Request for Office of Management and Budget Review and Approval
for Federally Sponsored Data Collection

Spectrum of Flavoring Chemical-Related Lung Disease

Section A

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SUPPORTING STATEMENT

This is a new data collection, and we are seeking OMB approval for two years. Contact with participants is expected to begin during FY 2013 and continue through FY 2014. The funding source is directly linked to this time frame and is not carried forward over fiscal years.

A. JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The National Institute for Occupational Safety and Health (NIOSH) will be conducting a study to investigate and characterize the spectrum of flavoring chemical-related lung disease, including restrictive lung disease, occurring among workers in the popcorn and flavoring manufacturing industries. In order to achieve our goals of understanding this spectrum, we need to collect information as described in this OMB supporting statement. The Occupational Safety and Health Act, Public Law 91-596 (section 20[a][1]) authorizes NIOSH to conduct research to advance the health and safety of workers (see Appendix A).

According to the Flavor and Extract Manufacturers Association, a total of 6,520 workers are employed in the flavorings industry or in laboratory activities in membership companies (Hallagan 2010). However, other workers in the food industry can develop respiratory problems from exposure to flavorings through the production of various products such as microwave popcorn and potato chips (Kreiss 2007). According to the Bureau of Labor Statistics, in 2011, there were over 100,000 workers employed as food batchmakers in the United States (Bureau of Labor Statistics 2011).

Previous studies on flavoring-exposed workers focused on bronchiolitis obliterans, a severe obstructive lung disease involving inflammation and scarring of the small airways called bronchioles for the following reasons. In 2000, NIOSH investigated a report of eight sentinel cases of bronchiolitis obliterans among former workers of a microwave popcorn plant in Missouri by testing the current work force, in partnership with the Missouri Department of Health and Senior Services. This cross-sectional health hazard evaluation demonstrated that current workers had a 27% prevalence of spirometric abnormalities (CDC 2002; Kreiss et al. 2002). Because the sentinel cases had fixed airways obstruction and a rare lung disease (Akpinar-Elci et al. 2004), we devoted our attention to the occurrence of similar undiagnosed cases with obstructive spirometry, who accounted for 18% of the workforce. In the intensive work that followed in other microwave popcorn plants in which we conducted health hazard evaluations from 2001 to 2003, we found bronchiolitis obliterans cases in four of five popcorn plants, but we did not extensively study the workers with restrictive spirometric abnormalities (Kanwal 2003; Kanwal and Martin 2003; NIOSH 2003, 2004a, 2004b). Workers at several flavoring manufacturing plants had developed severe fixed airways obstruction and other findings consistent with bronchiolitis obliterans (CDC 2007, Kanwal 2008). Results from the studies on obstructive lung disease in relation to flavorings exposure (specifically to artificial butter flavorings which contain diacetyl), as well as animal exposure studies, have indicated the seriousness of the lung disease that can occur, including placement on lung transplant lists and death. This work has led to a draft NIOSH criteria document for occupational exposure to diacetyl and 2,3-pentanedione (NIOSH 2011a). The proposed NIOSH recommended exposure limit for diacetyl is 5 ppb (eight-hour time-weighted average (TWA)) and 9.3 ppb (eight-hour TWA) for 2,3-

pentanedione. The corresponding proposed 15-minute short-term exposure limits are 25 ppb for diacetyl and 31 ppb for 2,3-pentanedione.

There may be worker sub-populations more susceptible to flavoring-related disease. In draft risk assessment modeling performed by NIOSH, a more susceptible sub-population of workers existed who showed lung function deficits at low cumulative exposure to diacetyl (NIOSH 2011a). The metabolism of diacetyl in the body may account for some of the differential susceptibility found in the risk models. A major enzyme responsible for diacetyl and 2,3-pentanedione metabolism is dicarbonyl/L-xylulose reductase (DCXR), which is also involved in the uronate cycle of glucose metabolism (Nakagawa et al. 2002; Hubbs et al. 2012). Differences in the DCXR gene, and thus the enzyme, may manifest differences in the ability to metabolize diacetyl. Work in diacetyl-exposed rats has indicated that the DCXR enzyme can be found in the membranes of the terminal bronchioles (Gardiner et al. 2009). We know of no work in humans on the distribution of DCXR in lung tissue; however, significant rodent work is ongoing (Hubbs et al. 2002, 2008, 2012; Morgan et al. 2012). Polymorphisms in genes responsible for protecting cells from or responding to reactive oxygen species, protein damage, or DNA damage may influence susceptibility to diacetyl-induced injury. As a class, α-diketones such as diacetyl and 2,3-pentandione cause toxicity through three described mechanisms (Hubbs et al. 2012): modification of essential proteins (Mathews et al. 2010); interactions with DNA (More et al. 2012); and cell injury (Amicarelli et al. 2003; Brouwers et al. 2010). There are many potentially important polymorphisms and mutations that could affect the susceptibility of workers to diacetyl-induced airway epithelial damage and the propensity to respond by developing bronchiolitis obliterans.

Several factors led us to examine the spectrum of lung disease, such as the occurrence of restrictive spirometric abnormalities, in flavoring-exposed workers. First, we have received case reports of severe restrictive lung disease in flavoring-exposed workers with no other evident explanation. Two of the current workers that participated in all medical surveys developed restrictive lung disease during our nearly three years of follow-up in the sentinel plant (NIOSH, unpublished data). Second, the 3.3-fold excess of obstructive disease among current workers at the sentinel microwave popcorn plant in comparison to the U.S. population was based on combining the 11 persons with pure obstruction with 10 persons with mixed obstructive and restrictive spirometric abnormalities. Had we combined the latter group with the 10 persons with pure spirometric restriction, we would have had an excess of restriction in comparison to the U.S. population. Of the 10 employees with pure spirometric restriction, seven had a low total lung capacity (TLC) consistent with the presence of restrictive lung disease (Kreiss et al. 2002). Third, we found excesses of restrictive spirometry in a flavoring manufacturing plant (NIOSH 2011b) and flavoring-exposed food production plant (NIOSH 2009), with little to no obstructive lung disease in either study population. Finally, NIOSH researchers conducting risk assessment analyses with our serial microwave popcorn data from the eight cross-sectional studies at the sentinel microwave popcorn plant have found strong relationships between decreases in forced expiratory volume in one second (FEV1) and cumulative exposure estimates, without differentiating between obstructive and restrictive abnormalities.

In microwave popcorn and flavoring workers, the occurrence of restrictive lung disease has not been systematically explored to date. The significance of this epidemiologic work is that past conclusions about the emerging lung disease hazard in flavoring-exposed workers can be corrected and extended, if necessary, to the full range

of conditions that employees, physicians, companies, workers' compensation insurance agencies, and regulators must take into account in their efforts to prevent the burden of disease associated with flavorings. Further work is required to explore the nature of the spirometric restriction that we have encountered. The over three-fold prevalence ratio for spirometric restriction among the workers in the flavoring plant compared to the U.S. population was adjusted for age, gender, race, and obesity. Even with a low positive predictive value of 58% for restrictive spirometry indicating low TLC (Aaron et al. 1999), this prevalence ratio raises the possibility of excess lung disease of a restrictive type. For the various reasons outlined above, we plan to conduct additional field work to investigate the spectrum of lung disease occurring in flavoring and microwave popcorn workers by collecting a medical and work history questionnaire and conducting clinical tests, including lung function testing (spirometry, bronchodilator testing, TLC, and lung diffusion capacity), high-resolution computed tomography (HRCT) scans, and blood collection for future genetic and biomarker testing.

1.1 Privacy Impact Assessment

Overview of the Data Collection System

Participants will be asked to complete job and medication forms prior to their medical appointment. Data from the questionnaire will be entered directly into a NIOSH computer during a face-to-face interview with the worker. All data collected for this project will be maintained according to CDC record schedule.

Items of Information to be Collected

Data collected from participants include: questionnaire responses, medication forms, and job history forms. Lung function test data (spirometry, diffuse lung capacity (DLCO), TLC, bronchodilator testing), blood banking, and HRCT will be collected as well. Individually identifiable information will be collected from participants, which includes: name, date of birth, mailing address, and phone number, along with a name, address, and phone number of a friend or relative that we can contact if we cannot reach the participant.

Questionnaire data includes:

- Medical information
- Employment information
- Smoking history
- Demographic data
- Other exposures

Identification of Website Content Directed at Children Under 13 Years of Age

This project does not involve any web-based data collection methods with content directed at children under 13 years of age.

2. Purpose and Use of Information Collection

This research project is funded by the National Occupational Research Agenda (NORA) to assess lung disease in relation to the use of flavoring chemicals in the popcorn and flavoring industries. Data collection will be carried out by NIOSH personnel and will only be performed one time. This study has been funded for the 2013-2015 fiscal years.

The goal of this project is to assess the spectrum of lung disease among workers exposed to flavoring chemicals. This will be done by performing additional lung testing and chest radiography on participants from a previously investigated flavoring plant and

microwave popcorn plant. The primary objective of this study is to investigate and characterize the possible presence of emerging lung disease in flavoring and food production industries to enable healthcare providers to identify work-related flavoring-related lung disease and aid companies in prevention efforts. A secondary objective is to study the natural history of lung disease among the popcorn workers that were studied between 2000 and 2003.

The target audiences of our project include 1) healthcare providers who evaluate and treat flavoring-exposed workers, 2) food production companies, 3) flavoring-exposed workers, 4) trade associations, 5) state health departments, and 6) the Occupational Safety and Health Administration.

Outputs of our project will include one or more NIOSH publications. We will also update the NIOSH flavorings website. Additionally, we will give presentations at major medical/scientific conferences and publish our findings in major peer-reviewed journals.

The potential impact of this research is the prevention of occupational lung disease in flavoring-exposed workers. With new knowledge about the types of excess lung disease occurring in flavoring workers, physicians can identify appropriate secondary prevention measures for affected workers and alert companies of the possible insufficiency of primary preventive measures undertaken to curtail exposures. Government can incorporate this new knowledge about the types of flavoring-related lung disease into more robust risk assessments, recommendations and regulatory actions. Only epidemiologic and physiologic research approaches will produce knowledge and consensus that can lead to preventive action.

2.1 Privacy Impact Assessment

Some identifiable personal information (i.e., names, addresses, phone numbers, and date of birth) will be collected during this study. In addition, data such as information on current and past employment and health state will be taken. This information could have an effect on the respondent's privacy if there were a breach of security. Therefore, privacy will be assured by using subject numbers and codes in all analysis work. In addition, individual level data from participants will only be available to study personnel. Subject files will be kept in a separate file location and any data entered into computer data bases will be entered only by subject number and code. Privacy is also enhanced through controlled access to the NIOSH facility and the office where the files will be stored along with the rest of the Field Studies Branch human subject data. The specific information derived from the participants in this study will be kept secure and will not be disclosed to others without written consent except as required by law. This information will be used for statistical and research purposes in such manner that no individual can be identified.

3. Use of Improved Information Technology and Burden Reduction

Almost all information (90%) that is collected will be done so electronically. NIOSH interviewers will use a computer-based questionnaire to complete all interviews with workers. All the interviews will be administered face-to-face, and the responses will be recorded by the NIOSH interviewer directly into a computer (see Appendix D). This is necessary to ensure the accurate collection of information. The consent, job history form, and medication form will be sent to the participant in the mail prior to the medical testing, and we will ask them to complete paper copies of the job history and medication forms and return these to us on the day of the medical test. It would not be feasible to

collect these forms electronically, since we do not have the capacity to email these to the participants.

4. Efforts to Identify Duplication and Use of Similar Information

NIOSH is in a unique position to study popcorn and flavoring manufacturing workers from our previous work through the Health Hazard Evaluation program. To our knowledge, no medical survey this extensive has been done to explore the spectrum of lung disease, including restrictive abnormalities, among this workforce. We have analyzed available spirometry data which documents over a three-fold excess of spirometric restriction among production workers in the flavoring plant and exposure-related excessive declines in spirometry during employment (NIOSH 2011b). To our knowledge, no medical questionnaire survey or additional medical tests exist with which to further document the existence of or nature of lung disease that may explain these spirometric abnormalities.

Findings from NIOSH's prior work showed that one of the eight sentinel cases in the microwave popcorn plant had restrictive spirometry, and some current workers developed restrictive lung disease during our nearly three years of follow up surveys in the sentinel plant (NIOSH 2006). Furthermore, had we combined the 10 persons with pure restriction with the 10 persons with mixed obstructive and restrictive spirometric abnormalities, we would have had an excess of spirometric restriction in comparison to the U.S. population. Of the 10 employees with pure spirometric restriction, seven had a low total lung capacity consistent with the presence of restrictive lung disease (Kreiss et al. 2002).

Our study uses spirometry in addition to other medical tests to further investigate the presence of lung disease in these two groups. These efforts are motivated, in part, by the evolving literature on constrictive bronchiolitis, including the spirometric findings in U.S. soldiers in Iraq and Afghanistan with biopsy-documented constrictive bronchiolitis. In the case series findings, spirometric abnormalities were rare and included both restrictive and obstructive abnormalities (King et al. 2011).

5. Impact on Small Businesses or Other Small Entities

No small businesses will be involved in this data collection.

6. Consequences of Collecting the Information Less Frequently

The activities involve a one-time collection of data. There are no legal obstacles to reduce the burden.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This request fully complies with the regulation 5 CFR 1320.5.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A. Attached is a copy of the Federal Register Notice (see Appendix B) which contains the request for comments on the proposed collection of information. CDC published the notice on November 16, 2012 (Volume 77, Number 222 (pages 68780-68782). One comment was received which was considered non-substantive, and a standard CDC reply was sent. Two other comments were received which were

considered substantive in nature. A detailed response was sent to each entity, and a summary of the responses is provided in Appendix C.

B. This project was subject to extensive external and internal review in 2011 when it was submitted as a NORA (National Occupational Research Agenda) project. Since this project was confidentially reviewed, we are unable to provide the names of reviewers. However, a copy of the evaluation is provided in Appendix E.

9. Explanation of Any Payment or Gift to Respondents

Participants who complete any portion of the medical testing will be given a token of appreciation for their time and interest. Although the questionnaire, consent, job and medication forms are only estimated to take 45 minutes to complete, there will be additional burden placed on respondents in terms of their travel to and from the testing site, and the additional time required to complete the clinical tests. We estimate that completion of the medical survey, including the HRCT, will take 3-3.5 hours. This will be done on the participant's own time and outside of work hours, which is a burden on the respondent. Therefore, we request to provide participants who complete any portion of the medical testing a $50 gift card to a local merchant. The use of gift cards can be beneficial in increasing response rates. The National Health and Nutrition Examination Survey (NHANES), which includes both an extensive questionnaire and clinical testing, routinely use monetary incentives to increase participation rate. Previous NIOSH studies which involve clinical testing have had difficulty recruiting respondents, and it has been found that participation can increase when there is an incentive. For example, in the NIOSH study "Workplace Stress Among Underground Coal Miners" (OMB No. 0920-0657), respondents received a $35 incentive for completing the test, and this was found to be very effective. Gift cards will be issued when the participant returns his/her control card to a NIOSH representative. The use of gift cards has been approved by the NIOSH IRB.

10. Assurance of Confidentiality Provided to Respondents

10.1 Privacy Impact Assessment Information

This submission has been reviewed by ICRO, who has determined that the Privacy Act does apply. The applicable System of Records Notice is 09-20-0147, Occupational Health Epidemiological Studies and EEOICPA Program Records. The data collection will involve collecting sensitive and/or personally identifiable information, which includes: name, address and phone number, birth date, race/ethnicity, gender, and questions on health and well-being. The collection of this information is covered under the CDC Privacy Act. NIOSH will use standard methods to ensure the security and privacy of this data. All data with personal identifiers will be stored on password protected computers; any paper copies with personal identifying information will be stored in locked file rooms or cabinets; data access will be restricted to only NIOSH personnel and contractors that are involved in the study. No names or other personal identifiers will be used to link results. Instead, NIOSH will link study results using a subject ID number assigned on the day of testing. The NIOSH data analyst will use subject ID numbers in all coding work. NIOSH maintains the linkage between name and ID number in a secure network file during and after the study. NIOSH owns the data and any collaborators will not have access to the linking information.

IRB Approval

This study has been approved by the NIOSH IRB; a copy of the approval letter is attached (see Appendix F). Participation in any part of the NIOSH study is completely voluntary, and participants may withdraw their consent at any time. A copy of the consent form is provided in Appendix G. Section IX of the consent form addresses the use of information and how respondents' data are protected. We also included an appendix which explains the CDC Privacy Act and under what circumstances data could be released.

11. Justification for Sensitive Questions

No questions that are considered sensitive will be used in this study. We do plan on collecting information on race, ethnicity, gender, and date of birth for the flavorings workers, and current smoking status for both study populations. Demographic information and smoking history are necessary to evaluate the results of the lung function tests.

12. Estimates of Annualized Burden Hours and Costs

A. We estimate that the maximum number of flavoring and popcorn workers that we would have at the two sites would be 274, with 162 popcorn workers and 112 flavoring workers as the expected sample sizes. Based on a two-year approval, the annualized burden is for 81 popcorn workers and 56 flavoring workers. Prior to the testing, participants will be sent an informed consent to review, and both a job history and medication form to complete. The consent form will take approximately 10 minutes to review. The job history and medication forms are estimated to take no more than 15 minutes (total) to complete. During the medical testing, a NIOSH team member will review the informed consent at the beginning of the appointment with the participant which will take approximately five minutes. The NIOSH-administered questionnaire will be about 20 minutes long. The total burden hours are 105.

Estimated Annualized Burden Hours

Type of Respondents	Form Name	No. of Respondents	No. of Responses per Respondent	Average burden per response (in hours)	Total burden hours
Popcorn workers	Informed consent	81	1	10/60	14
	Medication form	81	1	8/60	11
	Job history form	81	1	8/60	11
	Questionnaire	81	1	20/60	27
Flavoring workers	Informed consent	56	1	10/60	9
	Medication form	56	1	8/60	7
	Job history form	56	1	8/60	7
	Questionnaire	56	1	20/60	19
Total					**105**

Estimated Annualized Burden Costs

Type of Respondent	Form Name	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Popcorn workers	Informed consent	14	$13.26	$186
	Medication form	11	$13.26	$146
	Job history form	11	$13.26	$146
	Questionnaire	27	$13.26	$358
Flavoring workers	Informed consent	9	$13.26	$119
	Medication form	7	$13.26	$93
	Job history form	7	$13.26	$93
	Questionnaire	19	$13.26	$252
Total				**$1393**

B. These estimates are calculated from the U.S. Department of Labor's National Industry-Specific Occupational Employment and Wage Earnings in May 2011 for the average hourly rate of food batchmakers. Popcorn and flavoring workers are estimated using the average hourly wages for this occupation.
Website: http://www.bls.gov/oes/current/oes513092.htm#st

13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are none.

14. Annualized Cost to the Government

The annualized cost to the government is $78,019 for the first year and $54,034 for the second year. Equipment and supplies for FY 2013 and FY 2014 include general office supplies, supplies for the lung function testing, and $50 gift cards to reimburse participants for the time and expense incurred by participating in the medical surveys. Contractual costs in FY 2013 include the cost to locate study subjects (e.g., LexisNexis) and contracts to perform and read HRCT scans. Contractual costs in FY 2014 only relate to costs associated with performing and reading HRCT scans. Travel includes the costs for the two medical surveys, as well as travel to other stakeholder and national meetings. We expect between seven to nine government employees will be needed to conduct the

health surveys in FY 2013 and FY 2014. The total annualized costs to the government are $132,053.

Item	FY 2013	FY 2014		Total
Equipment and supplies	$10,150	$12,460		$22,610
Contractual	$52,350	$30,800		$83,150
Travel	$15,519	$10,774		$26,293
Annualized estimate of federal costs	$78,019	$54,034		$132,053

15. Explanation for Program Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

In July 2013, after we receive approval from OMB, we plan to notify potential participants who participated in previous NIOSH studies at the popcorn plant with a study announcement and informational fact sheet (see Appendices H and I). We will then recruit and schedule appointments for potential participants over the next few weeks. In August 2013, we will conduct the health survey, along with the lung function testing, HRCT, and blood draw. In FY 2014, we plan to notify and recruit participants from the flavoring manufacturing workers. We will conduct our medical evaluation site visit during FY 2014. Data collection for the popcorn workers would need to be completed during FY 2013, since funding is not carried forward over fiscal years.

Activity	Time Schedule
Notification of study to respondents	Immediately after OMB approval
Medical evaluation site visit of popcorn workers	1-3 months after OMB approval
Medical evaluation site visit of flavoring workers	12-15 months after OMB approval

All data management and analysis will be carried out using statistical software from the SAS Institute, Inc, Cary, NC. Data preparation will include the application of definitions for spirometry quality, medical test abnormalities, and smoking.

We will compare spirometry results with indices of exposure to flavorings. NIOSH has the most extensive diacetyl sampling data from nine environmental surveys at the microwave popcorn plant, and with collaboration with investigators from the Occupational Safety and Health Administration, we have created a job exposure matrix (JEM) for diacetyl, specific for job and time period for this workforce. This JEM has been used for risk assessment analysis for obstructive lung disease for the NIOSH criteria document (NIOSH 2011a).

There is little exposure assessment data for the flavoring manufacturing workers, and we will not have the ability to create cumulative diacetyl exposures for individuals or quantitative metrics of exposure for other types of flavoring chemicals. Instead, we will use job-based exposure metrics. For the flavoring manufacturing plant, we will collect job information, which will allow us to use job-based exposure indices.

We will analyze the results of the medical testing to look for evidence of lung disease. For the microwave popcorn workers and flavoring manufacturing workers, we will also analyze lung function longitudinally using previously collected data and the current data. We will qualitatively compare medical test findings between the microwave popcorn group and the flavoring manufacturing group. We will investigate if findings differed between microwave popcorn or flavorings manufacturing workers, job group within industry, and potential for flavorings exposure ascertained from questionnaire information. For the microwave popcorn workers, we will compare the lung testing findings to cumulative diacetyl exposure ascertained from the existing JEM. We will also analyze lung function longitudinally using previously collected data and the current data.

17. Reason(s) Display of OMB Expiration is Inappropriate

We are not requesting an expiration date display exemption.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.