrotic granuloma, secondary to histoplasmosis", a fungal lung infection, and the presence of "obliterative bronchiolitis" adjacent to the infectious nodule. The surgeon performing the lung biopsy notified Case 6's primary doctor that his biopsies showed "patchy nonspecific perivascular fibrosis and chronic inflammation."

Case 6 filed a claim for worker's compensation benefits, claiming lung damage from workplace exposures from his five month employment at Carmi Flavors. He also decided to transfer his care to a different primary doctor. A completely new illness history was described by this doctor, with Case 6 now stating that from the very first day he started working at Carmi, he had coughing, shortness of breath, and chest pain in the workplace. He claimed to have informed his employer of his symptoms, but was not told to seek medical attention.

Over the next year, Case 6's new doctor ordered a vast array of medical testing, including additional CT scans of the chest, multiple tests of pulmonary function, cardiac catheterization, sleep studies, and psychiatric evaluations. His primary doctor prescribed high doses of oral morphine to be taken on a routine basis, along with antidepressants and sleep medications. Over the next several months, Case 6 was admitted to several different Los Angeles area hospitals for episodes of acute chest pain and rapid heart rate, with myocardial infarctions and pulmonary embolisms ruled out on many occasions. On one of these emergent visits, a urine toxicologic screen was performed, which returned positive for cocaine.

Case 6 obtained additional counsel on top of his worker's compensation claims to file suit against the manufacturers and suppliers of flavorings to Carmi Flavors in January, 2007, claiming that his workplace exposures were responsible for his lung problems. He was eventually referred to UCLA for another lung transplant evaluation. He was seen there by an occupational medicine physician, who was provided a subset of his medical records. After his evaluation, Case 6 was referred to the UCLA transplant team "due to his bronchial

asthma.” However, instead of pursuing a transplant evaluation at UCLA, Case 6 decided to refer himself to Cedars-Sinai. In a history taken by the Cedars-Sinai transplant surgeon, Case 6 noted being initially evaluated for a lung transplant at USC, but then was asked by his lawyer to go somewhere else.

Over the next few months, Case 6 underwent a wide variety of pre-transplant testing at Cedars-Sinai, and reported decreasing his use of narcotic pain medications, which the transplant team demanded prior to considering him as a candidate. In his pre-transplant evaluation, the Cedars-Sinai transplant program director diagnosed Case 6 with “Bronchiolitis Obliterans and Organizing Pneumonia” (BOOP).

Case 6 underwent bilateral lung transplantation on May 28, 2009, with a postoperative course marked by extreme difficulties with pain control, as well as clinical signs of narcotic withdrawal. Pathologic analysis of his explanted lungs revealed severe chronic inflammation with findings that suggested two possible diagnoses: diffuse panbronchiolitis and chronic hypersensitivity pneumonitis. Neither constrictive bronchiolitis nor BOOP were mentioned by the Cedars-Sinai pathologist.

The appearance of Case 6’s diseased lungs removed during his transplant procedure suggested an ongoing exposure to harmful chemicals, likely from inhaled drugs of abuse, rather than from the residue of damage associated with his brief employment (less than five months) from three years earlier at the flavorings company. In addition, Case 6’s multiple emergency department presentations for episodes of acute chest pain and rapid heart rate were typical for individuals actively abusing crack cocaine or inhaled cocaine powder.

A medical consultant was asked to provide expert medical testimony for Case 6. He concluded that Case 6 had “bronchiolitis obliterans”, which he believed was confirmed by pathologic analysis of Case 6’s explanted lungs, even though this diagnosis was not even mentioned as a possible alternative by the treating pathologist, and was not supported by radiologic studies. After assuming somehow that Case 6 had bronchiolitis obliterans, this doctor reviewed various risk factors for bronchiolitis obliterans, such as infection, medication reactions, and rheumatologic conditions. He concluded that since none of the traditional risk factors for BO were present, that Case 6’s five month period of employment at Carmi Flavors must have been to blame for this diagnosed disease.

Settlement for Case 6 was achieved by all parties in October, 2011 for an undisclosed amount.

## Case 7

Case 7 started working at Gold Medal Products in 1990. For the first six years of her employment, she assembled electrical equipment used at food concessions, such as candy, popcorn, and cotton candy machines. For a few weeks at the end of 1995, Case 7 tested bucket pumps used to pump hot oil for popcorn machines, and occasionally performed soldering of the pump electrical connections. To test the pumps, she used coconut or corn oil, and then cleaned out the hoses with pressurized air. This oily mist sometimes blew into her hair and clothing, and she noted that sometimes she would cough during this activity.

In January, 1996, Case 7’s role changed to packaging various popcorn flavorings and powders, as well as test popping several batches

of popcorn. In late February, 1996, she went back to the bucket pump testing, where she worked for 2½ days prior to becoming ill with symptoms of coughing, muscle pains, shortness of breath with activity, and a rash on her leg that developed over the following weekend.

She was briefly admitted to the hospital and diagnosed with bronchitis. Tests of pulmonary function in April, 1996 showed restrictive changes, with an FVC of 41% of predicted, and an FEV1 of 45% of predicted. Her diffusion capacity was markedly low at 60% of predicted. A CT scan of her chest in June, 1996 showed interstitial fibrosis with traction bronchiectasis. A lung biopsy was performed on June 18, 1996, and found changes of interstitial pneumonia with no mention of small airway disease, possibly due to collagen vascular disease, or idiopathic. A CT scan 20 months later on February 23, 1998 was felt to show “moderate idiopathic pulmonary fibrosis” with significant honeycombing. Physical examination of Case 7’s lungs revealed diffuse inspiratory crackles, common in patients with interstitial lung fibrosis. She was treated with high doses of steroids, followed by long term immunosuppressant medications, and appeared to respond well to her medications, with much slower progression of her respiratory symptoms and stabilization of her pulmonary function testing.

From 1997 until 2005, Case 7 continued to work for Gold Medal assembling candy and popcorn machines, a task that created no dust or vapor exposures.

Case 7 filed a worker’s compensation claim in April, 2004 at the age of 56, stating that her exposures to diacetyl in the workplace caused her to develop “breathing problems.” Her claim was disallowed by the Ohio state bureau on worker’s compensation, which could find no causal relationship between her condition and the alleged source, popcorn flavoring. Her attorneys appealed the decision, and her claim was again disallowed in April, 2005, with the finding that Case 7 did not meet the burden of proof for confirming an occupational disease connected to her employment, and that her lung problems were not connected to her workplace exposures. Another appeal was also denied in July, 2005.

In September, 2005, Case 7 appealed her decision again, this time in the court of common pleas, but her appeal was dismissed without prejudice in March, 2006. In the dismissal notice, Case 7 was reserved the right to refile her claim again within one year, which she did not submit.

Case 7 filed suit against the manufacturers and suppliers of flavorings to Gold Medal Products in May, 2006, claiming that her workplace exposures to these products were responsible for her lung problems. Case 7’s attorney contacted an occupational physician to perform an independent medical evaluation and to act as an expert for the plaintiff. Despite having radiologic studies, pulmonary function tests, physical examination findings, and lung biopsy results that clearly supported a diagnosis of interstitial pulmonary fibrosis, the doctor concluded that Case 7, to a reasonable degree of medical certainty, should be diagnosed with “bronchiolitis obliterans syndrome.”

Beginning in April, 2007, defendants began filing motions for summary judgment, relying upon the decision of the Ohio industrial commission that Case 7’s breathing problems were not work-related. The trial court agreed, and granted all of the motions for summary judgment. Case 7’s attorneys appealed this decision as well, but the Ohio First District Court of Appeals affirmed the trial court’s judgment in July, 2008.

## Case 8

Case 8 spent her childhood in Mexico City and Tijuana, and moved to the United States as an early teen. After a series of retail and shipping/receiving type jobs, she worked at Carmi Flavors as a compounder of flavorings for eight years, from 1997 to 2005. After her first nine months of employment, while working with a vanilla powder, she developed a worsening cough and congestion, and was evaluated at an occupational health clinic. She had active wheezing on examination, which responded to a nebulized bronchodilator. She was diagnosed with “reactive airway disease,” and scheduled for pulmonary function tests. These indicated severe restrictive airway disease, with an FVC ranging from 35-46% predicted, and an FEV1 of 45-50% of predicted. Post-bronchodilator spirometry testing was not performed. Case 8’s working diagnosis shifted to “restrictive airway disease,” and her superiors at Carmi Flavors were advised of her breathing problems, and agreed to relocate her to a different work site at which she would have less potential for chemical exposures.

Over the next few days, Case 8 was reevaluated, continued to have diffuse wheezing, and was treated with oral steroids, as well as steroid and bronchodilator inhalers. She was diagnosed with asthma, and advised to avoid powders and dusts. Case 8 did not show up for several further scheduled medical evaluations, and was eventually discharged from care for lack of compliance. No follow up tests of pulmonary function were performed during this period.

Case 8 worked at Carmi for the next several years, with no reported respiratory health conditions other than occasional upper respiratory infections, which responded to antibiotics and decongestants. In 2004, almost six years later, she developed an occasional cough that gradually became more persistent, and was seen twice and treated for upper respiratory infections. In late 2005 she told her new primary care doctor that she had a recurrent cough over the past year, along with occasional chest pain and difficulty breathing. She was referred to a pulmonary specialist, and was placed on oral steroids and inhalers. She was advised to stop working completely, due to concerns that her workplace might be causing or worsening her breathing condition, and was referred for further testing.

A high resolution CT (HRCT) chest scan on November 30, 2005 showed some subtle patchy ground glass changes in both lung fields, and a listing of the chemicals in her work environment was obtained. She was felt to have occupational asthma or “reactive airways syndrome”, and was deemed to be totally disabled. Her last day of work at Carmi Flavors was December 21, 2005.

Pulmonary function testing was performed on January 18, 2006, and revealed signs of severe obstructive lung disease, with an FEV1 of 18% of predicted, and an FVC 34% of predicted, with signs of significant air trapping. A repeat HRCT the following week showed resolution of the ground glass changes, along with some scattered fibrotic changes in her lower lung fields. A lung biopsy was performed on March 7, 2006, and found to show evidence of granuloma formation with giant cells, along with focal areas of interstitial fibrosis. The overall pathologic impression was of hypersensitivity pneumonitis.

Case 8 was referred to UCLA for a second opinion. The occupational physician at UCLA noted that Case 8 kept two pet birds at home. In addition to hypersensitivity pneumonitis, it was felt that “bronchiolitis obliterans” should also be considered as a possible

alternative diagnosis, because of Case 8’s work exposures to “diacetyl-containing flavorings.” A second opinion regarding Case 8’s March lung biopsies was also obtained from a UCLA pathologist, who confirmed the presence of poorly formed granulomas, and did not feel that the tissue findings supported a diagnosis of bronchiolitis obliterans, a diagnosis he was specifically asked to consider.

Over the next several years, Case 8 had frequent spirometry testing, which generally showed her to have severe stable obstructive lung disease. Oxygen saturation testing showed normal resting values, with a mild drop following exercise, and she did not qualify for home oxygen therapy. She was referred to the UCLA transplant program in 2006 at the age of 44, and was eventually accepted into the program in July, 2009 after her pre-transplant studies.

Case 8 filed suit against the manufacturers and suppliers of flavorings to Carmi Flavors in 2007, claiming that her workplace exposures were responsible for her lung problems.

Case 8’s attorney contacted a medical consultant to perform an independent medical evaluation and to act as an expert for the plaintiff. Despite having radiologic studies, pulmonary function tests, a demonstrated clinical response to bronchodilators and oral and inhaled steroids, and lung biopsy results that all supported a diagnosis of hypersensitivity pneumonitis, this doctor concluded that Case 8 should be diagnosed with “bronchiolitis obliterans.” She had remained on the UCLA transplant list almost two and a half years after being accepted, a time period almost ten times longer than the national average wait time for her last UCLA-calculated “lung allocation score” [17]. Attorneys for Case 8 settled her case in January, 2012.

## Case 9

Case 9 was born in Mexico, and moved with his family to the United States at age 12. At the age of 21, he went to work for Olmarc, a contract packager for a variety of foods and beverages, where he was employed as a product inspector, and then as an assistant mixing supervisor, working with corn flour, starch, sugars, and flavorings. Most of what he mixed was in powdered form, and one of the products he helped make was microwave popcorn with butter flavoring. He did not recall having any breathing problems while working there, and said no one used respiratory protection at the plant for any job function.

After two years there, he went to work for Flavors of North America, later known as FONA International, where he acted as a compounder and production supervisor of liquid and powdered flavorings, and also performed spray drying of certain products. About midway through his eight and half year tenure there, he noticed having worsening shortness of breath with exertion over a two week period. He was seen at an emergency department in 1994, where he was told he had “asthma,” and was prescribed an inhaler. He had upper respiratory infections several times a year, but did not see a doctor very often for these, and he did not have any pulmonary function tests or other screening evaluations for his asthma.

In November, 1997, Case 9 left FONA and started working at Sterigenics, a contract sterilization services company for the medical device and pharmaceutical industries a few months later as a “materials handler” and operator. After ten months, he returned to Flavorchem

as a dry mixing compounder. Five months later, Case 9 underwent an occupational screening evaluation, which indicated an FEV1 of 1.22 L, a forced vital capacity of 3.05 L, and an FEV1/FVC ratio of 39%. It was concluded that Case 9 had severe obstruction as well as a low vital capacity, and he was not allowed to use a respirator at work. Company officials at Flavorchem recommended that he not work with vitamins or acetic acid, and Case 9 informed them that he would follow up with a lung specialist.

In December, 2001, Case 9 developed worsening back pain, cough, and hoarseness, and was diagnosed in the emergency room with an “acute exacerbation of asthma”, and was treated with oral steroids and a bronchodilator. A few weeks later, Case 9 was seen in clinic, where he was noted to have had a history of asthma for many years, along with a family history of asthma. He was a smoker and occasional drinker, and was noted to have wheezing on exam. He was again diagnosed with acute asthma, and placed on inhalers and cough suppressants.

He next complained of breathing problems a few years later, in April, 2004. He went to the emergency room, where he denied having any regular doctor, and commented that he usually just used his son’s asthma inhaler when he needed it, and didn’t go to the doctor himself. His oxygen saturation on room air was just 90%, and he had severe bilateral wheezing on lung exam, and needed to be admitted to the hospital. He related that he had carried a diagnosis of asthma for the past 14 years, and that for the past week, his breathing had been getting progressively worse. A pulmonary consult was ordered, along with intravenous steroids and frequent nebulizer treatments.

The consultant ordered a chest CT, which showed minimal scattered ground glass changes, thought to be related to Case 9’s severe asthma. Continued steroids and bronchodilators gradually improved his breathing, and he was discharged with a diagnosis of improved asthma, and maintained on inhaled bronchodilators. His lung consultant discovered a total of three prior hospital admissions for asthma exacerbations, and believed that his CT findings were due to “mucous plugging” associated with his asthma.

The next month, Case 9 experienced another episode of severe wheezing and difficulty breathing, despite continuing on inhalers and being treated with antibiotics for a presumed bronchitis. He was again admitted for “severe asthmatic bronchitis,” and had a high resolution chest CT on May 21, 2004 which showed air trapping and areas of mucus plugging and bronchial dilation, “...consistent with the patient’s history of asthma.”

Over the next six months, Case 9 was seen several times by his primary care doctor and pulmonologist, and maintained on inhalers with occasional courses of antibiotics for upper respiratory infections. Another spirometry exam on November 10, 2004 showed an FEV1 of 1.32 L, FVC of 2.94 L, not responsive to Albuterol. A follow up high resolution CT scan was performed on November 24, 2004, showing complete resolution of the previously seen ground glass changes. His lung doctor provided the good news to Case 9, and informed his primary care doctor that Case 9 had severe asthma that might be affected by work exposures, but Case 9 told him that it would be impossible for him to change jobs. Thus, Case 9 continued to work as a production supervisor, monitoring the company warehouse for materials, packaging, inventory, and cleanup; he also became the first supervisor trained on spray dried products.

In March, 2005, Case 9 was again admitted to the hospital for an “asthma exacerbation,” slowly improved over a four day period, and was discharged on oral steroids and antibiotics. During a follow up clinic visit a few weeks later, his lung doctor recommended a lung biopsy, which was done during a bronchoscopy procedure a week later, on March 22, 2005. Unfortunately, Case 9 did not tolerate the procedure well, and the biopsies were mostly inadequate, with only one specimen containing alveoli. This specimen showed marked chronic inflammation and focal acute inflammation; no bronchiolar lesions or granulomas were described. Bronchial washings were found to grow out 2+ *Candida* and 4+ *S. pneumonia*, consistent with an acute bacterial infection and possible yeast colonization associated with chronic steroid use. Neither a diagnosis of “bronchiolitis obliterans” nor of constrictive bronchiolitis was mentioned in the pathology report.

Over the next six months, Case 9 continued to be treated for asthma and occasional upper respiratory infections, which appeared to respond to antibiotics and occasional rounds of oral steroids. He was referred to a different pulmonary doctor by his primary care physician on November 30, 2005, who again described a significant family history of asthma, noted that Case 9’s children also had asthma, and that Case 9 had been diagnosed with asthma for at least 18 years. This pulmonary physician concluded that Case 9 had “...what we call chronic status asthmaticus,” associated with chronic moderate obstructive lung disease. Serum IgE levels were obtained, and found to be about twice their normal levels, a finding common in chronic asthmatic patients.

Another high resolution CT scan of the chest was done February 9, 2006, showing mild dilation of the upper airways, patchy areas of fibrosis in the upper lung lobes, and faint diffuse nodules. No mosaic pattern, ground glass changes, or air trapping was identified. Case 9’s primary lung doctor decided to get yet another expert opinion on Case 9’s lung disease, largely due to his persistent symptoms and inability to be weaned off of oral steroids.

Case 9 was seen on March 3, 2006 by the new pulmonologist, who again noted that Case 9 had a long history of asthma, had four siblings with asthma, and that two of his three children had asthma. Case 9 described working in a dusty environment, and there was concern that his workplace exposures might be worsening his asthma symptoms. He concluded that Case 9 had asthma that required high dose steroids for control. After some discussion with Case 9’s primary doctor and most recent lung doctor, Case 9 tried a new monoclonal antibody therapy used to treat patients with severe allergic asthma. His diagnosis remained as severe, complex asthma, perhaps with an occupational component.

In June, 2006, the lung doctor tasked with studying the Flavorchem facility contacted Case 9’s primary lung doctor, informing him that doctors at National Jewish Medical Center had been studying the flavorings industry, and found that many workers had “BOOP”, or bronchiolitis obliterans organizing pneumonia. Further, the doctor thought that BOOP, and not asthma, might be the cause of Case 9’s chronic difficult-to-treat symptoms. Case 9’s primary lung doctor decided he would treat the asthma as best he could, which he felt was still a major part of Case 9’s overall lung problems. He also decided to refer Case 9 to National Jewish Medical Center for another lung evaluation, his fourth in two years. The pulmonary physician noted in his referral

letter that Case 9's diffusing capacity also seemed to be decreasing, and that the National Jewish doctors could do a lung biopsy if they wanted to clarify the diagnosis, or they could send Case 9 back to his local institution for this biopsy.

On July 24, 2006, Case 9 traveled to Denver to be evaluated at National Jewish Medical Center. His family history of asthma and long-term personal history of asthma were again described, along with the seasonal variation in his symptoms that seemed to make his breathing much worse. On exam, he was found to have expiratory wheezing; a high resolution CT scan was ordered, which was felt to show signs of mosaic attenuation and air trapping. Case 9 was felt to probably have bronchiolitis obliterans and bronchiectasis, as well as asthma and severe allergies. Another serum IgE level was obtained, and found to be three times the limit of normal, consistent again with allergic asthma. Spirometry testing was performed and found to show severe obstruction, but with highly variable testing results, and Case 9 demonstrated a moderate response to bronchodilator therapy. Lung biopsy was considered, but then deemed unnecessary for making a "bronchiolitis obliterans" diagnosis. A trial of various chemotherapy agents, such as Methotrexate or Cytosan, was suggested as a reasonable course of action.

After returning home from Denver, Case 9 followed up with his primary lung doctor. After reviewing the opinions of the National Jewish doctors, Case 9's lung doctor changed his diagnosis from chronic severe asthma to severe work-related fixed airways obstruction, or "clinical bronchiolitis obliterans." Case 9's last day of work at Flavorchem was noted to be June 15, 2006, and he was terminated from employment on September 13, 2006 at the age of 41.

Case 9 was started on Methotrexate in mid- October, 2006 and remained on this drug until March, 2007, but the treatment was not improving his symptoms. Over the next six months, Case 9 appeared to stabilize on a regimen of oral steroids, inhalers, and occasional courses of antibiotics for upper respiratory infections. Repeat spirometry studies in August, 2007 showed an FEV1 of 1.26 L and an FVC of 2.77 L, stable results compared to studies from prior years. Case 9's primary lung doctor wanted him to be evaluated for lung transplant, despite his generally stable or improving symptoms. His symptoms and objective lung studies continued to remain stable over the next several years, with Case 9 continuing on a treatment plan of moderate doses of oral steroids, inhalers, and antihistamines. All of Case 9's symptoms and clinical findings appear consistent with severe chronic asthma, possibly made worse by occupational exposures to as yet unidentified agents.

Case 9 filed suit against the manufacturers and suppliers of flavorings to Flavorchem and FONA, claiming that his workplace exposures to these products were responsible for his lung problems. Most of the companies that Case 9 sued settled out of court for undisclosed amounts of money. In August, 2010, a verdict was reached for over \$30 million against BASF Corporation, the largest verdict in a flavorings case to date at that time. This result was supported by just one out of four pulmonary evaluations returning a conclusion of "bronchiolitis obliterans", and with three other expert evaluations determining a diagnosis of severe chronic asthma. In addition, this "bronchiolitis obliterans" conclusion was made in the absence of an adequate lung biopsy that could have better clarified Case 9's disease process. The verdict has been going through a lengthy appeals process.

## Case 10

Case 10 was born in Mexico in 1957, and came to the United States at the age of 22. He worked as a shipping clerk for a women's clothing retailer for ten years until the company was sold around 1990, then worked again as a shipping clerk for another women's clothing store until 2000. In late April, 2000, Case 10 started work at Carmi Flavors, where he helped other workers prepare and package powdered and liquid flavorings and performed cleanup activities at the facility.

Case 10 was evaluated for cough and congestion once in 2001, once in 2003, and again in 2004, receiving an acute bronchitis diagnosis on each occasion, and treated with respiratory inhalers, cough suppressants, and usually a course of antibiotics. In May, 2004, Case 10 had a chest x-ray that was read by the radiologist as showing changes of acute bronchitis.

Case 10's last day of work at the Carmi facility was Friday, February 3, 2006. At the end of his shift, he felt more tired than usual and had nasal congestion, which he attributed to working with powders. Over that weekend, his breathing seemed to get progressively worse and he asked his family to drive him to the ER on Monday morning. There, he reported a cough with fever for the past three days, and was wheezing on exam. His oxygen saturation was 96% on room air, and a chest x-ray showed signs of a "probable mild bronchitis." A white blood count was elevated at 12.5, and he was treated with intravenous antibiotics and steroids. He was discharged home with a diagnosis of acute bronchitis with bronchospasm, and was given an inhaler, a prescription for oral antibiotics, and a brief course of oral steroids. A sputum culture was later found to be positive (4+) for *H. influenzae*.

Case 10 was seen for follow up by a local family practice doctor the next day. A repeat chest film was ordered, which showed no signs of pneumonia. Two days later he was still complaining of a persistent productive cough. He continued on antibiotics and steroids, as well as his inhaler. One week later, he felt better, but noted feeling easily fatigued, and he had not returned to work. He had good oxygen saturations at 95%, but still had significant wheezing. A CT scan of the chest was performed on February 21, 2006, which showed mildly dilated bronchi in the upper lobes, along with patchy areas of scarring in the left lower lobe and upper lung fields. He was seen a few days later with slow improvement, and was given a diagnosis of bronchiectasis.

Three weeks later, Case 10 complained that his cough was getting worse, and was again wheezing on exam. Another round of antibiotics, steroids, and inhalers was prescribed, but at a follow up visit shortly thereafter, he was found to have a fever and a worsening productive cough. He had persistent wheezing, and was diagnosed with bronchiectasis and acute bronchitis, and again received a course of oral antibiotics and inhalers.

On March 24, 2006, Case 10 underwent a pulmonary consultation, where his exam showed bilateral diffuse wheezing and reduced breath sounds. His labs and radiologic studies were reviewed, and he was diagnosed with reactive airway disease secondary to recurrent bronchitis, and bilateral cylindrical bronchiectasis secondary to previous infection. The pulmonologist also suggested he may have hypersensitivity pneumonitis. A combined course of two broad spectrum oral antibiotics was started, and sputum cultures were obtained. A follow up CT scan was also recommended, as well as possible bronchoscopy with biopsy if his symptoms did not improve. At a follow up visit with

his family practice doctor on April 5, 2006, Case 10 felt much better, but still complained of increased sputum, and on exam had much less wheezing present. He was again diagnosed with bronchiectasis.

Case 10 met with an attorney on April 6, 2006, who referred him to a physician to provide an opinion as to whether any of his health complaints were work-related. The next day, Case 10 underwent a history and physical exam by this doctor, who concluded that Case 10 had bronchial asthma and bronchitis, as well as abdominal pain, and that these conditions were caused by industrial injuries at Carmi Flavors. This physician planned to obtain Case 10's medical records, and recommended another pulmonary consultation to evaluate Case 10's work exposures and their relationship to asthma and bronchitis, followed by treatment recommendations. He believed that Case 10 was "temporarily totally disabled" until his next appointment in a month's time. At this follow up visit on May 11, 2006, no medical records from Case 10's prior care were obtained. Case 10 complained of intermittent dyspnea and reduced exercise tolerance. On exam, no wheezing or rales were heard. Case 10 was referred to an internal medicine doctor for further evaluation and treatment, and was discharged from further care. Case 10's regular primary care doctor noted that this new referral doctor was selected for Case 10 by his lawyer.

An initial report was sent by the internist to Case 10's attorney. This doctor concluded that Case 10 had reactive airway disease as a result of chemical exposures he sustained at Carmi, as well as possible sinus disease. A battery of radiologic and laboratory testing was ordered, and in a progress report issued to Worker's Compensation on July 18, 2006 the internist provided a diagnosis of "sinusitis," and noted that "patient currently has no sinus problem." The report indicated that Case 10 could return to work with "no limitations or restrictions" as of July 18, 2006. In the interim, Case 10 was scheduled for bronchoscopy with biopsy by his pulmonary doctor. The procedure was performed on July 7, 2006, and bronchoscopy showed no signs of inflammation, but did show some bronchial enlargement. Trans-bronchial biopsies were performed, which showed "benign pulmonary alveolar" tissue and some nonspecific interstitial thickening. An open or VATS lung biopsy was recommended in order to accurately classify the interstitial process.

A follow up pulmonary clinic visit occurred on July 31, 2006, and the doctor recommended that Case 10 limit his exposures to any irritating substances, and planned to see him again in three months.

On November 30, 2006, Case 10 came back to the internal medicine clinic that had released him back to work just a few months earlier. No exam was documented, but he was noted to be on an antihistamine and two inhalers. In a report to the California Division of Worker's Compensation, a diagnosis of "asthma/COPD" was listed. A high resolution CT angiogram of the chest was performed on December 14, 2006 for the indication of "bronchiectasis." The study reported mild diffuse bronchiectasis with "no pulmonary parenchymal abnormality identified."

In January, 2007, Case 10's attorneys filed suit against the manufacturers and suppliers of flavorings to Carmi Flavors, alleging that Case 10, now 50 years old, had developed bronchiolitis obliterans as a result of his exposures to chemicals at the company. However, no treating provider had ever diagnosed him with this condition, even the physician Case 10 had been referred to by his lawyers.

A follow up report was issued to the California Division of Worker's Compensation by Case 10's attorney-designated internist on March 14, 2007, which now indicated a diagnosis of "bronchiolitis obliterans," despite this diagnosis being unsupported by radiologic or pathologic studies, and the report did not include any explanation for how Case 10's diagnosis could have shifted from bronchiectasis, to asthma and/or COPD, and finally to bronchiolitis obliterans.

Another follow up CT scan of the chest was obtained on June 4, 2007, which showed some minimal pleural markings, thought to reflect changes from a prior infection. Once again, "no acute pulmonary parenchymal abnormality" was identified. Another CT scan of the chest was obtained on January 2, 2008 for the indication of Case 10 having a "history of bronchiolitis obliterans." Mild scarring was seen in the lung base and lung apices, consistent with a prior infection. No other lung abnormalities were noted.

Case 10 was treated for bronchitis and sinusitis after an ER visit on January 26, 2008, and was admitted to the hospital for ten days for acute asthma and pneumonia. He was discharged on February 9, 2008. Another CT scan of the chest was done on February 5, 2008 for the indication of "interstitial lung disease," which showed mild bronchiectasis and no signs of interstitial or other airway disease.

Attorneys representing Case 10 settled their case in May, 2011.

## Case 11

Case 11 worked as a salesman at men's clothing stores from 1962 to 1973. He began working at a small manufacturer of flavorings used in the banking industry in 1973, performing tasks including sales, product manufacturing, purchasing of raw materials, and maintaining company finances. In 1982, he took over the business from his father-in-law and ran it until 1990, before selling out to a competitor. The company produced a number of products for several different bakeries, including butter flavorings. Case 11 remembered initially working with diacetyl about 10-12 hours a week during the mixing, heating and packaging of various flavorings, which increased to about 15-20 hours a week a few years later.

Case 11 poured several gallons of diacetyl at a time into large steel tanks, which were heated to around 110-115 degrees F. He never used a mask or any other form of respiratory protection while working with diacetyl, and remembered several episodes of choking and gagging after breathing the fumes of the flavorings he was making. No quantitative air sampling for diacetyl or other food flavorings in the workplace was noted in the medical records.

Case 11 first noticed problems with his breathing around 1986 at the age of 44, when he started having shortness of breath with physical activity, such as walking up stairs. He went to see his family doctor, who referred him to a lung specialist. He was diagnosed with occupational asthma, and was prescribed various inhalers, which did not seem to improve his condition. His breathing appeared to gradually worsen, and he elected to see another doctor, who admitted him to the hospital for ten days and performed an array of diagnostic testing. He was felt to have a combination of restrictive and obstructive lung disease, and was diagnosed with bronchial asthma, "possibly chemically induced," in the setting of a 23 pack year history of cigarette smoking. Different inhalers were prescribed, as well as some oral medications, but Case 11 continued to show signs of improvement.

Despite his increasing shortness of breath, Case 11 continued to manufacture butter flavorings at his small facility, and still did not use any respiratory protection. On the recommendation of a friend, Case 11 received another pulmonary consultation in 1989 and underwent more testing. A CT scan showed no signs of emphysema or interstitial lung disease. Different inhalers were prescribed, again with no relief. Case 11 was frustrated that no one could help him with his breathing, but still persisted with a full work schedule at the flavorings company, with no employees to assist him with his many responsibilities.

In April, 1991, Case 11 became so short of breath that he called his son to take him to the emergency room, where arterial blood gases showed a pH of 7.31, pCO<sub>2</sub> of 86, and a pO<sub>2</sub> of 41. Spirometry revealed an FVC 37% of predicted and an FEV<sub>1</sub> that was 20% of predicted, with a reduced Diffusion Capacity (DLCO), consistent with emphysema. A chest CT scan showed no evidence of interstitial lung disease or emphysema, but did note some scarring in the left lower lobe. A ventilation perfusion scan showed bilateral air trapping, consistent with COPD. Case 11 was admitted to the hospital for another ten days and diagnosed with severe chronic obstructive pulmonary disease with asthma and respiratory failure, and was told he would need to be on oxygen at home. During Case 11's hospitalization, OSHA contacted his treating doctors to see if an occupational exposure could have caused his problems, but the doctors noted that since Case 11 had closed his business, it was difficult to know what chemicals he might have worked with, how he might have been exposed to them, and if exposed, to what levels over time he might have experienced. Case 11 also was found to have acute bronchitis, with sputum cultures growing out *H. influenzae*. His overall clinical picture was felt to be consistent with underlying emphysema, despite having no changes consistent with this diagnosis on a chest CT. In addition, Case 11 was informed that his severe lung disease could not be effectively treated medically, and that he should be evaluated for lung transplant. He was advised to avoid further chemical exposures of any kind in the workplace.

In early 1992, Case 11 completed a detailed transplant workup, and was accepted on the transplant list at the University of Pennsylvania for single lung transplantation, with a diagnosis of "chronic bronchitis with end stage COPD and cor pulmonale." He refused his first opportunity for transplantation in August, 1992, but eventually underwent a successful single lung transplant in October, 1993, and was then able to be taken off of oxygen therapy. Pathologic examination of Case 11's explanted lung at the University of Pennsylvania showed diffuse emphysema in the left upper and lower lobes, with no signs of fibrosis. No tissue scarring or focal lung lesions were observed. Final pathologic diagnoses were of asthma, COPD, and mild pulmonary hypertension. Subsequent electron microscopy studies of Case 11's explanted lung showed "destroyed alveolar septae," with no mention of bronchiolar inflammation or fibrosis. These findings supported a diagnosis of severe emphysema.

Case 11 did well from a respiratory standpoint after his operation, but in the months following his procedure, he developed insulin-dependent diabetes, leading to complications of peripheral neuropathy and worsening vision. His diabetes and its complications were thought to be connected mostly to problems with weight gain and poor diet, as he had gained more than 50 pounds after his transplant, which may also have been influenced by his treatment with immunosuppressants.

A follow up high resolution CT scan of the chest in December, 1996 showed severe emphysema of his remaining native lung, and a clear left lung, along with minimal air trapping, suggesting a possible "very early manifestation of obliterative bronchiolitis." Subsequent studies in August, 1997 and January, 1999 showed no evidence of air trapping, a normal transplanted lung, and signs of diffuse emphysema throughout the native lung. After several years of struggling with his weight, Case 11 eventually was able to get his weight down and established much better glucose control, eventually getting off of insulin entirely in 2002. His pulmonary function remained remarkably stable, and actually slowly improved over the years, with forced vital capacities that varied from 65 to 90% of predicted normal values, and FEV<sub>1</sub> values that were 55-70% of normal.

Case 11 first thought his original breathing problems might be linked to chemicals in the workplace in March, 2004, after watching a newscast on television discussing workers exposed to butter flavoring and the incidence of lung disease. Although none of his treating doctors told him that he might have bronchiolitis obliterans, the disease mentioned on the news program, he decided to search for attorneys who were familiar with this litigation.

Case 11 obtained legal counsel, and obtained the pathology slides from his removed lung, which were sent to a pathology consultant in New Jersey in April, 2005. The original University of Pennsylvania pathology report that reported no signs of lung fibrosis was countered by the opinion of the consultant 13 years later, who felt he saw patchy constrictive bronchiolitis obliterans involving the smaller air passages in some of the sections, findings that were then attributed by the consultant to Case 11's prior exposures to diacetyl.

Case 11's attorneys filed suit against the manufacturers and suppliers of flavorings to Case 11's flavorings business over the years, alleging that Case 11 had developed bronchiolitis obliterans as a result of his exposures to chemicals at the company, despite the absence of this diagnosis anywhere in Case 11's historical treatment records. An undisclosed settlement with all involved parties was eventually reached in late 2007.

Case 11 passed away the following year in June at the age of 66, over 15 years after his lung transplant.

## Case 12

Case 12 immigrated to the United States from Mexico in late 2009, after owning and operating a grocery store for 14 years near his home town. He first worked in the US at a coffee roasting, processing and packaging facility, initially unloading sacks of coffee beans from delivery trucks, and delivering them to a coffee processing line, as well as packing and labeling finished products into boxes for shipping. After 3-4 months, he joined the janitorial/housekeeping crew of the company, where he performed basic cleanup functions, but could not recall using any cleaning chemicals during his job duties.

Around May or June, 2010, he started working as a "flavor specialist," weighing out 40 pound batches of coffee beans, and adding less than a pound of vanilla nut flavoring to the beans, which were then mixed at room temperature. He also worked with a coffee grinder to produce ground coffee, and was responsible for cleaning various machines and coffee containers with dry paper towels at the end of his shift.

In December, 2011, he became an operator of a machine that packaged finished coffee products into boxes, and then loaded them onto pallets. He stopped working at the company in January, 2012, but continued to receive salary and benefits until the end of August, 2012.

Case 12 reported that he first started feeling short of breath in September, 2011, with additional symptoms of a cough, loss of appetite, and weight loss. He treated with a local doctor, who saw him three times in late 2011, diagnosing him with seasonal and mold allergies, allergic rhinitis, and bronchitis. He was also advised to leave the flavorings room at work, due to his breathing complaints. As his symptoms were not resolving, he was referred for a second opinion. Chest films were found to be normal, but a high resolution CT scan on December 22, 2011 showed scattered calcified and non-calcified lung nodules on both sides of the chest, with tiny calcified granulomas. No mosaic pattern or air trapping was observed.

Case 12 underwent bronchoscopy and a VATS lung biopsy on January 13, 2012. Bronchoscopy showed normal airways, and review of his biopsy showed evidence of “subacute and chronic small airway disease”, consistent with a variety of different inflammatory lung conditions. No specific pathologic diagnosis was identified, despite input from the Mayo Clinic, which provided a second pathology opinion.

Spirometry studies done from December, 2011 until February, 2014, were of generally poor quality, but did not show signs of worsening function, and reported a steady improvement in Case 12’s forced vital capacity after leaving employment at the coffee facility. An immunologic workup found that Case 12 showed significant specific immune reactivity to multiple allergens present at the coffee facility, including green coffee beans, roasted coffee, and castor beans. In addition, markedly elevated levels of IgE were found in Case 12’s blood, further evidence of an active hyperimmune response.

A follow up high resolution CT scan of the chest was done on April 30, 2012, which again showed scattered calcified and non-calcified lung nodules on both sides of the chest, which were felt to have been most likely caused by old granulomatous lung disease.

Case 12 and his attorneys filed suit against the coffee manufacturing facility, claiming that his exposures to coffee flavorings had resulted in him developing obstructive bronchiolitis from “chemical fumes.” This claim was supported by an occupational medicine physician, despite the nonspecific lung biopsy findings that could represent a wide variety of inflammatory lung conditions, along with immunologic and radiologic studies that pointed to an immune-mediated lung disease, such as hypersensitivity pneumonitis.

In May, 2013, Case 12 went to work for Wal-Mart in the produce department, and continued to show gradual improvement in his respiratory function. His case against the coffee manufacturer was settled in 2014.

## Discussion

The rarity of constrictive bronchiolitis in the general population has limited the ability of epidemiologic evaluations to study various potential risk factors while controlling for known causes of CB. Therefore, until large-scale longitudinal assays are conducted, a comprehensive weight of the evidence-based risk assessment to determine whether a causative link exists between exposures to food flavorings

(such as diacetyl) and the risk of developing CB must rely on experimental data and a comprehensive scrutiny of case reports.

The case reports presented herein without the benefit of exposure data for the individual workers demonstrate inconsistencies in diagnoses, classification, and illustrate some of the complexities involved when attempting to link exposures to food flavorings with CB. Bearing this in mind, my objective with this case series was to provide pertinent facts regarding these individuals, the basis upon which conclusions were reached by their treating physicians, and then to suggest whether validity exists between a causal link between food flavoring exposure and the risk of developing CB.

The clinical evaluation of workers suspected of displaying an occupational basis for breathing problems is often a very complicated undertaking. At times, the cause may be clearly evident, as in the aftermath of a chemical spill, at which time the responsible agent(s) and concentration can be readily identified and appropriately treated [18-21]. In other circumstances, symptoms and complaints may be less sudden in onset, but progressive in nature, suggesting some type of hypersensitivity reaction or process of sensitization [22,23]. Other types of presentations may suggest responsible agents to be external to the workplace, such as seasonal environmental factors, personal habits (e.g., smoking, use of snuff, recreational drugs, glue sniffing), home-based exposures (e.g., pets, new carpeting or cabinets, wood-burning stoves), microbial agents (e.g., bacteria, viruses, etc), or other health conditions (e.g., obstructive sleep apnea, gastroesophageal reflux disease, AIDS, asthma) [24-26]. These agents and risk factors are commonly described in cases of fixed airway obstruction and refractory asthma [27-30].

With respect to occupational sources suspected of causing or contributing to breathing complaints, a comprehensive evaluation should include an assessment of the frequency, duration, and magnitude of the array of chemical exposures experienced by personnel engaged in the various job tasks [31,32]. In addition, the use or absence of protective equipment also needs to be included. In nearly all cases, it is important for physicians to have a thorough and complete work history, and ideally, some quantitative exposure data regarding the airborne concentrations of the chemicals suspected of causing the ailment. Without such data, it is nearly impossible to claim a “cause and effect relationship” between an agent and a particular lung disease.

When a rare disease is seen in specific sets of workers exposed to primarily one agent that the general population is rarely exposed to, it may be reasonable to suggest a causal link if the particular disease can be clearly diagnosed with sufficient confirmatory clinical, laboratory, radiologic, and, ideally, histologic evidence of the disease process in question. However, exposures to diacetyl and other food flavorings are generally ubiquitous, which limits the capacity of an individual to claim a causal link based solely on a history of exposure.

In a previous review of what has become known as “popcorn lung”, Dr. Weill and I closely examined the basis for the suggested link put forth by NIOSH and others between exposure to butter flavorings and CB [33]. We concluded that the clinical data presented by NIOSH were insufficient to prove an outbreak of CB in popcorn manufacturing workers, nor did they demonstrate a clear causal relationship.

In October, 2016, NIOSH issued criteria for a recommended standard for permissible airborne concentrations of diacetyl in the

workplace [34]. The American Conference of Governmental Industrial Hygienists (ACGIH) earlier established a Threshold Limit Value based on “Lung damage (bronchiolitis obliterans-like illness)” [35]. To date, the Occupational Safety and Health Administration (OSHA) has not put forth any occupational exposure limits for diacetyl.

In its evaluations of microwave popcorn manufacturing facilities, NIOSH considered butter flavoring mixers the population at greatest risk for developing bronchiolitis obliterans. The cases presented herein worked in environments where exposures to flavorings and related chemical agents would often be expected to be much less intense than those experienced by historical mixers of butter flavorings.

In the group of workers summarized in this investigation, a great diversity exists with respect to the descriptions of their job responsibilities, duration and magnitude of exposure, agents to which the individuals were exposed, clinical diagnoses identified by treating physicians prior to lung biopsy, and tissue diagnoses provided by pathologists at the treating institutions as well as confounding factors such as smoking, infectious disease, or other environmental exposures. A comprehensive description of each case study inclusive of the available data was provided. However, despite radiologic, pathologic, and clinical evidence that clearly pointed to alternative disease processes, some clinicians [usually hired or referred by attorneys] suggested that these subjects should have been diagnosed with CB. It is of interest that in most cases, the determinations of CB reached by the clinicians were not substantiated by radiologic, pathologic, or physiologic observations, but appeared to have been arrived at mostly by speculation.

Interestingly, studies in animal models have not succeeded in recreating damage to the terminal airways similar to those seen in cases of human CB, despite simulated exposures that examined air concentrations of diacetyl or butter flavoring often hundreds of times higher than levels reported by NIOSH in their health hazard evaluations of manufacturing settings where flavorings compounds had been employed [36-39]. Some later animal studies, attempting to remove “nasal scrubbing” as a reason for failing to find disease in rodents, resorted to directly instilling a liquid solution of diacetyl into the animal airways - - an exposure model that would seem scarcely comparable to what would be experienced by workers in flavorings manufacturing settings [40]. Studies regarding a similar compound in structure and perceived flavor to diacetyl, 2,3-pentanedione, demonstrated some minimal fibrotic changes in the bronchioles of a few specimens from rats, but not mice, and these were observed only at the very highest exposure concentration in the study (200 ppm for 6 hours/day, 5 days/week, for 12 exposure periods) [41]. Studies comparing diacetyl to 2,3 pentanedione in rats suggested that the latter chemical had a greater effect on airway reactivity, and that flavorings could act as both smooth muscle relaxants and constrictors, and that their mechanism of action was complex [42].

Identifying diacetyl as a cause of CB is complicated by the fact that diacetyl is a ubiquitous chemical in our society. Diacetyl is present as an additive, by-product, or chemical of combustion in a wide variety of consumer products and environmental sources. These range from dairy products, such as yogurt, ice cream, milk products, cream, butter, cheeses and salad dressings [43-46], to wines and beers [47-49], to juices and vegetables [50,51], as well as coffee, cocoa, caramel and vinegar [52]. Diacetyl can also be created as

a combustion product, measured in automobile exhaust fumes and cigarette smoke [53-55]. Diacetyl is known to be produced naturally in humans as part of normal metabolism [52]. Despite these widespread and varied sources for human exposures to endogenous and environmental diacetyl, little research has been performed to estimate or quantify the typical ambient non-occupational exposures to diacetyl. The levels of these exposures, which presumably need to be considered when assessing the risk of respiratory tract injury from occupational sources, have not been well characterized. At present the focus has chiefly concentrated on levels of diacetyl and related dicarbonyl compounds within solutions or solid media, rather than on volatilized air concentrations associated with diacetyl present within a given product. Recent preliminary studies of red wines, however, appear to suggest that off-the-shelf bottles of cabernet sauvignon and port wines routinely deliver air concentrations of diacetyl well above the strict guidelines recommended by NIOSH [56].

Current available scientific information indicates that clinical evidence or compelling animal studies do not support diacetyl and/or butter flavoring as being responsible agent(s) for causing fixed obstructive lung disease in flavorings workers. However, as demonstrated by my review, diagnostic methodologies employed by some physicians appear to demand more rigorous scrutiny, particularly when conclusions used to support significant regulatory initiatives are not based upon radiologic, pathologic, or physiologic findings. In many cases, the potential impact of alternative respiratory risk factors, both internal and external to the workplace, were ignored or downplayed. This lack of attention is a critical oversight, as these additional factors may be causing or contributing to respiratory symptoms and complaints expressed by workers. In several of the cases I have outlined, the diagnostic impressions of CB or bronchiolitis obliterans “syndrome” were made by a single individual, with treating physicians often never mentioning or confirming either diagnosis. Respiratory tract injuries to flavorings workers have been clearly demonstrated in various occupational settings, but a precise clinical diagnosis of these injuries, in my experience, has been impaired by the lack of an accepted multidisciplinary strategy for evaluating affected workers. Clearly, a reliable methodology for assigning a diagnosis of CB needs to be established [57].

Despite the substantial numbers of individuals who have claimed to have been severely affected by exposures to airborne flavorings, often to the point of considering lung transplantation, pathologic evidence of CB has rarely been clinically confirmed. Hence, there does not appear to be sufficient clinical data to conclude that CB represents an “index disease” for exposure to flavorings agents. Animal models, predominantly mice and rat studies, have failed to provide a mechanistic understanding for how exposures to diacetyl and/or butter flavoring and its substitutes might lead to terminal airway fibrosis, and these studies have not clearly reproduced the terminal airway changes characteristic of CB.

A diagnosis of constrictive bronchiolitis can often be very difficult to assign, and is even more difficult when a lung biopsy has not been performed, as occurred for cases 1 and 2. When lung biopsy is performed, there is always a risk of sampling error, mitigated by obtaining tissue from multiple sites in the lungs. The relatively small number of cases I have presented may not be representative of the entire population of flavorings workers who may have sustained injury from

flavorings exposures. However, the consistently flawed approach to diagnosis I have witnessed during my involvement with flavorings-related lung injuries in multiple regions throughout the country suggests that the problem of jumping to a diagnosis of constrictive bronchiolitis in the face of insufficient, and often conflicting clinical data, is not isolated. Radiologic studies showing air trapping and/or a mosaic pattern can provide support for diagnosing constrictive bronchiolitis, as well as many other conditions [58,59]. Many of the chest CT scans performed did not specify expiratory phase exams, which are more sensitive for detecting these changes [60].

## Conclusion

Additional studies using animal models more similar to the respiratory behaviors and anatomic structures of humans should be explored. This would serve to reduce claims by NIOSH researchers that their failure to find evidence of CB in rodents arises not because diacetyl and/or butter flavoring are not capable of causing CB, but because these animals are obligate nose-breathers, and thus cannot reproduce the breathing patterns of humans. In addition, future studies should provide exposure comparisons with other well characterized chemical inhalants to more definitively identify the risk of diacetyl and related chemicals. Accurately distinguishing respiratory tract damage due to irritant effects arising from very high air concentrations of low molecular weight organic compounds, from true chemical-specific damage to the airways will be important to properly characterize the risk of irreversible lung disease. In cases where CB is in the differential diagnosis, confirmatory histological assays should be conducted in order to properly diagnose the patient and embark upon an effective treatment regimen.

Diacetyl is widely present within a wide variety of consumer products, and is released by many environmental sources, both natural and man-made. Understanding the levels of these common additional airborne exposures that have not been associated with adverse health effects will help to provide a reasonable threshold for estimating human health risk for respiratory tract injury with respect to diacetyl and related compounds.

Characterizing the health risk of respiratory exposures to chemicals used in the manufacturing of flavorings, or the use of flavorings to create other consumer products, should adhere to the same rigorous application of scientific and medical principles as has been performed for other historical complex disease associations. To do otherwise would be a disservice to those we seek to protect.

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