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

Spectrum of Flavoring Chemical-Related Lung Disease

Section B

Principal Investigators:

Rachel L. Bailey, DO, MPH
Jean M. Cox-Ganser, PhD
National Institute for Occupational Safety and Health
Division of Respiratory Disease Studies
Phone: 304-285-5818
Fax: 304-285-5820

April 5, 2013

Table of Contents

B. COLLECTION OF INFORMATION EMPLOYING STATISTICAL METHODS

1. Respondent Universe and Sampling Methods

Study population A will be recruited from the current and former workers of the sentinel microwave popcorn plant that participated in NIOSH testing conducted from 2000 through mid-2003. Participation among current workers from Population A in previous surveys ranged from 71%-91%. We will invite the 132 participants who had abnormal results on any NIOSH spirometry test to join this study. Of these 132 workers, 74 had at least one test showing an obstructive or mixed pattern, and 58 had a restrictive pattern. Study population A will also include 30 workers chosen at random who had normal spirometry on their last test. Approximately half of this workforce is male and 83% is Caucasian. At least 16% of workers were identified to be of Hispanic origin.

Study population B is composed of 112 workers from the flavorings plant for whom we have historical spirometry data collected by medical providers between 1998 and 2009. This population is primarily male (86%) and Caucasian (77%). From the most recent spirometry test available on these workers, 30 had a restrictive pattern, one had a mixed pattern, and three had an obstructive pattern. There were an additional 5 workers with spirometry results in the normal range but with indications of excessive drop in FEV1 over time.

Respondents	Number
Study population A	162
Study population B	112
Total respondent universe	274

2. Procedures for the Collection of Information

We will recruit participants for the medical testing as follows. For study population A, we have addresses and telephone numbers which were current as of the date of their most recent NIOSH test. Participants also provided contact information for a person who would know how to get in touch with the participant in case of relocation. We will conduct searches to update and/or verify the addresses on file using Accurint® (LexisNexis®). For study population B, we will work with the Union to obtain current contact information by supplying the name, gender, race, and age from our existing database. For people we cannot locate through the Union, we will conduct searches for contact information using Accurint® (LexisNexis®). One month before each study, we will contact invitees from the study populations by mail (with return receipt). The mailing will include an invitation letter (Appendix H) which will include the NIOSH toll-free number, an informational handout (Appendix I), job history form (Appendix J), medication form (Appendix K), and an informed consent (Appendix G). The materials are available in both English and Spanish.

Two weeks before the medical study, we will phone potential participants that we have not heard from to recruit them for the study. If the potential participant wishes, we will mail him or her a packet containing the invitation letter, informed consent, informational handout, job history form, and medication form, if they did not receive it already in the mail. Participants will be asked to complete the job history and medication forms prior to their appointment. The job history form will take approximately 10 minutes to complete, and the medication history should take no more than 5 minutes.

When participants arrive at the testing site, we will provide them a copy of the informed consent and encourage them to read it. We will then have a NIOSH employee explain the main points of the informed consent, ensure that the person fully comprehends the consent, and answer any additional questions. At that time, we will record the person's name, age, gender, and any medications currently being taken on a control card. During the medical testing, we will use computer-assisted, interviewer-administered questionnaires to ascertain respiratory symptoms and diagnoses, work history with microwave popcorn and/or flavorings, exposures to other lung hazards, and cigarette smoking history (Appendix D). This will take 20 minutes or less. We will have a Spanish translator available during the testing.

3. Methods to Maximize Response Rates and Deal with Non-Response

To encourage participation in the questionnaire, we will send an informational package to all potential participants prior to our visit explaining the purpose of the study. Copies of the letter and informational fact sheet are provided in Appendices I and J, respectively.

To maximize response, we will contact potential participants by phone to ask them if they would like to participate in the NIOSH study and to answer any questions or address any concerns they may have in regards to participating. We will make five attempts to reach the participant by telephone.

Due to the time commitment required to complete the medical evaluation, along with the fact that several participants will have to travel several miles to the testing site, we plan to offer remuneration to all participants who complete any portion of the study. We will compensate participants with gift cards to a local merchant for their time and effort.

4. Tests of Procedures or Methods to be Undertaken

The following procedures will be done as part of this study:

A. NIOSH questionnaire

Trained NIOSH interviewers will administer a computerized questionnaire to both the popcorn and flavoring workers to collect demographic information, work history, lower respiratory symptoms, physician diagnoses of respiratory conditions, cigarette smoking history, and medication use (Appendix D). The questionnaires were developed from instruments used in previous studies conducted as part of our Health Hazard Evaluations in the popcorn and flavoring industries (OMB Approval No. 0920-0260, Expires 11/30/2014). The questionnaires have been translated into Spanish, and Spanish interpreters will be present to assist. Expected time to complete the questionnaire is approximately 20 minutes.

B. Job history and medication forms

Prior to their appointment, participants will be asked to complete both a job history and medication form and bring these with them (Appendices J and K). This will help facilitate the collection of information during the questionnaire and medical testing. Since we had interviewed study population A between 2000 and 2003, they will only be asked to provide their work history since we last interviewed them. For study population B, we ask them to provide their complete work history since beginning employment.

C. Clinical tests

NIOSH will also be offering participants several clinical tests to determine lung function status. The complete list of clinical tests is given in the table below.

Study Group	Clinical Test
Popcorn workers with normal spirometry	Spirometry DLCO TLC HRCT Blood draw
Popcorn workers with abnormal spirometry	Spirometry DLCO TLC HRCT Blood draw Bronchodilator test
Flavoring workers with normal spirometry	Spirometry DLCO TLC HRCT Blood draw
Flavoring workers with abnormal spirometry	Spirometry DLCO TLC HRCT Blood draw Bronchodilator test

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

The following individuals will be involved in the design, collection and analysis of the data obtained in this study:

Rachel Bailey, DO, MPH – Medical Officer, Field Studies Branch, Division of Respiratory Disease Studies, NIOSH, Morgantown WV, 304-285-5757, feu2@cdc.gov is a co-principal investigator for this study and will be involved in the design, collection, and analysis of the medical data.

Jean Cox-Ganser, PhD – Senior Scientist/Advisor, Field Studies Branch, Division of Respiratory Disease Studies, NIOSH, Morgantown WV, 304-285-5818, jjc8@cdc.gov is a co-principal investigator on this project and is also the Research Team leader. She will provide oversight of the study, as well as be involved in the design, collection and analysis of data.

Sandra White, MS – Project Manager/Epidemiologist, Field Studies Branch, Division of Respiratory Disease Studies, NIOSH, Morgantown WV, 304-285-6094, sqg8@cdc.gov will be involved in the design, collection and analysis of data.

Kathleen Kreiss, MD – Physician/Advisor, Field Studies Branch, Division of Respiratory Disease Studies, NIOSH, Morgantown WV, 304-285-5800, kxk2@cdc.gov is the Branch Chief and will provide oversight in the design and analysis of data.

Kathleen Fedan, BS – Statistician, Field Studies Branch, Division of Respiratory Disease Studies, NIOSH, Morgantown WV, 304-285-6289, kbk1@cdc.gov will be involved in the design, collection, and analysis of data.

Brian Tift, MS – Computer Specialist, Field Studies Branch, Division of Respiratory Disease Studies, NIOSH, Morgantown WV, 304-285-6097, bet5@cdc.gov will be involved in the design, collection, and analysis of data.

Nicole Edwards, MS – Health Scientist, Field Studies Branch, Division of Respiratory Disease Studies, NIOSH, Morgantown WV, 304-285-6311, zwc1@cdc.gov will be involved in the collection, management, and analysis of data.

REFERENCES

Aaron SD, Dales RE, Cardinal P [1999]. How accurate is spirometry at predicting restrictive pulmonary impairment? Chest 115:869-873.

Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K [2004]. Bronchiolitis obliterans syndrome in popcorn production plant workers. Eur Respir J 24:298–302.

Amicarelli F, Colafarina S, Cattani F, Cimini A, Di Ilio C, Ceru MP, Miranda M [2003]. Scavenging system efficiency is crucial for cell resistance to ROS-mediated methylglyoxal injury. Free Radic Biol Med 35:856-71.

Brouwers O, Niessen PM, Haenen G, Miyata T, Brownlee M, Stehouwer CD, De Mey JG, Schalkwijk CG [2010].Hyperglycaemia-induced impairment of endothelium-dependent vasorelaxation in rat mesenteric arteries is mediated by intracellular methylglyoxal levels in a pathway dependent on oxidative stress. Diabetologia 53:989-1000.

Bureau of Labor Statistics, Department of Labor. May 2011 Occupational Employment and Wages, 51-3092 Food Batchmakers. [Available at http://www.bls.gov/oes/current/oes513092.htm#st]. Date accessed: March 2013.

CDC [2002]. Fixed obstructive lung disease in workers at a microwave popcorn factory--Missouri, 2000–2002. MMWR 51:345-347.

CDC [2007]. Fixed obstructive lung disease among workers in the flavor-manufacturing industry--California, 2004–2007. MMWR 56:389–393.

Gardiner DW, Goldsmith WT, Morris JB, Battelli LA, Friend S, Castranova V, Hubbs AF [2009]. Adhesion molecule expression and cytotoxicity in diacetyl exposed rat lungs [Abstract]. Toxicologist 108(1):432.

Hallagan J [2010]. Letter of October 19, 2010, from John Hallagan, General Counsel Flavor Extract Manufacturers Association, based upon 2010 Industry Survey, to L. McKernan, Education and Information Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services.

Hubbs AF, Battelli LA, Goldsmith WT, Porter DW, Frazer D, Friend S, Schwegler-Berry D, Mercer RR, Reynolds JS, Grote A, Castranova V, Kullman G, Fedan JS, Dowdy J, Jones WG [2002]. Necrosis of nasal and airway epithelium in rats inhaling vapors of artificial butter flavoring. Toxicol Appl Pharmacol. 185:128-35.

Hubbs AF, Cumpston AM, Goldsmith WT, Battelli LA, Kashon ML, Jackson MC, Frazer DG, Fedan JS, Goravanahally MP, Castranova V, Kreiss K, Willard PA, Friend S, Schwegler-Berry D, Fluharty KL, Sriram K [2012]. Respiratory and olfactory cytotoxicity of inhaled 2,3-pentanedione in Sprague-Dawley rats. Am J Pathol. 181:829-44.

Hubbs AF, Goldsmith WT, Kashon ML, Frazer D, Mercer RR, Battelli LA, Kullman GJ, Schwegler-Berry D, Friend S, Castranova V [2008]. Respiratory toxicologic pathology of inhaled diacetyl in sprague-dawley rats. Toxicol Pathol. 36:330-44.

Kanwal R [2003]. Letter of July 2, 2003, from R. Kanwal, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services, to Frank Morrison, Nebraska Popcorn Clearwater, NE.

Kanwal R, Martin S [2003]. Letter of May 13, 2003, from R. Kanwal and S. Martin, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services, to Keith Heuermann, B.K. Heuermann Popcorn, Inc. Phillips, NE.

Kanwal R [2008]. Bronchiolitis obliterans in workers exposed to flavoring chemicals. Curr Opin Pulm Med 14:141–146.

Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes EJ, Enright PL [2002]. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. N Engl J Med 347:330–338.

Kreiss K [2007]. Flavoring-related bronchiolitis obliterans. Curr Opin Allergy Clin Immunol 7:162-167.

MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J [2005]. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26:720-735.

Mathews JM, Watson SL, Snyder RW, Burgess JP, Morgan DL [2010]. Reaction of the butter flavorant diacetyl (2,3-butanedione) with N-α-acetylarginine: a model for epitope formation with pulmonary proteins in the etiology of obliterative bronchiolitis. J Agric Food Chem 58:12761-8.

More SS, Raza A, Vince R [2012].The butter flavorant, diacetyl, forms a covalent adduct with 2-deoxyguanosine, uncoils DNA, and leads to cell death. J Agric Food Chem 60:3311-3317.

Morgan DL, Jokinen MP, Price HC, Gwinn WM, Palmer SM, Flake GP [2012]. Bronchial and bronchiolar fibrosis in rats exposed to 2,3-pentanedione vapors: implications for bronchiolitis obliterans in humans. Toxicol Pathol 40:448-65.

Nakagawa J, Ishikura S, Asami J, Isaji T, Usami N, Hara A, Sakurai T, Tsuritani K, Oda K, Takahashi M, Yoshimoto M, Otsuka N, Kitamura K [2002]. Molecular characterization of mammalian dicarbonyl/L-xylulose reductase and its localization in kidney. J Biol Chem 277:17883-17891.

NIOSH [2003]. Hazard evaluation and technical assistance report: Agrilink Foods Popcorn Plant, Ridgway, IL. By Sahakian N, Choe K, Boylstein R, Schleiff P. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2002–0408–2915.

NIOSH [2004a]. Hazard evaluation and technical assistance report: American Pop Corn Company, Sioux City, IA. By Kanwal R, Boylstein R, Piacitelli C. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2001–0474–2943.

NIOSH [2004b]. Hazard evaluation and technical assistance report: ConAgra Snack Foods, Marion, OH. By Kanwal R, Kullman G. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2003–0112–2949.

NIOSH [2006]. Hazard evaluation and technical assistance report: Gilster-Mary Lee Corporation, Jasper, MO. By Kanwal R, Kullman G, Fedan K, Kreiss K. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2000–0401–2991.

NIOSH [2009]. Hazard evaluation and technical assistance report: Report on an investigation of buttermilk flavoring exposures and respiratory health at a bakery mix production facility, General Mills, Los Angeles, CA. By Day G, Cummings K, Kullman G. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2008–0230–3096.

NIOSH [2011a]. Draft criteria for a recommended standard: Occupational exposure to diacetyl and 2,3-pentanedione. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH; external review draft; August 12, 2011. [Available at: http://www.cdc.gov/niosh/docket/archive/docket245.html]. Date accessed: March 2013.

NIOSH [2011b]. Health Hazard Evaluation Report: Lung Function (Spirometry) Testing in Employees at a Flavorings Manufacturing Plant --- Indiana. By Kreiss K, Piacitelli C, Cox-Ganser J. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA No. 2008-0155-3131.