Understanding Long-term Respiratory Morbidity in Former Styrene-Exposed Workers: Medical Survey

Request for Office of Management and Budget Review and Approval for Federally Sponsored Data Collection
OMB Control # XXXX-XXXX; expiration date x/xx/xxxx

Supporting Statement A

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- **Goal of the study:** The goal of the proposed project is to understand the long-term respiratory health effects of styrene-exposed workers. The objective of the proposed study is: (1) to characterize work exposures by acquiring job histories and comparing with historical exposure levels obtained from a past industrial hygiene survey, (2) to examine the prevalence of respiratory morbidity by duration and level of styrene exposure, (3) to apply research biomarkers of lung injury to a styrene-exposed workforce, and (4) to describe the prevalence of color vision impairment in former workers no longer exposed to styrene and the association of color vision impairment with the presence of respiratory morbidity.

- **Intended use of the resulting data:** The study finding will be used to develop effective prevention strategies for styrene exposed workers and be distributed to the medical and scientific communities, labor groups, and industry through the following mechanisms: 1) conference presentations, 2) peer-reviewed scientific journals, 3) worker fact sheets; 4) CDC styrene website; 5) NIOSH Science Blog; 6) Twitter messages; and 7) Facebook messages. Fact sheets will be disseminated to workers through labor unions and made available to state health departments.

- **Methods to be used to collect:** Standardized questionnaire, lung function testing (spirometry, impulse oscillometry, multiple-breath washout, bronchodilator reversibility), blood collection, , and color vision assessment

- **The subpopulation to be studied:** Styrene-exposed workers employed ≥1 day at a Washington boatbuilding plant during Jan 1, 1959–September 30, 1978.

- **How data will be analyzed:** We will compare the prevalence of symptoms and lung function abnormalities among styrene workers and a sample of the general population using NHANES data adjusting for sex, age, race/ethnicity, and smoking. We will compare the prevalence of respiratory symptoms and lung function abnormalities to previous styrene exposure levels using prevalence ratio regression modeling and generalized linear modeling.

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A. Justification

1. Circumstances Making the Collection of Information Necessary

This is a new Information Collection Request (ICR) from the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. Under Section 20(a) (1) of the Occupational Safety and Health Act (29 U.S.C. 669) (Appendix A), NIOSH has the responsibility to conduct research to prevent occupational illness. NIOSH is requesting a two year approval from OMB.

In the United States, an estimated 1.6 million persons suffer work-related chronic obstructive pulmonary disease (COPD) and over 2 million suffer work-related asthma, at an annual cost of over $6.5 billion. Styrene is a common chemical used in the manufacturing of reinforced plastics and synthetic rubbers [1]. Styrene is used in the production of automobile parts, boats, computer housings, food containers, wind energy components, and many other products [2-4]. In 2008, over 12 billion pounds of styrene were produced in the United States. An estimated 90,000 U.S. workers are potentially exposed to styrene at more than 5,000 U.S. manufacturing plants [5]. Occupational exposure to styrene has been associated with deleterious health effects, including changes in color vision, mucous membrane irritation, hearing loss, and neurocognitive impairment [2, 6, 7]. Styrene is also considered possibly carcinogenic to humans [8, 9]. Workplace exposure to styrene has also been associated with cases of non-malignant respiratory disease (NMRD) [10-22].

Workplace styrene exposure most commonly occurs through inhalation and skin contact [10, 11, 23]. Additionally, research has attributed styrene exposure to the development of upper and lower respiratory inflammation, and non-malignant respiratory diseases [1-3, 12-14, 23]. Case reports have documented an association of obliterative bronchiolitis, eosinophilic bronchitis, and asthma diagnoses with occupational styrene exposure [1-3, 12-14]. However, the mechanisms by which styrene produces an inflammatory response that progresses into lung diseases are still not well understood [2].

Styrene exposure has been associated with non-malignant respiratory disease. NIOSH investigators have conducted mortality analyses for a cohort of 5,204 workers exposed to styrene at two reinforced plastic boatbuilding plants in Washington during 1959–1978 [24-26]. Workers with high styrene exposures (≥5 parts per million), and tenure <1 year and ≥1 year had 2.6 and 2.0 times higher mortality rates from chronic obstructive pulmonary disease, respectively, compared with the general population [25]. Previous epidemiologic studies of styrene exposure and respiratory disease have been limited to case reports, cross-sectional studies of current workers, and mortality studies [27]. Each of these types of studies had important limitations. NIOSH's understanding of the long-term respiratory health effects of styrene is limited, but critical to developing effective prevention strategies

1.1 Privacy Impact Assessment

NIOSH proposes a one-time information collection using a questionnaire (Attachment 3). The

questionnaire will be administered by trained NIOSH staff at the medical survey sites in Bellingham, WA and Kelso, WA. Each participant will be interviewed individually in a private room. Responses will be entered into a laptop computer by the interviewer. All data collected will be maintained according to CDC record schedule.

Questionnaire data to be collected includes:

- Individually identifiable information (name, date of birth, mailing address, and phone number, along with the name, address, and phone number of a friend or relative who can be contacted if the participant cannot be reached)
- Demographic data
- Medical information
- Employment information
- Smoking history

The questionnaire is quite similar to one used by NIOSH's Health Hazard Evaluation program during field investigations under OMB Approval No. 0920–0260, expiration 10/31/2020.

In addition to the collection of information in the questionnaire, the study includes medical testing (spirometry, impulse oscillometry, fraction of exhaled nitric oxide, multiple-breath washout, bronchodilator reversibility testing for impulse oscillometry and spirometry, and blood biomarkers of inflammation). Participation is voluntary. Research participants will be recruited to participate in the study through an information session, an invitation letter (Attachment 17), and the telephone. To participate in the medical testing (including the questionnaire), each research participant will be required to review and sign an informed consent document (Attachment 19).

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

A.2 Purpose and Use of Information Collection

This research project is funded through 2022 by the National Occupational Research Agenda (NORA) to understand the long-term respiratory health effects of occupational styrene exposure. Data collection will be carried out by NIOSH staff and will only be performed one time. The data collected in this study will be analyzed by NIOSH researchers to evaluate the relationship between styrene exposures and respiratory disease. These findings will be used to better understand the long-term respiratory health effects of styrene and develop effective prevention strategies. Findings will be disseminated to the medical and scientific communities, labor groups,

and industry through scientific presentations, peer-reviewed publications in the scientific literature, fact sheets targeted at workers in industries using styrene, and messages on NIOSH's Facebook and Twitter accounts.

Previous epidemiologic studies of styrene exposure and respiratory disease have been limited to case reports, cross-sectional studies of current workers, and mortality studies. Each study type has important limitations. Case reports have limited strength of evidence. Cross-sectional studies provide unreliable estimates of the health of a cohort of workers because of the healthy worker effect, and likely underestimate the respiratory morbidity associated with styrene exposure as ill workers leave the workforce earlier. Mortality studies rely on death certificate data, which have limited sensitivity for detecting occupational lung diseases. Furthermore, obliterative bronchiolitis does not have a specific diagnostic code. Thus, workers who died from recognized obliterative bronchiolitis were likely to have had their diagnosis misclassified on death certificates as chronic obstructive pulmonary disease, which is often attributed solely to tobacco use and not occupational exposures.

An understanding of the long-term respiratory morbidity of former styrene-exposed workers, and the impact of styrene exposure on ensuing respiratory disease processes would help to better inform stakeholders regarding the respiratory health risks associated with inhalational exposure to styrene. These data would also (1) help determine the risk to workers with styrene exposures below the NIOSH recommended exposure limit; (2) inform stakeholders about whether additional preventive efforts are necessary to further reduce worker exposure to styrene; and (3)serve to evaluate the utility of blood specimen testing as a method of surveillance for workers at high-risk of occupational lung disease. In total, this project will help evaluate both traditional (e.g., spirometry) and less-often used (e.g., impulse oscillometry) technologies that can potentially be used to screen workers for small airways and other lung disease across multiple industries.

Data collection instruments for this research project:

Questionnaire (**Attachment 3**)
NIOSH interviewers trained in administering standardized questionnaires will administer a computerized questionnaire to collect demographic information, detailed job history during and after the worker's tenure at the boatbuilding plant, upper and lower respiratory symptoms, physician diagnoses of respiratory diseases, history of hearing loss, cigarette smoking history, and medication use. The questionnaire should take about 45 minutes.

Standard operating procedure for Exhaled Nitric Oxide (FeNO) (**Attachment 4**)
NIOSH technicians trained in administering lung function tests will use a NIOX Mino device (Aerocrine; Solna, Sweden) to measure the FeNO using American Thoracic Society guidelines and NIOSH/RHD's SOP. This test takes about 5 minutes.

Standard operating procedure for Impulse Oscillometry (**Attachment 6**)
NIOSH technicians trained in administering lung function tests will use an impulse oscillometry machine (CareFusion Corp., San Diego, CA) following the manual and NIOSH/RHD SOP to perform impulse oscillometry. This test takes about 10 minutes.

Standard operating procedure for Nitrogen Multiple Breath Washout (**Attachment 7**)
NIOSH technicians trained in administering lung function tests will use a portable lung function machine (ndd Medical Technologies, Inc., Andover, MA) to perform a multiple-breath washout test following the NIOSH/RHD SOP. This test takes about 30 minutes.

Standard operating procedure for Spirometry (**Attachment 8**)
NIOSH Certified and experienced NIOSH technicians will administer the spirometry tests following the NIOSH/RHD SOP and using a dry rolling-seal spirometer interfaced to a personal computer. This test takes about 10 minutes.

Standard operating procedure for Bronchodilator test (**Attachment 10**)
If a study participant has an abnormal spirometry test (only a small percentage of study participants will qualify for the bronchodilator reversibly test), the participant will be administered a bronchodilator inhaler medication (i.e., albuterol), which can open the airways in some persons (e.g., asthmatics), after which spirometry and impulse oscillometry will be repeated. Study participants with baseline spirometry results within the normal range will not be offered the bronchodilator reversibility test. To administer the bronchodilator (albuterol) the NIOSH/RHD SOP will be used. This test takes about 20 minutes.

Standard operating procedure for Color vision test (**Attachment 12**)
NIOSH trained technicians will use the Lanthony D-15 Color Test (desaturated) (Richmond Products, Albuquerque, NM) to perform vision assessment following the NIOSH/RHD SOP. This test takes about 5 minutes.

Standard operating procedure for Blood test (**Attachment 16**)
NIOSH experienced certified phlebotomist will collect blood samples following the NIOSH/RHD SOP. This takes about 5 minutes.

Questionnaire and medical survey Consent form (**Attachment 19**)
Before being allowed to participate, each research participant must give his or her written informed consent. Each potential research participant will meet privately with an experienced NIOSH investigator familiar with administering informed consent forms before study participation begins. The NIOSH investigator will verbally explain the purpose of the study, study procedures, risks to participating in the study, and answer any questions from the research participant. This takes about 15 minutes.

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.

A.3 Use of Improved Information Technology and Burden Reduction

NIOSH interviewers will use a computer-based questionnaire (Attachment 3) to complete all interviews with participants. Responses will be recorded by the NIOSH interviewer directly into a laptop computer. This approach reduces the burden of participation and ensures accurate data collection.

A.4 Efforts to Identify Duplication and Use of Similar Information

NIOSH researchers have conducted a thorough literature review of all on NMRD among styrene-exposed workers. Previous epidemiologic studies of styrene exposure and respiratory disease have been limited to case reports, cross-sectional studies of current workers, and mortality studies [27].

Each study type has important limitations. Furthermore, NIOSH researchers have followed a cohort of 5,204 workers exposed to styrene at two reinforced plastic boatbuilding plants in Washington State during 1959–1978 [24-26]. In a recent mortality analysis of the boatbuilders' cohort, workers with high styrene exposures had a greater than two times higher mortality rate from COPD compared with the general population [25]. Additionally, the number of decedents from COPD under the age of 55 was higher than expected based on the U.S. death rate from COPD during 1968–2011; suggesting these deaths were unlikely to be attributable solely to tobacco use. Currently, no studies have evaluated the long-term respiratory morbidity in styrene-exposed workers.

A.5 Impact on Small Businesses or Other Small Entities

No small businesses will be involved in this data collection

A.6 Consequences of Collecting the Information Less Frequently

This request is for a one time data collection.

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

This request fully complies with the regulation 5 CFR 1320.5.

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

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A 60-day Federal Register Notice was published in the *Federal Register* on February 28, 2020 vol. 85, No. 40, pp. 11988-11990 (see Attachment 2). One public comment was received (Attachment 2.1). The comment outlined the concerns regarding collecting data from individuals exposed to styrene over 30 years ago and recommended the CDC identify a population of workers at a current operating reinforced plastic plant and follow overtime in a longitudinal study. NIOSH agrees with the limits of a retrospective study. The study limitations were considered during study design and will be addressed during data analysis.

B

There were no personal consults outside NIOSH.

A.9 Explanation of Any Payment or Gift to Respondents

Respondents will be offered a $50 gift card to offset some of the financial challenges of traveling to the medical survey site.

A.10 Assurance of Confidentiality Provided to Respondents

This submission has been reviewed by ISSO, who has determined that the Privacy Act does apply (Attachment 22). The applicable System of Records Notice is 09-20-0147, "Occupational Health Epidemiological Studies." The data collection will involve collecting individually identifiable information, including name, date of birth, mailing address, and phone number. All collected data will be transmitted to NIOSH. Data will be treated in a secure manner and will not be disclosed, unless otherwise compelled by law.

On the day of data collection, each participant will be assigned a subject identification (ID) number. Response data will be collected in identifiable form but de-linked from identifiers and subsequently retrieved by NIOSH data analysts using the subject ID number. NIOSH will maintain the linkage between name and ID number in a secure network file. The linkage will be maintained for as long as the records are maintained per the CDC record schedule.

NIOSH owns the data and collaborators will not have access to the linking information. Blood samples will be analyzed by contract laboratories. The contract laboratories will receive de-identified samples labeled only with the assigned code (subject identification number). The contract laboratories will report results to NIOSH using the assigned code.

The data collection has been reviewed and approved by the NIOSH Institutional Review Board (IRB). A copy of the approval letter is included (Attachment 21).

10.1 Privacy Impact Assessment

Individuals are informed that participation is voluntary in the informed consent document for the questionnaire and medical testing (Attachment 19).

NIOSH will use multiple methods to ensure the security and privacy of the data. All data with personal identifiers will be stored on password protected computers; no hard copies with personal identifying information will be retained at NIOSH; data access will be restricted to only

NIOSH staff involved in the study. Security is also enhanced through controlled access to the NIOSH facility.

The data collected in this study will be maintained under the System of Records Notice 09-20-0147, "Occupational Health Epidemiological Studies."

A.11 Institutional Review Board (IRB) and Justification for Sensitive Questions

IRB Approval

The data collection materials have been reviewed and approved by IRB (Attachment 21).

Sensitive Questions

Sensitive questions will not be included in this data collection. Information on race, ethnicity, and smoking history will be collected for the purpose of evaluating the results of the lung function tests. Social security number will not be collected.

A.12 Estimates of Annualized Burden Hours and Costs

The maximum number of respondents is estimated to be 676 over a two year period. Prior to questionnaire administration and medical data collection, respondents will be asked to review the informed consent document (Attachment 19). The informed consent document will take about 15 minutes to review and sign. The questionnaire (Attachment 3) will take about 45 minutes to complete. The NIOSH interviewer will read the questions to the participant and record the study participant's response. After the questionnaire, respondents have the option to participate in the medical survey. There are no forms associated with the medical survey which consists of the exhaled nitric oxide (5 minutes), impulse oscillometry (10 minutes), spirometry (10 minutes), bronchodilator test (20 minutes), multiple-breath washout (30 minutes), color vision test (5 minutes), and blood test (5 minutes). Thus, the total burden time per participant is a maximum of 145 minutes.

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 (in hours)
Boatbuilder Cohort Members	Questionnaire and medical survey consent form	338	1	15/60	85
	Questionnaire	338	1	45/60	254
	Exhaled nitric oxide	338	1	5/60	28
	Impulse oscillometry	338	1	10/60	56
	Spirometry	338	1	10/60	56
	Bronchodilator test	25	1	20/60	8
	Multiple-breath washout	338	1	30/60	169
	Color vision test	338	1	5/60	28
	Blood test	338	1	5/60	28
Total					712

Estimated annualized burden cost

Type of Respondents	Form name	Total burden (in hours)	Hourly wage rate	Total respondent cost
Boatbuilder Cohort Members	Questionnaire and medical survey consent form	85	$23.00	$1,955.00
	Questionnaire	254	$23.00	$5,842.00
	Exhaled nitric oxide	28	$23.00	$644.00
	Impulse oscillometry	56	$23.00	$1,288.00
	Spirometry	56	$23.00	$1,288.00
	Bronchodilator test	8	$23.00	$184.00
	Multiple-breath washout	169	$23.00	$3,887.00
	Color vision test	28	$23.00	$644.00
	Blood test	28	$23.00	$644.00
Total				$16,376.00

The value assigned for the hourly wage rate is based on the average U.S. hourly wage rate for production occupations from the Current Population Survey, Bureau of Labor Statistics, U.S. Department of Labor. Median weekly earnings of full-time wage and salary workers by detailed occupation and sex. Available at: http://www.bls.gov/cps/cpsaat39.htm. (Accessed January 2020)

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

There are no other costs to respondents or record keepers.

A.14 Annualized Cost to the Government

The estimated annualized cost to the government is $447,153. This cost includes pro-rated salary and benefits for the NIOSH staff involved in data collection and analysis; supplies; contractual agreements with laboratories, pathologists, and radiology centers; and travel to Bellingham, WA and Kelso, WA for data collection.

Item	Cost
Personnel	$285,038
Supplies	$31,125
Contractual	$78,263
Travel	$52,727
Total	$447,153

A.15 Explanation for Program Changes or Adjustments

This is new data collection.

A.16 Plans for Tabulation and Publication and Project Time Schedule

Immediately following OMB approval, we will schedule a trip to conduct informational presentations about the Washington boatbuilding cohort in the Bellingham, WA and Kelso, WA areas. During these presentations, we will review the history of the cohort, review past analyses, and provide an information sheet about our research project. After the informational presentations, we will recruit participants for medical testing by both mail and telephone. Data collection will be conducted about one to six months later, depending on NIOSH staff availability. Reporting individual results to respondents will be a priority following data collection and should be completed within two to three months. Subsequently, the focus will turn to aggregate analyses of the data, with an emphasis on the relationship between exposure and lung health outcomes.

Descriptive statistics will be used to illustrate the distribution of adverse health outcomes. Where possible, we will compare the proportion of participants with adverse health outcomes to the proportion expected in the general population using data from the National Health and Nutrition Examination Survey. Specifically, we will determine prevalence ratios (observed over expected) using indirect standardization for race, sex, age, cigarette smoking status, and body mass index. Prevalence ratio regression models will also be used to evaluate the prevalence of respiratory symptoms in relation to previous styrene exposure levels. Linear regression will be used to model percent predicted lung function values in relation to previous styrene exposure levels.

Results of the aggregate analyses will first be reported to the boatbuilder cohort, trade groups, and labor unions. Later, they will be presented at scientific meetings and prepared for publication in the scientific literature.

Infection Control Procedures:
We plan to delay the medical survey until travel restrictions for NIOSH staff are lifted. NIOSH will not conduct research studies involving large groups during active SARS-CoV-2 transmission. For this study, we cannot do the interviews virtually because the participant will have the medical testing after the interview. During the medical survey, we will incorporate all current CDC/NIOSH guidelines to minimize the risk of SARS-CoV-2 transmission for study participants and NIOSH staff. Currently, the spirometry and multiple-breath washout SOPs have a safety section, which includes infection disease control procedures including using disposable mouthpieces, and daily cleaning and disinfecting of all equipment. The safety sections will be updated with new CDC/NIOSH SARS-CoV-2 prevention guidelines before conducting the medical survey.

Project time schedule

Activity	Time schedule
Informational presentations	**6-12 months after OMB approval**
Invitation letters sent to respondents	**6-12 months after OMB approval**
Data collection	**12-24 months after OMB approval**
Individual results reported to respondents	**12-24months after OMB approval**
Analyses	**24-36 months after OMB approval**
Aggregate results reported to company and employee representative	**18-36 months after OMB approval**
Presentation at scientific meetings	**24-36 months after OMB approval**
Publication	**24-48 months after OMB approval**

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

The display of the OMB expiration date is not inappropriate.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.

A. 19 References

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