

Introduction to the NIOSH Human Research Protocol Template

Tool:	NIOSH Human Research Protocol Template*
Purpose:	To provide an instructional template for use in development of an Institutional Review Board (IRB) protocol submission
How to use this template:	<p>It is important to incorporate all sections of the template into your protocol and to do so in the same order. If a section is not applicable to your study, please retain it, but indicate that it is not applicable by writing “N/A” under the section heading. Where appropriate, use cross-references, rather than duplicating text. If it is necessary to add additional subheadings at the third or lower level, please use the available heading styles so that they will be included when the table of contents is updated. This template contains two types of text: instruction/explanatory text and example text.</p> <p>Instruction/explanatory text is indicated by [blue text in brackets] and should be deleted prior to finalizing the protocol. This text provides information on the content that should be included in the protocol. It also notes if a section should be left blank. For example, many headings include the instruction, “No text is to be entered in this section; rather it should be included under the relevant subheadings below.”</p> <p>Example text is included to further aid in protocol writing and should be modified to suit the design, and conduct of the study, or it may be deleted if it is not relevant. Within example text, a need for insertion of specific information is notated by <angle brackets>. Example text is indicated in text boxes.</p> <div data-bbox="521 831 699 884" style="background-color: #e0e0e0; padding: 5px; text-align: center;"> <p>Example</p> </div> <p>Headers and footers: The header of this template should be updated with the specific information requested in the <angled brackets>, including the shortened protocol title. You can remove the reference to the protocol template from the footer.</p>
Version control	<p>Version control is important to track protocol development, revisions, and amendments. It is also necessary to ensure that the most recently updated and IRB approved version of a protocol is used by all staff conducting the study. With each revision, the version number and date located in the header of each page should be updated. When making changes to an approved and “final” protocol, the protocol amendment history should be maintained (see Section 8.56, Protocol Amendment History).</p> <p>The latest version will be next in number, for instance protocol XX-NIOSH-xx_v1 would be updated to XX-NIOSH-xx_v2.</p>

* This template is based on a previous [NIH Protocol Template for Behavioral and Social Sciences Research Involving Humans](#). It maintains much of the content and structure of the NIH template but has been tailored to CDC/National Institute for Occupational Safety and Health research.

Understanding Long-term Respiratory Morbidity Among Former Styrene-Exposed Workers: High-resolution Computed Tomography (HRCT) Testing

[STARS Number:] TBD

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National Institute for Occupational Safety and Health

Respiratory Health Division

Version 1.0

Date: XXXX

All versions should have a version number and a date. Protocol amendments should be documented using a clean and marked copy. For protocol amendments, please provide a high-level summary of all revisions in Protocol Amendment History.

Contents

1. PROTOCOL SUMMARY.....	4
1.1. Abbreviations and Special Terms.....	4
1.2. Study Overview.....	5
1.3. Investigators.....	8
1.4. Study Schema.....	10
2. INTRODUCTION.....	11
2.1. Background.....	12
2.2. Study Rationale.....	13
2.3. Objectives and Data Collection Measures.....	13
3. STUDY DESIGN.....	14
3.1. Overall Design Description.....	15
3.2. Description of the Study Intervention/Clinical Trials.....	15
3.3. Study Procedures and Evaluations.....	16
3.4. Statistical Considerations.....	17
3.4.1. Statistical Hypotheses and Research Questions.....	17
3.4.2. Sample Size Determination.....	17
3.4.3. Data Analysis.....	18
4. STUDY POPULATION.....	18
4.1. Vulnerable Population.....	18
4.2. Eligibility/Selection Criteria.....	19
4.2.1. Inclusion Criteria.....	19
4.2.2. Exclusion Criteria.....	20
4.2.3. Lifestyle Considerations.....	21
4.2.4. Screening and Screen Failures.....	22
4.2.5. Study/Participant Discontinuation or Withdrawal.....	22
4.2.6. Lost to Follow Up.....	23
4.3. Strategies for Recruitment and Retention.....	24
4.4. Regulatory, Ethical and Study Oversight Considerations.....	25
4.4.1. Informed Consent Process.....	25
4.4.2. Reasonable Person Standard.....	25
4.4.3. Key Information Standard.....	25
4.4.4. Consent and Other Informational Documents Provided to Participants.....	25
4.4.5. Consent Procedures and Documentation.....	26
4.5. Risk/Benefit Assessment.....	26

4.5.1.	Known Potential Risks.....	26
4.5.2.	Known Potential Benefits.....	27
4.5.3.	Assessment of Potential Risks and Benefits.....	28
5.	SAFETY AND UNANTICIPATED EVENTS.....	28
5.1.	Response to Situations Related to Imminent Danger.....	28
5.2.	Safety Assessments.....	29
5.2.1.	Safety Oversight.....	30
5.2.2.	Protection for Researchers.....	31
5.3.	Adverse Events and Serious Adverse Events.....	31
5.3.1.	Definition of Adverse Events.....	31
5.3.2.	Adverse Event Reporting.....	32
5.3.3.	Definition of Serious Adverse Events (SAE).....	32
5.3.4.	Serious Adverse Event Reporting.....	32
5.4.	Unanticipated Problems.....	33
5.4.1.	Definition of Unanticipated Problems.....	33
5.4.2.	Unanticipated Problems Reporting.....	33
5.4.3.	Reporting Unanticipated Problems to Participants.....	34
6.	DATA MANAGEMENT.....	34
6.1.	Returning of Research Results.....	34
6.2.	Confidentiality and Privacy.....	35
6.3.	Future Use and Storage of Data.....	37
6.4.	Data Management and Sharing Policy.....	38
7.	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS.....	38
7.1.	Additional Considerations.....	38
7.2.	Appendices.....	38
7.3.	Protocol Amendment History.....	49
7.4.	Risk Identification, Assessment and Disclosure Table.....	49
8.	REFERENCES.....	50

1. PROTOCOL SUMMARY

1.1. Abbreviations and Special Terms

Abbreviation	Special term
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COPD	Chronic obstructive pulmonary disease
NMRD	Non-malignant respiratory disease
HRCT	High-resolution Computed Tomography
ALARA	As low as reasonably achievable
ACR	American College of Radiology
HIPPA	Health Insurance Portability and Accountability Act

1.2. Study Overview

Study Description: Digital analysis of HRCT images is an emerging technology and has shown promise as a sensitive detection tool for small airways disease and could help decrease the variability in imaging results read by radiologists. Through our study, we hope to demonstrate how digital analysis of HRCT images could provide additional information in evaluating occupational-related small airways disease. Study participants will be offered inspiratory and expiratory thin section HRCT scans to calculate the degree of air trapping. Digital analysis of images from this study will be compared with digital analysis of HRCT images on record from previous small airway disease studies to evaluate the use of this technology as an option for detecting occupational-related small airways disease.

Objectives: To contribute to a better understanding of the use of digital analysis of HRCT images in the evaluation of work-related small airways disease.

Study Population:

Sample Size: 70

Description of Sample: Research participants for the HRCT scan study will be selected from study participants in the styrene medical survey study (IRB Approved protocol 19-NIOSH-51), which is composed of randomly selected members of the NIOSH cohort of workers employed ≥ 1 day at one of two reinforced plastic boatbuilding plants in Washington state during 1959–1978. HRCT scan will be offered to randomly selected medical survey study participant who completed the questionnaire and lung function testing during the medical survey, reported a job position with high styrene exposure on the questionnaire, and had respiratory symptoms or lung function abnormalities consistent with small airways disease.

Special Populations: N/A

NIOSH Staff as Human Subjects: NA

Recruitment: Study participants from the styrene medical survey study will be notified of eligibility and recruited through an invitation letter (Appendix 1) with a toll-free number and informational handout describing the HRCT scan study (Appendix 2).

Study Procedures/Design: *High-resolution computed tomography:*

NIOSH will contract, through the government contracting process, with two radiology facilities (one near Bellingham, WA and one near Kelso, WA) to perform HRCT imaging. Under the government contract, the radiology centers will be

responsible for checking in the study participants, reviewing standard radiology procedures and policies, performing the HRCT scans using the ALARA principles, and providing a board-certified radiologist reading of the HRCT scans. As part of the NIOSH contract, the radiology centers will be required to be ACR accredited to demonstrate they practice high quality medicine, personnel are well qualified to perform HRCT scans and all evaluations will be conducted by board-certified radiologist, who will use the International Classification of HRCT for Occupational and Environmental Respiratory Diseases. The board-certified radiologists will provide the initial read and develop a radiology report. The radiology report will be securely provided to NIOSH for review and reporting to study participants. NIOSH will insert the board-certified radiologist's report in the participant's notification letter (Appendix 3). If the board-certified radiologist would identify an urgent medical concern during the initial reading, the NIOSH physician will call the study participant with the HRCT scan results before sending the notification letter. The board-certified radiologist will be blinded to the study participants' lung function test results. The NIOSH contracts will also state the radiology centers will have to follow HIPPA regulations for all medical paperwork and release forms collected from the study participants before undergoing the HRCT scan.

In addition to the two radiology facilities in Washington State, NIOSH will contract with the National Jewish Health Department of Radiology to perform a digital analysis of the HRCT scans. HRCT images will be de-identified and saved as digital images on a compact disc and mailed to the contracted research laboratory. HRCT images will be analyzed using computational methods including densitometry and digital analysis that allows for quantification of radiologic changes in severe lung disease and decreases inter-reader variability. Densitometry is a method where distributions of HRCT pixel intensities within the lungs are evaluated using simple thresholds or summary statistics derived from intensity histograms. These methods are established for quantification of emphysema and air trapping, but do not adequately describe subtle digital patterns that can be appreciated visually and are important in assessment of inhalational lung disease. Image texture is a quality formed by patterns in both pixel intensities and spatial arrangement. Previous studies have shown digital analysis can be used to identify centrilobular nodularity related to small airways abnormalities in smokers, and we hypothesize similar abnormalities can be detected in other forms of small airway disease. The contracted research laboratory will apply methods for quantitative description of image texture to develop classifiers for automatic detection and quantification of key disease patterns on HRCT. These methods will include modern machine learning approaches including convolutional neural networks and deep learning. All findings during the digital analysis of the HRCT scans will be used for research purposes only and individual results will not be returned to the study participants. At the end of the study, copies of HRCT scans will be destroyed.

Duration of tests and/or study:

Estimated time from enrollment to completion of data collection is 2 months

Key Words:

Styrene, COPD, obliterative bronchiolitis, boatbuilders, non-malignant respiratory diseases, occupational lung disease, asthma, occupational asthma

1.3. Investigators

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Role in Study: Epidemiologist

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1.4. Study Schema

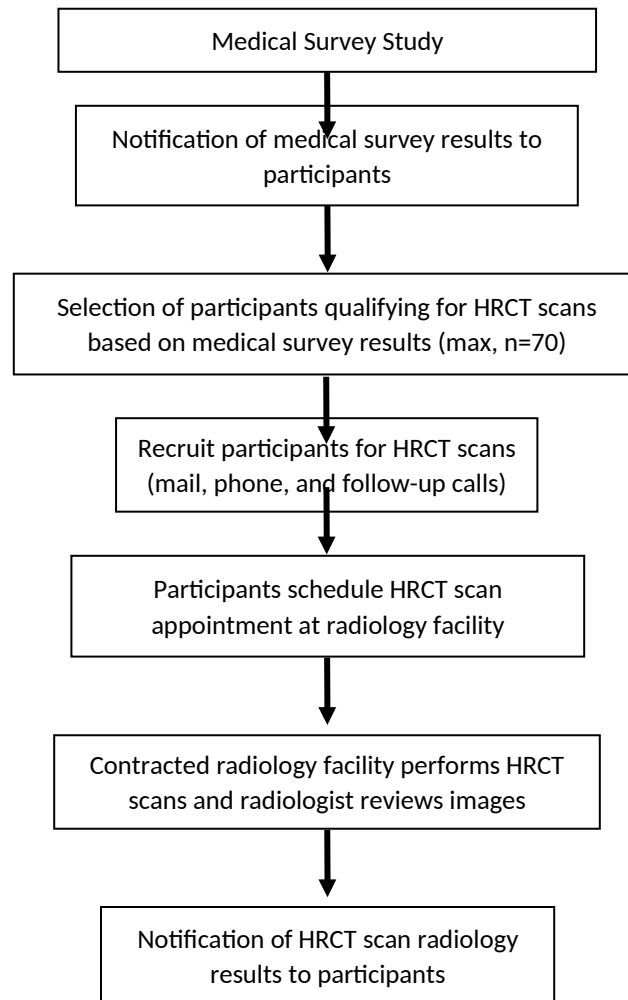


Figure: Flow of HRCT scan section of study

2. INTRODUCTION

2.1. Background

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) [12-22].

NIOSH's recently published review of the literature revealed: (1) 10 case reports of obliterative bronchiolitis (a rare disease marked by scarring of the small airways that can be mistaken for COPD, which is far more common) among persons exposed to styrene, including one case in a worker who replaced another worker diagnosed with obliterative bronchiolitis, a highly unusual occurrence for a rare respiratory disease; (2) eight case reports of occupational asthma among workers exposed to styrene, including six with abnormal inhalation challenges to styrene; (3) four cases of chronic dyspnea that occurred among workers who had a short-term exposure to high styrene levels in a shared confined space; (4) 13 (87%) of 15 cross-sectional studies of workers provided at least suggestive evidence of an association between styrene exposure and airflow limitation or NMRD; and (5) six (67%) of the nine mortality studies analyzing COPD among workers exposed to styrene demonstrated excess COPD-related mortality [23].

Additionally, NIOSH investigators have conducted mortality rate analyses for a cohort of 5,204 workers exposed to styrene at two reinforced plastic boatbuilding plants in Washington State during 1959–1978 [24-26]. The mean 8-hour styrene concentration for all high-exposure jobs in the two plants was 42.5 and 71.7 ppm and ranged from 11.8 to 106.0 ppm across 6 job titles at facility A and 7 job titles at facility B [24]. Of the 5,204 workers, 2,063 were considered to have had high styrene exposure (≥ 5 parts per million) and 3,141 had minimal (“low”) exposure (< 5 parts per million). In a recent analysis, workers with high styrene exposures, and tenure < 1 year and ≥ 1 year had 2.60 (95% confidence interval [CI] = 1.70–3.81) and 2.02 (1.08–3.46) times higher mortality rates from COPD, respectively, compared with the general population [25]. Investigators also calculated a standardized rate ratio (SRR) for workers in the high-exposure cohort compared with the low-exposure cohort for both COPD and lung cancer mortality. The SRR for COPD was 1.96 (95% CI = 0.80–3.92) compared with a lung cancer SRR of 0.77 (95% CI = 0.42–1.41), indicating all deaths from COPD were not likely attributable solely to tobacco use. In our recent analysis of the 157 decedents from the Washington boatbuilders cohort who died from NMRD, we investigated decedents who died at age < 55 years as these deaths were unlikely to be attributable solely to tobacco use [27, 28]. We identified one decedent who died from “bronchiolitis” in his 30’s and 9 decedents who died from COPD before age 55 years; of the COPD decedents, 7 had known disease onset in their 30’s [$n=1$], early 40’s [$n=3$], and 40’s not further specified [$n=3$] [27]. The number of early COPD deaths in this cohort is unusual as the U.S. death rate from COPD during 1968–2011 was low for persons aged < 55 years, ranging from fewer than 0.10–0.35, 1–2, and 6–10 deaths per 100,000 population among persons aged 25–34, 35–44, and 45–54 years, respectively) [27, 29].

Previous epidemiologic studies of styrene exposure and NMRD have been limited to case reports, cross-sectional studies of current styrene-exposed workers, and mortality studies [23]. Each of these study types 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 [30], and likely underestimate the potential respiratory morbidity associated with styrene exposure as ill workers undoubtedly leave the workforce earlier. Mortality studies rely on death certificate data, which have limited sensitivity in

the detection of occupational lung diseases, including obliterative bronchiolitis. Furthermore, individual cases of obliterative bronchiolitis caused by occupational exposure to styrene are likely to have their illnesses attributed to non-occupational exposures, including tobacco use. Because obliterative bronchiolitis does not have a specific diagnostic code, workers who died from recognized obliterative bronchiolitis were likely to have had their diagnoses misclassified as COPD on death certificates, which can lead to misclassification of death as solely a tobacco-related disease and not an occupational lung disease [31]. To date, no published studies have examined the prevalence of respiratory morbidity among living former workers exposed to styrene. Understanding the respiratory health of former workers after styrene exposure ended and before death would allow for improved characterization of the risk of respiratory disease throughout a worker’s lifetime, including a description of risk for workers with and without prior tobacco use.

2.2. Study Rationale

An understanding of the long-term respiratory morbidity of former styrene-exposed workers, and the impact on ensuing respiratory disease processes, would help to better inform physicians and the styrene industry regarding potential long-term respiratory health risks associated with inhalational exposure to styrene. Furthermore, digital analysis of HRCT images is an emerging technology and has shown promise as a sensitive detection tool for small airways disease and could help decrease the variability in imaging results read by radiologists. Through our study, we hope to demonstrate how digital analysis of HRCT images could provide additional information in evaluating occupational-related small airways disease.

2.3. Objectives and Data Collection Measures

Objectives	Data Collection and Measures	Justification for Measures
Primary		
The primary objective is to contribute to a better understanding of the use of digital analysis of HRCT images in the evaluation of work-related small airways disease.	Study participants will be offered inspiratory and expiratory thin section HRCT scans to calculate the degree of air trapping. Digital analysis of images from this study will be compared with digital analysis of HRCT images on record from previous small airway disease studies to evaluate the use of this technology as an option for detecting work-related small airways disease.	HRCT imaging is considered a sensitive test for detection of small airway disease but can have a lot variability between radiologist readings. Digital analysis of HRCT scans has shown to reduce the variability.

3. STUDY DESIGN

3.1. Overall Design Description

The primary objective of this project is to contribute to a better understanding of the use of digital analysis of HRCT images in the evaluation of work-related small airways disease.

Specific aims of this study are:

Aim 1: Identify the presence of lung disease and characterize it.

Aim 2: Compare results with HRCT scans to de-identified HRCT images from the NIOSH flavoring study, a cohort of workers exposed to diacetyl, a known chemical to cause small airway disease.

To accomplish our objective and aims, NIOSH will recruit up to 70 participants from a previous NIOSH study (detailed description in IRB Approved protocol 19-NIOSH-51). Research participants who participated in the styrene boatbuilders medical survey and identified as having previous high styrene exposures, and respiratory symptoms or lung function abnormalities consistent with small airway diseases like obliterative bronchiolitis, will be offered inspiratory/expiratory thin section HRCT. We will perform HRCT scan imaging of the entire chest in keeping with as low as reasonably achievable (ALARA) principles. We will use the International Classification of HRCT for Occupational and Environmental Respiratory Diseases [30]. NIOSH will hire, through the government contracting process, two radiology facilities (one near Bellingham, WA and one near Kelso, WA) to perform HRCT imaging using the same protocol used during the NIOSH Flavorings study (IRB Approved protocol 13-DRDS-01) and the COPDGene study [32]. The board-certified radiologist will be blinded to the lung function test results of the participants. After the board-certified radiologist reads the HRCT scans and develops the radiology report, the report will be securely provided to NIOSH for review and reporting to study participants. Participants will have the option to accept or decline to receive their HRCT scan radiology report results. Completion of the HRCT scan will mark the end of research subject participation and is not expected to take more than 15 minutes to complete. HRCT scans for all participants will be completed over two one-week periods.

For the digital analysis of the HRCT scans, NIOSH has contracted with the National Jewish Health Department of Radiology to perform a digital analysis. All findings during the digital analysis of the HRCT scans will be used for research purposes only and individual results will not be returned to the study participants. The digital analysis results will be compared to the de-identified HRCT images from the NIOSH flavorings study.

3.2. Description of the Study Intervention/Clinical Trials

N/A

3.3. Study Procedures and Evaluations

NIOSH will collaborate with their contracting partners at the Department of Radiology National Jewish Health to identify eligible radiology facilities who are qualified to perform HRCT scans. Factors that will determine radiology facility eligibility will be CT scanner model, location near Bellingham, WA and near Kelso, WA and facility's experience in performing HRCT scans.

Once the two radiology facilities are under contract with NIOSH, recruited research participants will be scheduled an HRCT scan appointment at the radiology facility closest to their home address. The research participant will undergo two volumetric chest HRCT scan examinations: one at full inspiration and one at the end of a normal expiration. These HRCT scans will be reconstructed with a slice thickness of 0.625, 0.75, or

0.9 mm depending on the type of CT scanner unit to achieve near-isotropic voxels. Inspiratory scans will be acquired at 200 mAs and expiratory scans at 50 mAs. All scans were acquired at 120 kVp. The Department of Radiology National Jewish Health will provide recommendations on HRCT scan protocols based on CT scanner model used by the contracted radiology facility. All HRCT scan protocols will be based on the CT protocols used for the COPD Gene Study and the NIOSH Flavorings study [32]. The radiology facility's board-certified radiologist will be responsible for providing the clinical read of the HRCT scans and develop a radiology report. The clinical report will be securely provided to NIOSH for review by the research physician and sent to research participants, who elect to receive their clinical results. The radiology facilities will be required to be in compliance with HIPAA regulations for all medical paperwork and release forms collected from the research participants before and after undergoing the HRCT scan. Patient-identifying information will be removed by NIOSH in compliance with HIPAA.

3.4. Statistical Considerations

3.4.1. Statistical Hypotheses and Research Questions

Results of this research will provide the information needed to answer the following questions:

- 1.) Do the HRCT scans results support the respiratory abnormalities identified during styrene medical survey?
 - What additional information can we learn about small airway disease?
- 2.) Compared to the HRCT scans from the NIOSH flavoring study, a cohort of workers who have been exposed to diacetyl, a chemical known to cause small airways disease.
 - Compared the distribution of air trapping in HRCT scans from the NIOSH Flavoring study to the distribution of air trapping in HRCT scans in the styrene cohort, does this cohort have more or less small airway disease than expected?

3.4.2. Sample Size Determination

Sample size determination was based off the estimated number of research participants from the styrene medical survey (IRB Approved protocol 19-NIOSH-51) who is expected to report a high styrene exposure and report respiratory symptoms or have lung function abnormalities consistent with small airway diseases. Funding for HRCT scan also determined the study's sample size.

3.4.3. Data Analysis

To test our first statistical hypothesis, we will review correlations between HRCT air trapping measurements and other lung function testing (IOS, spirometry, Nitrogen washout) results from the styrene medical survey.

For our second statistical hypothesis, we will compare the mean air trapping values (T-test) and distribution of air trapping between the styrene cohort HRCT scans and the NIOSH flavorings HRCT scans.

4. STUDY POPULATION

4.1. Vulnerable Population

To be a member of the NIOSH boatbuilder cohort, workers had to be employed at one of two boatbuilding facilities one or more days between 1959 and 1978, which is over 43 years ago. The youngest members of this cohort are currently 67 years old; therefore, children will be excluded from this research project. Prisoners will also be excluded from this research project because of travel requirements to the radiology facility. We will incorporate all CDC/NIOSH guidelines to safeguard research participants.

4.2. Eligibility/Selection Criteria

To be included in the HRCT scan study, research participants will have had to complete the styrene medical survey study (IRB Approved protocol 19-NIOSH-51), which is composed of randomly selected members of the NIOSH cohort of workers employed ≥ 1 day at one of two reinforced plastic boatbuilding plants in Washington state during 1959–1978. HRCT scans will be offered to randomly selected medical survey study participant who completed the questionnaire and lung function testing during the medical survey, reported a job position with high styrene exposure on the questionnaire, and had respiratory symptoms or lung function abnormalities consistent with small airways disease.

4.2.1. Inclusion Criteria

In order to be eligible to participate in the HRCT scan study, an individual must meet all the following criteria:

- Provision of signed and dated informed consent form
- Participated in and completed the styrene medical survey
- Reported a job position with high styrene exposure on the questionnaire
- Reported respiratory symptoms on the questionnaire or had lung function abnormalities consistent with small airways disease

4.2.2. Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in the HRCT scan study:

- Does not sign and date the informed consent form
- Did not participate and complete the styrene medical survey
- Did not report a high styrene exposure job position on the questionnaire
- Did not report respiratory symptoms on the questionnaire or had lung function abnormalities consistent with small airways disease

4.2.3. Lifestyle Considerations

The day of the HRCT scan, research participants will be asked to:

- Avoid wearing metal jewelry, clothing with metal zippers, or metal buttons to the radiology facility
- Avoid smoking or using other tobacco products for one hour before the HRCT scan
- Avoid eating or drinking anything for 4 hours before the HRCT scan.

- Bring a list of prescription and non-prescription medications that the research participant takes on a regular basis

However, research participants will still be able to participate in the HRCT scan study even if they forget to follow the special instructions and no information will be collected by NIOSH researchers prior to the research participant signing the informed consent form.

4.2.4. Screening and Screen Failures

N/A

4.2.5. Study/Participant Discontinuation or Withdrawal

Research participant may drop out of the study at any time, for any reason without penalty or loss of benefits to which they are otherwise entitled.

4.2.6. Lost to Follow Up

N/A

4.3. Strategies for Recruitment and Retention

Up to 70 research participants who reported job positions with previous high styrene exposures, and respiratory symptoms or lung function abnormalities consistent with small airway disease, will be recruited for inspiratory/expiratory thin section HRCT. To be considered for the HRCT scan, research participants will have had to complete the questionnaire and lung function testing during the styrene medical survey (IRB Approved protocol 19-NIOSH-51). We will contact research participants who meet the specific study requirements by both mail and telephone. The mailing will include an invitation letter (Appendix 1) that will include the NIOSH toll-free number. When an individual agrees to participate and schedules an HRCT scan appointment, we will then send them a copy of the informed consent document (Appendix 4) and informational handout describing the HRCT scan (Appendix 2). One week before the HRCT scans appointment, research participants will receive an appointment reminder call.

4.3.1. Informed Consent Process

We will obtain written informed consent from the research participants at the time of the HRCT scan. Each potential research participant will meet privately with a NIOSH investigator experienced with administering informed consent forms before study participation begins. The NIOSH investigator will verbally explain the procedure for HRCT scan study and answer any questions from the research participant. Before being allowed to participate, each research participant must give his or her written informed consent (Appendix 4). We will retain the signed consent form and the participant will receive a copy of the consent form for his or her personal records. During the consent process, the participant will have the option to accept or decline to receive the HRCT scan radiologist's report. The completed consent forms will be collected and stored in a locked case until the NIOSH personnel returns to NIOSH. Once returned to NIOSH, the completed consent forms will be stored in a locked filing cabinet at NIOSH for the duration of the study and required retention period.

4.3.2. Reasonable Person Standard

The literature and previous NIOSH studies have been reviewed as part of determining what information would be material or key to prospective research participants. Furthermore, Cincinnati researchers who have worked with this cohort on past studies provided input on what members of the NIOSH boatbuilder cohort would want to know to decide to participate in the HRCT scan study. NIOSH has followed a cohort of 5,204 workers employed ≥ 1 day at Tollycraft or Uniflite boatbuilding plants during January 1, 1959–September 30, 1978 since 1978 [26-28]. As of 2021, approximately 3,000 members of the cohort were known to be living, and the majority resided in the Bellingham and Kelso areas. This research project will be open to all living members of the NIOSH boatbuilder cohort who live in the Bellingham and Kelso, WA areas. From previous work with this cohort population, 85% of the boatbuilder cohort are male, 94% are white, and all speak fluent English. The cohort is composed of an older worker population (median age for different exposure and tenure groups range from 66 to 71 years).

RHD at NIOSH is a multidisciplinary research group that includes physicians, epidemiologists, industrial hygienists, laboratory investigators, medical technicians, certified spirometry technicians, and administrative support staff. RHD has a long history of successfully combining innovative laboratory, environmental, and medical epidemiologic approaches to understanding and preventing emerging occupational respiratory hazards, including nylon flock, cobalt, bioaerosols, indium tin oxide, flavorings, and chemicals such as diacetyl generated during coffee production. The styrene study design was based off the design used for the Health Hazard Evaluation (HHE) program's medical data collection process. RHD has been organizing and collecting data to evaluate respiratory health among workers from a variety of industries through the HHE program for over 15 years. HHE program designs their data collection process to make sure the worker knows everything they need to know before deciding to participate and NIOSH employees are trained to ease worker anxiety about participating. Although the HHE program has never specifically documented questions asked by workers during the informed consenting process, the most common questions asked include: how long the survey will take, will the testing hurt, how do I get my personal results, and will my personal results be shared with my employer. Over the past several decades, RHD/NIOSH has revised and updated the invitation letters, information sheets, informed consent forms, and notification letters to provide workers and study participants all the needed information for them to decide to participate or not while keeping the information in the simplest form. In addition to RHD/NIOSH's vast field experience that provides us an understanding of what a reasonable worker wants to know to decide to participate in any of NIOSH's field investigations, we have enrolled Dr. Alice Shumate to assist with the project. Dr. Shumate is an epidemiologist with the NIOSH Center for Maritime Safety and Health Studies. Through this role she works closely with maritime industry workers and has field experience working with shipbuilders. Her assistance will add to RHD/NIOSH's understanding of what the boatbuilder cohort needs to know to decide to participate in the research project.

Key Information Standard

This study meets the requirements of 45 CFR 46.116(a)(5)(i), the Key Information standard, in that a concise and focused presentation of the key information is presented to prospective research participants at the beginning of the informed consent process in clearly-understandable language. The Flesch-Kincaid Grade Level of the HRCT scan informed consent forms have been graded at 11.0 (without the required legal language).

Participation in the HRCT scan study is completely voluntary. Potential risks to study participants include unintentional disclosure of personal identifiable information, radiation exposure from the HRCT scan, experiencing discomfort or claustrophobia during the HRCT scan, or referral by their personal healthcare

provider for further unnecessary medical evaluations from an HRCT scan result being outside the “normal” range. Research participants will be informed of such risks during verbal and written consent. They will also be provided contact information about obtaining pertinent study information after their participation.

A brief explanation of the study will be presented verbally and on the written consent form to each potential research participant at the time of the medical survey by a NIOSH researcher. The setting for obtaining consent will be in a private room at the radiology facility. To obtain written consent, the NIOSH researcher will have the potential research participant read and sign the consent form with the description of the study (Appendix 4).

Study participants will be informed of any benefits and risks associated with participation in the study. Each study participant will receive an unsigned copy of the informed consent document. In case of a medical emergency, NIOSH will summon emergency medical aid by calling 911. In the unlikely event of an emergency during the HRCT scan study, the radiology facility physician and medical staff will stabilize the research participant up until the arrival of emergency medical services (EMS). Emergency care will be handed over to EMS at the time of their arrival.

4.3.3. Consent and Other Informational Documents Provided to Participants

Potential HRCT scan research participants will be sent an invitation letter (Appendix 1) describing the HRCT scan study. When a potential research participant schedules an appointment for an HRCT scan, the researchers will send the potential research participants a copy of the informed consent document (Appendix 4) and an informational handout describing the HRCT scan study (Appendix 2). The informational handout includes the following special instructions: (a) Avoid wearing metal jewelry, metal zippers, or metal buttons to the HRCT scan; (b) Try not to smoke or use other tobacco products for 1 hour before HRCT scan; (c) Try not to eat food or drink anything 4 hours before HRCT scan; (d) Bring list of prescription and non-prescription medications that the participant takes on a regular basis.

Consent forms describing in detail the study, procedures, benefits, and risks will be given to the prospective participant and written documentation of informed consent will be completed prior to starting the study. The following consent materials are submitted with this protocol (Appendix 4).

4.3.4. Consent Procedures and Documentation

We will obtain written informed consent the research participants at the time of the HRCT scan. Each potential research participant will meet privately with a NIOSH investigator experienced 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. Before being allowed to participate, each research participant must give his or her written informed consent (Appendix 4). Prospective participants will be informed that they may voluntarily terminate the HRCT scan at any point without prejudice to themselves and that research personnel may terminate a test at any time if they feel it is indicated. Each person who chooses to participate will sign the informed consent document. We will retain the signed consent form and the participant will receive a copy of the consent form for his or her personal records. During the consent process, the participant will have the option to accept or decline their HCRT scan clinical report. The completed consent forms will be collected and stored in a locked case until the NIOSH research team

returns to NIOSH. Once returned to NIOSH, the completed consent forms will be stored in a locked filing cabinet at NIOSH for the duration of the study and required retention period.

4.4. Risk/Benefit Assessment

Known Potential Risks

Potential risks for research participants include unintentional disclosure of personal identifiable information collected during the HRCT scan study, radiation exposure for research participants who qualify for the HRCT, experiencing discomfort or claustrophobia during the HRCT scan, referral by their personal healthcare provider for further unnecessary medical evaluations from an HRCT scan result being outside the “normal” range, and potential psychological effects from receiving results outside the “normal” range. Research participants will be informed of such risks during verbal and written consent. They will also be provided contact information about obtaining pertinent study information after their participation.

Research Risk, Identification, Assessment and Disclosure Table

Potential research-related harm or discomfort or inconvenience to subject	Probability? (Percentage, if known, or: • Negligible • Low • Medium • High)	Severity of Risk? • 4 - Severe • 3 - Marginal • 2 - Low • 1 - Negligible)	Is this a minimal risk?	Will this risk be minimized and if so, how?	If applicable, page where this is described in protocol	If applicable, section where it is described in Informed Consent Form (ICF)Form
Radiation exposure	Low	4	No	HRCT scans will be performed using the as low as reasonably achievable (ALARA) principles to minimize the risk of radiation exposure.	Section 4, Page 17-18	ICF, Section 7
Discomfort or claustrophobia	Low	Low	Yes	Participants who experience any discomfort or claustrophobia may withdraw at any point from the study without prejudice to themselves	Section 4, Page 17-18	ICF, Section 7
Breach in confidentiality	Low	Low	Yes	HHIPA Laws will be followed at the radiology facility and NIOSH will remove the research participation name	Section 4, Page 17-18	ICF, Section 7

				and identifying factors. Transfer of information will follow secure data transfer processes listed in the protocol.		
Unnecessary follow up testing because clinical results are outside the “normal” range	Low	Low	Yes	Research participants will have the opportunity to accept or decline the clinical results of their HRCT scan.	Section 4, Page 17-18	ICF, Section 7
Psychological effects from receiving results outside the “normal” range.	Low	Low	Yes	Research participants will have the opportunity to accept or decline the clinical results of their HRCT scan.	Section 4, Page 17-18	ICF, Section 7

4.4.1. Known Potential Benefits

Cohort members who choose to participate in this research project might help other workers in styrene-exposed professions. However, there will not be any direct benefits for the participants.

4.4.2. Assessment of Potential Risks and Benefits

The risk to research participants in this study is above the probability and magnitude of harm or discomfort ordinarily encountered in daily life. Risks to study subjects include the following: a) radiation exposure; b) discomfort or claustrophobia occurring during the HRCT scan; c) breach in confidentiality; d) further unnecessary medical evaluations from a HRCT scan result being outside the “normal” range; and f) potential psychological effects from receiving results outside the “normal” range.

HRCT scan imaging will be performed in keeping with the principal to administer the lowest possible dose of radiation. Several steps will be taken to minimize the risk of a breach in confidentiality. First, all NIOSH study personnel must complete IRB/ethics training. Second, research participant’s identifying information will exist only on source documents to allow for participant follow-up. Third, all source documents will be stored in a locked cabinet or on a secure server only accessible to a limited number of NIOSH study investigators. Fourth, NIOSH will remove name and identifying features from the HRCT digital images, therefore radiology personnel completing the digital analysis will be blinded to the person’s study group.

5. SAFETY AND UNANTICIPATED EVENTS

5.1. Response to Situations Related to Imminent Danger

N/A

5.2. Safety Assessments

Each potential research participant will meet privately with an experienced NIOSH investigator familiar with administering informed consent forms before the HRCT scan begins. The NIOSH investigator will verbally explain the purpose of the HRCT scan, risks to participating in the HRCT scan, and answer any questions about the HRCT scan study from the research participant. The NIOSH investigator will remind the research participant that their participation is voluntary, and they may request to stop the HRCT scan at any time without penalty. Research participants will be required to sign the informed consent forms before meeting with the radiology facility medical personnel. The radiology facility's medical personnel will be responsible for reviewing standard radiology patient procedures and policies with each study participant before starting the HRCT scan. The HRCT scan may be stopped by the radiology facility's medical personnel without the research participant's consent if the radiology medical personnel believe there is risk to the research participant's safety or health.

5.2.1. Safety Oversight

Safety monitoring of research participants during the HRCT scan will be overseen by the contracted radiology facilities healthcare professionals. The medical personal and physicians at the radiology facilities will be performing the HRCT scans using the ALARA principles. The NIOSH contract will confirm the radiology facility healthcare providers are experienced at monitoring patients during HRCT scans and trained in basic emergency medical procedures. Furthermore, the NIOSH contract will confirm the facilities are equipped with emergency medical equipment including an automatic external defibrillator (AED) and at least a basic first aid kit. In the unlikely event of an emergency during the HRCT scan, healthcare professionals from the radiology facilities will provide basic first aid or CPR to the study participant up until the arrival of emergency medical services (EMS). No other medical treatment will be offered until EMS arrives and all emergency care will be handed over to EMS at the time of their arrival.

5.2.2. Protection for Researchers

N/A

5.3. Adverse Events and Serious Adverse Events

5.3.1. Definition of Adverse Events

Adverse events (AEs) refer to any untoward medical occurrences, whether considered study related or not.

5.3.2. Adverse Event Reporting

AEs will be reported to the IRB immediately and at minimum within 48 hours from notification of the incident onset. Other, non-serious adverse events will be reported within five business days.

5.3.3. Definition of Serious Adverse Events (SAE)

Serious adverse events (SAEs) refer to anything that causes death, is considered a life-threatening event, requires hospitalization, leads to incapacity, is a substantial disruption of a subject's quality of life, or causes a congenital anomaly/birth defect.

5.3.4. Serious Adverse Event Reporting

SAEs will be reported to the IRB immediately and at minimum within 48 hours from notification of the incident onset. Other, non-serious adverse events will be reported within five business days.

5.4. Unanticipated Problems

5.4.1. Definition of Unanticipated Problems

Unanticipated problems (UAPs) are those not anticipated to have occurred and were not addressed as a potential risk during the initial review.

5.4.2. Unanticipated Problems Reporting

UAPs will be reported to the IRB immediately and at minimum within 48 hours from notification of the incident onset. The project officer will complete a CDC Incident Report form 01254, which will be submitted to the NIOSH IRB with signature form 01379 within 10 days of problem identification.

5.4.3. Reporting Unanticipated Problems to Participants

Participants will be verbally informed of any unanticipated problems which occur during or immediately following their HRCT. As soon as is feasible, the project officer will contact the participant to discuss the problem, any risk that might accrue to the participant, and how the problem has been addressed.

6. DATA MANAGEMENT

6.1. Returning of Research Results

The radiology facility's board-certified radiologists will provide the clinical read for the HRCT scans and develop a radiology report. The radiology report will be securely provided to NIOSH for review and reporting to study participants. Participants have option to accept or decline to receive their HRCT scan results during the consent process. NIOSH will insert the radiologist's report in the participant's notification letter (Appendix 3). If the board-certified radiologist would identify an urgent medical concern during the

clinical reading, the NIOSH physician will call the study participant with HRCT scan results before sending the notification letter. In addition to two radiology facilities in Washington State, NIOSH will contract with the National Jewish Health Department of Radiology to perform a digital analysis of the HRCT scans. All findings during the digital analysis of the HRCT scans will be used for research purposes only and individual results will not be returned to the study participants.

At the completion of the HCRT scan study, a presentation will be made to the boatbuilder cohort providing the group results from the HRCT scan study. During the boatbuilder presentation, no individual participant results will be identified. The presentation will aggregate the results based on exposure level or job category. Groups with less than three employees will be not be reported to reduce the likelihood of research participant identification.

Results from the HRCT scan study will also be shared with the scientific research community through peer reviewed scientific manuscripts.

6.2. Confidentiality and Privacy

Certificate of Confidentiality:

Section 301(d) of the Public Health Service Act (PHSA) states the Secretary of Health and Human Services shall issue Certificates of Confidentiality (CoCs) to persons engaged in biomedical, behavioral, clinical, or other research activities in which identifiable, sensitive information is collected. CDC research in which identifiable, sensitive information is collected, as defined by Section 301(d), is deemed issued a CoC and therefore researchers are required to protect the privacy of individuals who are subjects of such research in accordance with Section 301(d) of the PHSA.

Consistent with Section 301(d), a CoC applies to this research because it involves Human Subject as defined by 45 CFR part 46. Therefore, NIOSH and any of its collaborators, contractors, grantees, investigators or collaborating institutions that receive “identifiable, sensitive information” as defined by subsection 301(d) of the PHSA shall not:

- Disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive
- information about such an individual and that was created or compiled for purposes of the research.

Disclosure is permitted only when:

- Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable disease to State and local health departments), excluding instances of disclosure in a Federal, State, or local civil, criminal, administrative, legislative, or other proceeding;
- Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

NIOSH and its contractors conducting this research are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the research is managed in compliance with subsection 301(d) of the PHSA. Contractors and grantees are also required to ensure: 1) that any investigator or institution not funded by CDC/NIOSH who receives a copy of identifiable, sensitive information protected by this CoC, understands that it is also subject to the requirements of subsection 301(d) of the PHSA; and 2) that any subrecipient that receives funds to carry out part of this CDC award involving a copy of identifiable, sensitive information protected by a CoC understands that it is subject to subsection 301(d) of the PHSA.

All research participants will be informed of the CoC protections and the limits to protections provided by this CoC through the informed consent. Therefore, all study staff will receive training on the importance of protecting the confidentiality of human research subjects and of personal information acquired, including the collection of biological specimens.

System of Records Notices (SORN):

HHS System of Records Notices (SORNs) are required for studies in which the Privacy Act is applicable. As required by The Privacy Act, HHS publishes SORNs to provide public notice of the records it maintains about individuals, which are retrieved by personal identifiers. Each SORN describes the types of information contained in the records, the legal authority for collecting and maintaining the records, how the records are used within the HHS, and the purposes (referred to as “routine uses”) for which HHS may disclose the records to non-HHS parties without the individual record subject’s consent.

09-20-0147 Occupational Health Epidemiological Studies and EEOICPA Program Records and WTC Health Program Records. Categories of Individuals Covered by the System: The segment of the population exposed to physical and/or chemical agents or other workplace hazards that may damage the human body in any way. Some examples are: 1) organic carcinogens; 2) inorganic carcinogens; 3) mucosal or dermal irritants; 4) fibrogenic materials; 5) acute toxic agents including sensitizing agents; 6) neurotoxic agents; 7) mutagenic (male and female) and teratogenic agents; 8) bio-accumulating non-carcinogen agents; 9) chronic vascular disease-causing agents; and 10) ionizing radiation. Additionally, workers employed by the Department of Energy and its predecessor agencies and their contractors are also included, as are cancer-related claimants under the Energy Employees Occupational Illness Compensation Program Act of 2000 (EEOICPA). Individuals enrolled in or otherwise claiming eligibility and qualification for enrollment in the WTC Health Program created under Title XXXIII of the Public Health Service Act.

6.3. Future Use and Storage of Data

It is CDC/NIOSH policy that the results and accomplishments of the activities that it funds should be made available to the public. The project officer will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant or company).

If the data is of interest to an individual external to NIOSH, a data sharing agreement specific to the dataset and the proposed use will be developed. The agreement would address all specifications as listed in the CDC/ATSDR Policy on Releasing and Sharing Data in the sub-section titled “Release of data for public use” as well as any additional specifications prescribed by DSR confidentiality requirements. Data shared with an individual external to NIOSH will be de-identified to further insure confidentiality protections. Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

6.4. Data Management and Sharing Policy

Data collection and management for this project will be monitored by the Project Officer. Images and the clinical radiology report from the HRCT scan study will be downloaded onto compact discs by the radiology facility and secure mailed to the Project Officer at NIOSH. At NIOSH, only the Project Officer, the study Medical Officer, NIOSH technicians with CITI training and assigned to this study will have access to view the HRCT scans and clinical radiology reports. Results will be incorporated into a single database where each subject will be identified by a unique study number. For all data, confidentiality will be assured by using only the unique study number in all analyses. Subject files will be kept in a separate file location and any data entered into computer databases will be entered only by subject number. Confidentiality is enhanced through controlled access to the NIOSH facility and locked office(s) where files will be stored in accordance with Field Studies Branch procedures for protecting human subject data. Only NIOSH researchers working on this project will be allowed to view the data. The specific information derived from the subjects in this study will be kept confidential and not disclosed to others without written consent except as required by law. This information will be used for research purposes in such manner that no individual can be identified. For the digital analyses, the HRCT scan images will be de-identified by NIOSH data technicians and sent by secure mail to the Department of Radiology National Jewish Health.

Data collected for this study will only be publicly available in the form of summary data and data tables. Summary data and data tables will be distributed to the medical and scientific communities, labor groups, and industry through the following mechanisms: a) conference presentations; b) published scientific manuscripts; c) fact sheets targeted at workers in industries using styrene; d) CDC website e) NIOSH Science Blog; f) messages on Twitter; and g) messages on Facebook.

7. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

7.1. Additional Considerations

N/A

7.2. Appendices

Appendix 1: Invitation letter to boatbuilder cohort members to participate in HRCT scan

National Institute for Occupational
Safety and Health (NIOSH)
1095 Willowdale Road

Centers for Disease Control
and Prevention (CDC)

Morgantown, WV 26505-2888

Month XX, 20XX

Dear _____,

Thank you for participating in the National Institute for Occupational Safety and Health (NIOSH) study to understand the long-term respiratory effects among former styrene-exposed workers. In this research study, some participants who worked in high styrene exposures areas are being offered a high-resolution computed tomography (HRCT) scan. HRCT is a sensitive type of X-ray (also known as a CT scan or CAT scan) that has been found to be more effective in detecting lung diseases like obliterative bronchiolitis, which is a rare, irreversible lung disease defined by narrowing of the bronchioles from inflammation and fibrotic changes. Because you had a higher exposure to styrene and you reported respiratory symptoms or lung test results outside the normal range, we are offering you this test. **Your participation is completely voluntary.**



The **HRCT scan is FREE** and will be offered on **Month XX, 2020 or Month XX, 202X**. The HRCT scan will take place at **XXX clinic/hospital**. We have enclosed an informational handout that describes the test. It is important that you know that your medical test results will only be available to you, and if you wish, your personal physician.

If you would like to schedule an appointment for this medical testing, please contact us at 1-800-232-2114. If you have any questions about this research study, you can either contact us at 1-800-232-2114 or email Dr. Tomasi at yx4@cdc.gov.

Sincerely,

Suzanne E. Tomasi, DVM, MPH, DACVPM
Project Officer

Appendix 2: Information sheet provided to research participants in the HRCT scan

  High-resolution Computed Tomography (HRCT) Lung Study	
Who is being offered this test?	<ul style="list-style-type: none"> Participants in the NIOSH study looking at long-term respiratory diseases among former styrene-exposed workers with high styrene exposures and respiratory symptoms or lung function abnormalities consistent with obliterative bronchiolitis.
Why are we conducting this test?	<ul style="list-style-type: none"> HRCT scans have been found to be more effective in detecting lung diseases like obliterative bronchiolitis and will help NIOSH understand the long-term health effect of styrene-exposed workers. <p>High-resolution computed tomography (HRCT) of the chest</p> <ul style="list-style-type: none"> This is an X-ray test. We will request you to wear a gown and remove metallic objects such as jewelry. We will ask you to lie down on the scanner table. We will then ask you to take a deep breath, hold it, and then blow out. The test will take about 15 minutes.
Are there any special instructions?	<p>Jewelry, Metal Zippers, or Metal Buttons</p> <ul style="list-style-type: none"> Please avoid wearing metal jewelry, metal zippers or metal buttons to the HRCT scan. <p>Cigarettes, Cigar, Pipe, or Other Tobacco Products</p> <ul style="list-style-type: none"> Please try not to smoke or use other tobacco products for 1 hour before your HRCT scan. If you forget, you can still be tested! <p>Foods and drinks</p> <ul style="list-style-type: none"> Please try not to eat or drink anything for 4 hours before the HRCT scan. If you forget, you can still be tested! <p>Medication</p> <ul style="list-style-type: none"> Please bring a list of prescription and non-prescription (over-the-counter) medication that you take on a regular basis to the HRCT scan. Please take all medications as prescribed before the HRCT scan.
Will you keep my medical information private?	<ul style="list-style-type: none"> This research is covered by a Certificate of Confidentiality from the Center for Disease Control and Prevention. This makes it nearly impossible for NIOSH to reveal your personal information to anyone without your consent.
How can I get more information?	<ul style="list-style-type: none"> Contact Dr. Suzanne Tomasi at NIOSH: 304-286-6115 or 1-800-232-2114 or yt4@cdc.gov

[Protocol Title:] Understanding Long-term Respiratory Morbidity Among Former Styrene-Exposed Workers: High-resolution Computed Tomography (HRCT) Testing

Version 1.0

[Protocol Number:] Principal Investigator: Suzanne E. Tomasi

Date: XXXX

Appendix 3: Notification letter of HRCT scan radiology report scan

Appendix 4: Consent
scan study



form for HRCT

Consent for a High-resolution computed tomography (HRCT) Study of the Chest

Long-term Respiratory Diseases among Former Styrene-Exposed Workers

You are being asked if you would like to volunteer for a research study. This document gives you information about the study. A member of the research team will review this study with you. They will answer all your questions. Please read the information below. Ask questions about anything you do not understand before deciding if you want to volunteer.

Key Information: This study will be done to help the National Institute for Occupational Safety and Health (NIOSH) understand the long-term respiratory health effects among styrene-exposed workers and help develop effective prevention strategies for future styrene-exposed workers. This study will be done once at **XXX Radiology Center in Bellingham/Kelso**, WA and take less than 1 hour. During this research project, you will have an X-ray test called a high-resolution computed tomography (HRCT) scan of the chest. HRCT scans have been found to be more effective in identifying small airway lung diseases. The HRCT scan will help NIOSH understand the long-term health effect of styrene-exposed workers. This X-ray test exposes you to radiation. Radiation is a risk factor for cancer. The risk of cancer is related to radiation dose. The HRCT scans will be done using the lowest possible dose of radiation. The radiation dose you will receive during the scan is between 3 and 4 millisieverts (mSv). For comparison, the radiation dose associated with chest X-ray is 0.1 to 0.2 mSv, and the natural background radiation dose from sources in the environment is between 2 and 3 mSv per year. This study is completely voluntary. You may choose to be in this study or not. You may drop out of the study at any time, for any reason without penalty or loss of benefit to which you are otherwise entitled. Some individuals may not choose to participate due to the inconvenience of having to travel to radiology facility, the time involved in participating in the HRCT scan, or feeling uncomfortable with providing personal medical information to the federal government. However, this could be an opportunity for you to receive this expensive medical test for free.

Who is doing the study?

The National Institute for Occupational Safety and Health (NIOSH) is a federal agency that studies worker safety and health. We are part of the Centers for Disease Control and Prevention (CDC).

Why is NIOSH doing this study?

This study is to understand the long-term respiratory health effects among styrene-exposed workers and develop effective prevention strategies. HRCT scans have been found to be more effective in detecting lung diseases like obliterative bronchiolitis, which is a rare, irreversible lung disease defined by narrowing of the bronchioles from inflammation and fibrotic changes. The HRCT scan will help NIOSH understand the long-term health effect of styrene-exposed workers.

Consent for a High-resolution computed tomography (HRCT) Study of the Chest

Long-term Respiratory Diseases among Former Styrene-Exposed Workers

What is required for me to participate?

In order to join this study, you must have completed the medical survey in XXX and worked in a department at Uniflite or Tollycraft boatbuilding plants with a history of a high exposure to styrene. Additionally, you reported respiratory symptoms (coughing, shortness of breath, or wheeze) or your lung test results were outside the normal range. You must also review and sign this informed consent form.

What will I be asked to do?

- **High-resolution computed tomography (HRCT) of the chest:**
 - This is an X-ray test. We will request you to wear a gown and remove metallic objects such as jewelry. We will ask you to lie down on the scanner table. We will then ask you to take a deep breath, hold it, and then blow out. The test will take about 15 minutes.

When and where will you need me?

- This test will be done at XXX in Bellingham/Kelso, WA.
- The consent form and HRCT scan should take less than an hour, which includes any time waiting.

Are there any risks?

- This X-ray test exposes you to radiation. Radiation is a risk factor for cancer. The risk of cancer is related to radiation dose. The HRCT scans will be done using the principle to administer the lowest possible dose of radiation. The radiation dose you will receive during the scan is between 3 and 4 millisieverts (mSv). For comparison, the radiation dose associated with chest X-ray is 0.1 to 0.2 mSv, and the natural background radiation dose from sources in the environment is between 2 and 3 mSv per year.
- If you are pregnant or may be pregnant, you will not be allowed to have the HRCT scan because of potential risk of radiation to the unborn baby.
- A test result may be outside the range of "normal" even though nothing is wrong. This could result in your healthcare provider recommending further medical testing that, ultimately, may not have been necessary.
- HRCT scans might identify abnormalities such as mass-like lesions that require further medical testing by your personal healthcare provider and cause a psychological effect.
- Unintentional disclosure of personal identifiable information collected during the HRCT scan.

NIOSH will take precautions to minimize potential risks. The HRCT scans will be done using the principle to administer the lowest possible dose of radiation. To minimize unintentional disclosure of personal identifiable information, all documents will be stored in a locked cabinet or on a secure server only accessible to a limited number of study investigators. All testing results or samples will be labeled with a unique ID number.

Is my participation voluntary?

This study is completely voluntary. You may choose to be in this study or not. You may drop out of the study at any time, for any reason without penalty or loss of benefits to which you are otherwise entitled.

Consent for a High-resolution computed tomography (HRCT) Study of the Chest

Long-term Respiratory Diseases among Former Styrene-Exposed Workers

What if I'm harmed?

NIOSH will summon the medical treatment staff at the XXX radiology center. If NIOSH finds your injury was a direct result of participation in the study and if appropriate documentation is provided, NIOSH may provide short-term medical treatment that it deems necessary to treat the immediate medical needs arising from the injury. In general, no long-term medical care or financial compensation of research-related injuries will be provided by NIOSH, the CDC, or the Federal Government. However, if you believe NIOSH has been negligent in conducting the research study and you believe you have suffered a harm as a result, you have the right to pursue a legal remedy under the Federal Tort Claims Act (28 U.S.C. §§ 2671-2680 and 28 U.S.C. § 1346(b)). To learn more about how to file a Federal Tort claim, call the General Law Division of the HHS Office of the General Counsel at (202) 619-2155 or go to <https://www.hhs.gov/about/agencies/ogc/key-personnel/general-law-division/index.html>.

Will I be reimbursed or paid?

We will not pay or reimburse you for taking part.

Are there other benefits?

- You will receive this medical test free of charge.
- Workers exposed to styrene may benefit from the results of this evaluation.

How will I receive my results?

At the bottom of the consent form, you will be given the option to accept or decline your HRCT scan results. If you choose to receive your results, NIOSH will provide you with the results of your HRCT scan. We will mail your results in a letter to the address you provide. If the clinical read of your HRCT scan identifies any urgent medical concerns, a NIOSH physician will contact you by phone within in 3-5 days after the scan. Otherwise, individual HRCT scan results will be mailed in 1-2 months from the date of your scan. We will present summarized lung function and HRCT scan results to the whole cohort in Bellingham, WA and Kelso, WA once all test results have been analyzed. When this presentation has been scheduled, you will receive an invitation.

Consent for a High-resolution computed tomography (HRCT) Study of the Chest

Long-term Respiratory Diseases among Former Styrene-Exposed Workers

Will my personal information be kept private?

This research is covered by a Certificate of Confidentiality from the Centers for Disease Control and Prevention. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the CDC which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

HS System of Records Notices (SORNs) are required for studies in which the Privacy Act is relevant. As required by The Privacy Act, HHS publishes SORNs to give public notice of the records it keeps. These are found by personal identifiers. Each SORN describes the types of information contained in the records, the legal right for collecting and keeping the records, and how the records are used within HHS. It also contains the purposes (referred to as "routine use") for which HHS may share the records to non-HHS parties without the participant's consent.

09-20-0147 Occupational Health Epidemiological Studies and EEOICPA Program Records and WTC Health Program Records. **Categories of Individuals Covered by the System:** The segment of the population exposed to physical and/or chemical agents or other workplace hazards that may damage the human body in any way.

NIOSH is authorized to collect your personal information and will protect it to the extent allowed by law. This research study will result in identifiable information that will be placed in a locked environment on a secured NIOSH campus. Only de-identified study information will be utilized in the research data reports and publications. De-identified information could also be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or a legal representative. NIOSH may collect and keep information about you, including your results from this study, along with your personal identifiable information collected based on three laws passed by Congress. These laws are:

- 1) The Public Health Service Act (42 U.S.C. 241)
- 2) The Occupational Safety and Health Act (29 U.S.C. 669)
- 3) The Federal Mine Safety and Health Act of 1977 (30 U.S.C. 951)

Future Research

Identifiers might be removed from the identifiable private information and that, after such removal, the

Consent for a High-resolution computed tomography (HRCT) Study of the Chest

Long-term Respiratory Diseases among Former Styrene-Exposed Workers

information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

Whom can I talk to if I have questions?

For questions about this research study, including concerns and complaints, contact the principal investigator, Suzanne Tomasi, DVM, MPH at (304) 285-6115, yxc4@cdc.gov, or 1-800-232-2114.

For questions about your rights, your privacy, or harm to you, contact the Chair of the NIOSH Institutional Review Board in the Human Research Protection Program at (513) 533-8591.

Requesting Results of the HRCT Scan

- I would like to receive my HRCT scan results. Please mail them to me at the following address:

If urgent, please call me at: _____

- I would like to only receive my HRCT scan results if they suggest that medical follow-up is need
- I do not want to receive any of my HRCT scan results.

Your signature

I was told about this test. Any questions I had were answered. I agree to be in this test.

Printed name of participant [*Optional*]

Participant signature

Date

I have accurately described about this test to the participant.

Consent for a High-resolution computed tomography (HRCT) Study of the Chest

Long-term Respiratory Diseases among Former Styrene-Exposed Workers

NIOSH representative signature

Date

7.3. Protocol Amendment History

N/A

7.4. Risk Identification, Assessment and Disclosure Table

Potential research-related harm or discomfort or inconvenience to subject	Probability? (Percentage, if known, or: • Negligible • Low • Medium • High)	Severity of Risk? • 4 - Severe • 3 - Marginal • 2 - Low • 1 - Negligible)	Is this a minimal risk?	Will this risk be minimized and if so, how?	If applicable, page where this is described in protocol	If applicable, section where it is described in Informed Consent Form (ICF)Form
Radiation exposure	Low	4	No	HRCT scans will be performed using the as low as reasonably achievable (ALARA) principles to minimize the risk of radiation exposure.	Section 4, Page 17-18	ICF, Section 7
Discomfort or claustrophobia	Low	Low	Yes	Participants who experience any discomfort or claustrophobia may withdraw at any point from the study without prejudice to themselves	Section 4, Page 17-18	ICF, Section 7
Breach in confidentiality	Low	Low	Yes	HHIPA Laws will be followed at the radiology facility and NIOSH will remove the research participation name and identifying factors. Transfer of information will follow secure data transfer processes listed in the protocol.	Section 4, Page 17-18	ICF, Section 7
Unnecessary follow up testing because clinical results	Low	Low	Yes	Research participants will have the opportunity to accept or decline	Section 4, Page 17-18	ICF, Section 7

are outside the “normal” range				the clinical results of their HRCT scan.		
Psychological effects from receiving results outside the “normal” range.	Low	Low	Yes	Research participants will have the opportunity to accept or decline the clinical results of their HRCT scan.	Section 4, Page 17-18	ICF, Section 7

If all the potential risks are minimal, classify the study accordingly.

*Minimal risk means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

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