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WASHINGTON DC

DEPARTMENT OF ENVIRONMENTAL AND OCCUPATIONAL HEALTH
SCHOOL OF PUBLIC HEALTH AND HEALTH SCIENCES

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December 3, 2009

Margaret Hamburg, MD
Commissioner
US Food and Drug Administration
5630 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Hamburg:

In September 2006, the Project on Scientific Knowledge and Public Policy at the George Washington University School of Public Health and Health Services submitted a petition to the U.S. Food and Drug Administration (FDA) requesting that the agency cancel the "generally recognized as safe" (GRAS) designation for the food-flavoring agent diacetyl. We submitted our petition (copy attached) pursuant to section 409(b)(1) of the *Federal Food, Drug and Cosmetic Act*, 21 *Code of Federal Regulations (CFR)* 171.130 and as provided in 21 *CFR* 10.30. In March 2007, we received a response to our petition from the Director of the Office of Food Additive Safety, indicating that the agency had not reached a decision on our petition.

More than three years have passed since we filed that petition. We respectfully request information on the status of your scientific review and a timeline for next steps. We note that the docket containing our petition[1] includes a letter from Cecile Rose, MD, MPH reporting the case of an individual with significant lung disease whose only inhalational exposure was heavy, daily consumption of butter-flavored microwave popcorn. Exposure levels in the individual's home were similar to those documented in the quality assurance areas of microwave-popcorn manufacturing plants where workers with lung disease were identified.[2]

Three years have passed since we filed our petition calling on FDA to cancel the GRAS designation for diacetyl. The evidence remains strong: breathing diacetyl vapors causes lung disease, and there is no evidence of a safe exposure level. The FDA's current GRAS

FDA-2006-P-0518 LET

[1] http://www.fda.gov/ohrms/dockets/dockets/06p0379/06p0379.htm
[2] Kanwal R et al. (2006). Evaluation of flavorings-related lung disease risk at six microwave popcorn plants. *J Occup Environ Med* 48(2): 149-57.

THE PROJECT ON SCIENTIFIC KNOWLEDGE AND PUBLIC POLICY
2100 M STREET, NW • SUITE 203 • WASHINGTON, DC 20037 • 202-994-0774 • FAX 202-994-0011
WWW.DEFENDINGSCIENCE.ORG

designation for diacetyl is not supported by scientific evidence. We again urge the FDA's prompt action to cancel the GRAS designation for diacetyl until proper testing is completed and the results are independently evaluated.

Sincerely,

Celeste Monforton, DrPH, MPH
Assistant Research Professor
Environmental & Occupational Health

Susan Wood, PhD
Associate Professor of Health Policy and
Environmental & Occupational Health

Enclosures

cc: Dockets Management Branch
Room 1061, 5630 Fishers Lane,
Rockville, MD 20852

THE GEORGE WASHINGTON UNIVERSITY MEDICAL CENTER
WASHINGTON, DC

DEPARTMENT OF ENVIRONMENTAL AND OCCUPATIONAL HEALTH

SCHOOL OF PUBLIC HEALTH AND HEALTH SCIENCES

September 8, 2006

Andrew C. von Eschenbach, MD
Acting Commissioner
US Food and Drug Administration
5630 Fishers Lane
Rockville, Maryland 20852

Dear Dr. von Eschenbach:

We submit the following petition, pursuant to section 409(b)(1) of the *Federal Food, Drug and Cosmetic Act*, 21 *Code of Federal Regulations (CFR)* 171.130, and as provided in 21 *CFR* 10.30 for a citizen petition. There is compelling evidence that breathing diacetyl vapors causes lung disease, and there is no evidence of a safe exposure level. Since no studies have been conducted on the effects of breathing diacetyl by consumers, it is not yet possible to identify a safe level of airborne exposure. Therefore, the US Food and Drug Administration (FDA)'s designation of diacetyl as "generally recognized as safe" (GRAS) is not supported by scientific evidence. We urge the FDA's prompt action to cancel the GRAS designation for diacetyl until proper testing is completed and the results are independently evaluated.

Action Requested:

We request a revocation of the designation "generally regarded as safe" (GRAS) for the chemical diacetyl (2,3-butanedione, CAS Reg. No. 431-03-8). Diacetyl is a commonly used food flavoring with a buttery odor and flavor; it is chemically synthesized from methyl ethyl ketone.[1] Because a growing body of scientific evidence links inhalation of diacetyl to bronchiolitis obliterans and other forms of respiratory impairment, the FDA can no longer allow the GRAS designation for this food additive. We provide below our justification and

> "an assertion of the facts, supported by data, showing that new information exists with respect to the food additive [diacetyl]...that new data area available as to toxicity of the chemical...may justify amendment or repeal" of its GRAS designation. (21 *CFR* 171.130)

Statement of Grounds:

In the last few years, the National Institute for Occupational Safety and Health (NIOSH) has identified numerous cases of lung disease and impairment among workers exposed to diacetyl in food production plants.[2,3,4] Dozens of workers employed at popcorn plants have developed

occupational lung disease, and at least one has died. Several of these workers are on lung transplant lists.[5,6] The disease may not be limited to workers who have extremely high exposure; NIOSH scientists reported respiratory impairment among quality control workers who were exposed to diacetyl by cooking and opening bags of freshly popped microwave popcorn.[7] These findings are particularly relevant as the quality control workers' tasks imitate the action of typical consumers who consume microwave popcorn.

The sentinel cases in the most recent outbreak of bronchiolitis obliterans occurred in microwave popcorn plant workers from Jasper, Missouri, who were diagnosed in 1999. NIOSH began an investigation at a Missouri plant where eight current or former workers had developed the disease. NIOSH scientists found that respiratory symptoms were linked with exposure to diacetyl and the butter flavoring agents. Workers at this plant had cough and shortness of breath at a rate 2.6 times higher than what would be expected in the U.S. population. Twice as many workers as expected reported being told by their physicians that they had asthma or chronic bronchitis. Lung function testing revealed that three times as many workers as expected had obstruction to airflow. These results were reported first in the Center for Disease Control and Prevention's *Morbidity and Mortality Weekly Report*[8] in April 2002 and then in the *New England Journal of Medicine* in August 2002.[9] In all, NIOSH has conducted six investigations at 10 microwave popcorn facilities and has found respiratory impairment among workers at a majority of the plants.[10]

Since the initial reports focused on individuals employed in microwave popcorn factories, the disease is often called "popcorn workers lung."[11,12] It has become clear, however, that the disease has struck workers in other segments of the food and flavorings industries, and is not limited to microwave popcorn facilities.[13] The California Department of Health Services has recently reported two cases among diacetyl-exposed workers employed at factories at which the flavorings are produced.[14]

Laboratory studies have confirmed the role of diacetyl in the development of bronchiolitis obliterans. A manufacturer of diacetyl conducted a study in 1993 in which researchers exposed rats to pure diacetyl. After one four-hour period of exposure to the chemical, the sacrificed animals revealed an "abundance of symptoms indicative of respiratory tract injury."[15] To our knowledge, the manufacturer never reported these results to the government or published them in the scientific literature. Following the outbreak of bronchiolitis obliterans among the microwave popcorn-packaging workers, NIOSH carried out several toxicological studies on diacetyl and other butter flavoring substances. In one, rats were exposed for a single six-hour period to airborne concentrations of heated butter flavoring, of which diacetyl was the primary constituent. The scientists reported significant lung damage among rats with exposure as low as 203 parts per million.[16] In another study, NIOSH scientists exposed rats to pure diacetyl and found similar results.[17] Most recently, a study using guinea pigs and found exposure to diacetyl caused adverse effects to respiratory tissue and structure.[18]

In addition to the epidemiological and toxicological evidence described above, diacetyl fails to meet the definition of GRAS in another respect. Under FDA regulations, diacetyl can only be designated as GRAS provided its use conforms to good manufacturing practice. (21 *CFR* 184.1278) The plain meaning of "good manufacturing practice" suggests that exposure to diacetyl under normal production processes will be safe. This plain meaning is contradicted by the number of diacetyl-exposed workers suffering from bronchiolitis obliterans and other forms of respiratory impairment.

Furthermore, we know of no research into the health effects of exposure of consumers, including vulnerable individuals and children, to airborne diacetyl or artificial butter flavor during the preparation of foods.

In summary, there is compelling evidence of disease caused by breathing diacetyl vapors, and there is no evidence that there is a safe exposure level below which exposure does not cause lung disease. Therefore, it is incorrect to designate diacetyl as "generally recognized as safe" since there is no evidence that it is safe and extensive evidence that breathing it is hazardous.

Environmental impact:

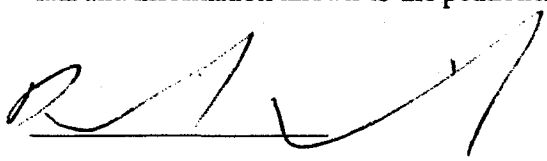
No exclusion claimed.

Economic impact:

Statement not required.

Certification:

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.



David Michaels, PhD, MPH
Director
Project on Scientific Knowledge and Public Policy
George Washington University
2100 M Street NW, Suite 203
Washington, DC 20037
202-994-2461
eohdmm@gwumc.edu

Enclosure

cc: Dockets Management Branch
Room 1061, 5630 Fishers Lane,
Rockville, MD 20852

References

[1] Title 21, Part 184, § 184.1278 Diacetyl.

[2] National Institute for Occupational Safety and Health. Preventing lung disease in workers who use or make flavorings. NIOSH Publication No. 2004-110, 2004. Available at: http://www.cdc.gov/niosh/docs/2004-110/

[3] Michaels D, Monforton C. Scientific evidence in the regulatory system: Manufacturing uncertainty and the demise of the formal regulatory system. *J Law Policy* 2005;13(1): 17-41. Available at: http://www.defendingscience.org/upload/Scientific-Evidence-in-the-Regulatory-System-Manufacturing-Uncertainty-and-the-Demise-of-the-Formal-Regulatory-System.pdf

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

MAR 0 6 2007

David Michaels, PhD, MPH
Director
Project on Scientific Knowledge and Public Policy
George Washington University
2100 M Street NW
Suite 203
Washington, District of Columbia 20037

Re: Docket No. 2006P-3079/CP1

Dear Dr. Michaels:

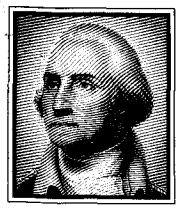
This letter is in response to the citizen petition you submitted that was filed on September 12, 2006, which requests the Food and Drug Administration to cancel the generally recognized as safe (GRAS) designation of diacetyl, affirmed in 21 CFR 184.1278, until testing is completed.

The purpose of this response is to advise you, in accordance with 21 CFR 10.30(e), that we have not reached a decision on your petition within 180 days of the filing of the petition because of the limited availability of resources and other agency priorities.

Sincerely yours,

Laura M Tarantino

Laura M. Tarantino, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition



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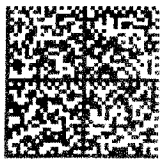

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Dockets Management Branch
Room 1061, 5630 Fishers Lane,
Rockville, MD 20852

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The George Washington University Medical Center
Department of Environmental and Occupational Health
2100 M Street, NW, Suite 203A
Washington, DC 20037