*Plan Revised in Response to Public Comments*

# Testing for Beryllium Sensitization,

# A Community Service in Elmore, OH

**June 16, 2006**

**Agency for Toxic Substances and Disease Registry**
**U.S. Department of Health and Human Services**
**Atlanta, Georgia 30333**

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APPENDICES

# 1.0 PLAN OVERVIEW

## 1.1 Summary

The purpose of this community service is to provide an opportunity for individuals who want to be tested for immune sensitivity to beryllium. This opportunity will be limited to concerned individuals who live within 1 ¼ miles from the Brush-Wellman facility in Elmore, Ohio (the facility), household contacts of workers at this facility, employees of local machine shops that contract to machine beryllium alloys and their household contacts, and individuals diagnosed with sarcoidosis. Up to 200 people who express interest and volunteer will be offered this opportunity for testing.

The processing facility in Elmore has produced commercial beryllium metal and beryllium alloys for decades. During the 1990's, this facility released up to 1100 pounds of beryllium per year to the ambient air.[1] After beryllium metal extraction ended in 2000, the amount of beryllium released annually to ambient air declined significantly. While current releases are not considered hazardous, past violations of the EPA air contaminant limits occurred on three separate occasions (1980, 1989, 1990). To prevent incidental off site migration of beryllium dust on workers' clothes, this facility has had long-standing requirements for workers to wear company-supplied work clothes and to shower at the end of each shift. Until recently, these requirements were self-monitored. While the industrial hygiene practices at Brush Wellman have been examplary in recent years, similar practices have not been instituted at the local machine shops that have contracted to work with beryllium alloys produced at the Brush Wellman facility in Elmore.

Beryllium exposure in the workplace is known to be a human health hazard. Inhaled beryllium is deposited in the lungs and can lead to immunologic sensitization (BeS) among susceptible individuals. Some of these sensitized people progress to chronic beryllium disease (CBD). Physicians may diagnose individuals without known occupational exposure to beryllium as "sarcoidosis," a granulomatous disease that resembles CBD. CBD can be distinguished from "sarcoidosis" by the beryllium lymphocyte proliferation test (BeLPT).[2]

## 1.2 Definitions

In this plan, the term *facility* refers to the Brush Wellman facility in Elmore, OH. The terms *beryllium exposure, exposure*, and *exposure potential* are used interchangeably. For efficiency in characterizing exposure potential, the present tense terms *live, work*, and *share* are equivalent to and include the past tense forms *lived, worked*, or *shared.* The term *sensitized* always implies immunologic sensitization to beryllium, whether the final diagnosis is BeS or CBD.

A number of descriptive phrases are used to simplify the plan presented here. Some have been adapted or are specific to this testing plan, while others are in general use. Please refer to these definitions as needed throughout the text.

*background sensitization rate* – the unknown low level prevalence of beryllium sensitization among local residents that is not associated with work-related exposure or living near the Brush Wellman facility–for comparison purposes, assumed to be 1%;

*BeLPT* –the beryllium lymphocyte proliferation test;

*beryllium-related health effects* – changes in health status that may occur after exposure to beryllium, including --

a) beryllium sensitivity *(BeS),* and,

b) chronic beryllium disease *(CBD);*

*confirmed sensitization – two abnormal blood BeLPT results*

*Elmore area* -- the area less than 15 miles from site boundary (Appendix J.2);

*false negative BeLPT* –a normal test result for a person who is *sensitized*;

*false positive BeLPT*– an abnormal test result for a person who is *not sensitized*;

*household contacts* -- individuals who live with a *beryllium worker;*

*local machinists* – in this plan, refers to current or former employees of the local machine shops that machine beryllium alloys;

*near the site* – the area 1.25 mi from site boundary, or less (Appendix J.1);

*unrecognized cases– BeS or CBD* in someone who never worked at the facility.

The processing facility has an established health and safety program to protect their workers. As part of this program, current employees are tested periodically for sensitivity to beryllium. Some past employees of the facility were recently tested by NIOSH.[3] We do not plan to include current or past facilty employees. The household contacts of facility workers are eligible, as are the household contacts of workers at the local machine shops that contract or contracted to machine beryllium alloys.

## 1.3 Personnel

The table below lists the primary project personnel.

**Table 1. Personnel and Affiliations**

| Name | ATSDR Division* / Role |
|---|---|
| Tom Sinks, PhD | ATSDR / Senior Manager |
| Dan Middleton, MD, MPH | DHS / Plan Leader |
| Peter Kowalski, MPH, CIH | DHAC / Plan Co-Leader |
| Loretta Bush, BS | DHAC / Communications |
| Jennifer Fink, MPH | DHS / Telephone Interviews |
| Robin Lee, MPH | DHS / Informed Consent |
| Carolyn Harris | DHS / Project Officer |
| Steve Inserra, MPH | DHS / Mapping and Eligibility |
| Alden Henderson, PhD, MPH | DHS / Implementation |

* DHS is the ATSDR Division of Health Studies.
* DHAC is the ATSDR Division of Health Assessment and Consultation.

**Contractor**: the *Michigan Public Health Institute (MPHI)* will assist with certain aspects of this project (see timeline).

# 2.0 INTRODUCTION

## 2.1 Background Science

### 2.1.1 Mechanical Properties of Beryllium

Beryllium is lighter than aluminum, stiffer than steel, and dimensionally stable over a wide range of temperatures. These characteristics make it an important structural material in space technology,[4] finding applications in the windshield frames of space vehicles, brakes on the shuttle aircraft, satellite mirrors, space telescopes, and inertial guidance systems. Beryllium metal is also used as a reflector in nuclear reactors and to make certain components of nuclear weapons.

Beryllium is alloyed with copper, nickel, aluminum, and magnesium. The useful attributes of beryllium alloys are related to strength, hardness, fatigue and corrosion resistance, and electrical and thermal conductivity. For example, beryllium is alloyed with copper to make electrical contacts, non-sparking tools, springs, switches, golf clubs, bicycle frames, and dental prostheses.

Beryllium oxide (BeO) is used to make ceramics.[4] BeO is an excellent heat conductor and a good electrical insulator, making it useful in closely packed electronic devices. Because it is transparent to microwaves, it can also be used in microwave ovens.

Beryllium also forms water-soluble salts with flouride, chloride, and sulfate ions. These salts are useful catalysts in certain chemical reactions and have a role in glass manufacture.[4] Enthusiasm for this important metal is tempered by an appreciation of the association between exposure to respirable forms (particles, dusts, fumes) and a potentially fatal lung disease (CBD).[5]

### 2.1.1 Granulomatous Lung Diseases (GLD)

Granulomatous lung diseases result from infectious etiologies ( e.g., bacterial, fungal, viral, or helminthes), and from non-infectious etiologies (e.g., exposure to beryllium, coal dust, or silica). For some granulomatous diseases, the etiology has not yet been established (e.g., sarcoidosis, amyloidosis).

CBD and sarcoidosis are clinically similar. Indeed, sarcoidosis may be a group of disease processes with similar clinical presentations, but different etiologies and prognoses. As a diagnosis of exclusion, the term sarcoidosis does little to help establish etiology, select appropriate interventions, or determine prognosis.

If sarcoidosis is diagnosed without excluding CBD, then CBD remains a potential etiology.[6] Making the diagnosis of CBD identifies the exposure and helps to guide appropriate medical and exposure interventions for the patient. It may also protect others by calling attention to the outcome as a *sentinel health event.*

### 2.1.2 History of CBD in the United States

The symptoms of CBD include arthralgias, chest pain, cough, or dyspnea with relatively mild exertion. Physical examination may reveal hepatosplenomegaly, inspiratory rales, and lymphadenopathy. These findings are not very specific and CBD cannot be reliably distinguished from sarcoidosis by clinical findings alone.[6]

The first CBD cases at a fluorescent lamp manufacturer in Salem, MA (1930's) were initially misdiagnosed as sarcoidosis, creating what was thought at the time to be an "epidemic of sarcoidosis." *Berylliosis* (now called CBD) was recognized as a disease in the United States in the mid-1940's.[7]

The U.S. Beryllium Case Registry was established in 1952.[8] Admission to the Beryllium Case Registry required documentation of *exposure,* plus at least three of four specified *clinicopathologic criteria* (see the table that follows).

Clinicopathologic Criteria for the U.S. Beryllium Case Registry *

1. Clinical symptoms of a lower respiratory tract disorder
2. Reticulonodular infiltrates on chest radiography
3. Restrictive or obstructive impairment of pulmonary function or a depressed diffusing capacity for carbon monoxide
4. Histologic demonstration of noncaseating granulomas and/or mononuclear cell interstitial infiltrates on lung biopsy specimens

** These criteria were used from 1952 to 1970. The Beryllium Case Registry is closed.*

The Beryllium Case Registry grew to include approximately 900 cases. Newman et al. reviewed the registry cases and concluded that the clinical presentation and rate of disease progression varied, the benefit of interrupting the exposure pathway had not been demonstrated, and the effects of potential risk factors were unknown.[5]

Sixty-five of the cases in the Beryllium Case Registry were associated with environmental exposures: 23 people were exposed in their residence to contaminated work clothes brought home by beryllium workers and 42 people were exposed to off-site air pollution.[6] These environmental cases were reported prior to 1960.

CBD was thought to have disappeared with improvements in industrial hygiene practices, but modern immunologic testing with the BeLPT demonstrated that exposed workers are still at risk for CBD. BeLPT testing has only rarely been extended to the communities nearby.

## 2.2 Modern Diagnostic Tests

*Granulomatous lung disease* is most clearly demonstrated when a biopsy specimen collected during bronchoscopy reveals granuloma formation, or (minimally) a mononuclear cell infiltration.[9] Lavage fluid collected during the bronchoscopy typically reveals a lymphocytosis.

The beryllium lymphocyte proliferation test (BeLPT) was developed to identify individuals who were *sensitized to beryllium.* In general terms, the BeLPT is performed by culturing T-lymphocytes from peripheral blood or bronchoalveolar (lung) fluid with and without beryllium salts. The proliferative response of lymphocytes stimulated by beryllium is compared to that of unstimulated lymphocytes, based on their uptake of tritiated thymidine.

The ratio of the response of stimulated lymphocytes to that of unstimulated lymphocytes is called the stimulation index (SI). Two elevated indices out of six are reported as an *"abnormal"* BeLPT test result; if only one of the six indices is elevated, the result is reported as a "borderline" BeLPT test result. A second abnormal BeLPT test result provides confirmation of sensitization *(BeS).* [10] In current medical practice, there is some diviersity if opinion – some specialists do accept one "abnormal" and one "borderline" as sufficient confirmation of sensitization. [11]

Researchers have assessed the value of various clinical tests used to identify beryllium disease.[12, 13] The predictive value of the BeLPT was higher than the chest radiograph, spirometry results, symptom reports, and clinical examination results. There was some evidence that abnormalities in gas exchange during exercise occur early in CBD, but the tests were more intrusive and less acceptable for screening. The thin-section CT was found to be more sensitive than plain chest radiographs, but delivered more radiation and still missed approximately 25% of CBD cases.

The BeLPT has changed the diagnostic criteria for CBD. Documented exposure to beryllium is less important; the diagnosis of CBD currently depends on demonstrating both a g*ranulomatous lung disease* and *immunologic sensitization to beryllium*. [13, 14] In a study of exposed workers, a confirmed positive BeLPT had a positive predictive value for CBD of almost 50%.[15]

Beryllium sensitization can be established by testing lymphocytes from the peripheral blood or fluid from bronchoalveolar lavage. A negative blood test does not exclude the possibility of beryllium sensitization – false negative test results are not uncommon. While bronchoalveolar lymphocytes provide greater sensitivity,[12,13] they must be collected during a bronchoscopy, which is not part of this community service.

## 2.3 Justification

In 2002 ATSDR stated that current releases from the plant to ambient air or through worker take home did not present a public health hazard. ATSDR did not have sufficient information to determine whether past releases from these pathways was (or was not) a public health hazard. Some information about past releases is available, but we do not know if these past releases presented a health hazard or not.

ATSDR is aware of a possible community-acquired case of chronic beryllium disease (CBD). This person was a household contact of a Brush Wellman-Elmore worker. The initial (incorrect) diagnosis was sarcoidosis. While this patient had more than one potential exposure pathway, exposure and disease are well-documented among household contacts of beryllium workers.

During the public comment period, ATSDR was contacted by other members of the community who were household contacts of Brush Wellman workers. Some of them had been given a diagnosis of sarcoidosis without excluding CBD and wished to be tested for sensitization.

ATSDR has reviewed a listing of CBD deaths among Ohio residents from 1990 to 2003. These data were made available to ATSDR from the Ohio Department of Health. A total of 20 Ohio residents who died during this time period had beryllium disease listed as the underlying cause of death on their death certificates. Among the 88 counties in Ohio, the cumulative mortality rate from CBD per 100,000 persons was highest in the counties of Ottawa (7.32), Sandusky (3.24), and Wood (2.48) during this time period. Limited occupational information is available from the death certificates. Of the six deaths in Ottawa, Sandusky, and Wood County, the occupational statement for four individuals suggests exposure to beryllium at work. In addition, death certificates for two additional deaths suggest a possible link to beryllium-related employment. Occupational statements on the two remaining deaths however do not suggest an association with workplace exposures to beryllium. ATSDR has not determined if these individuals were Brush Wellman workers, household contacts of Brush Wellman workers, contract machinists, or simply resided near the Brush Wellman plant.

ATSDR believes that there is sufficient information available to support the plan to offer testing to individuals requesting it.

### 2.3.1 Exposure

Testing for beryllium sensitization will be offered to up to 200 people who wish to be screened. Because resources are limited, testing will be offered to those individuals most likely to benefit based on their potential for exposure.

Individuals could have been exposed to beryllium that left the facility over a period of decades in the following ways:

a) as airborne releases,

b) as beryllium alloys sent to be machined locally, or

c) incidentally, on the clothes of beryllium workers.

There are a number of factors that may influence the risk of sensitization, including exposure levels, particle size, time since first exposure, and individual susceptibility.

During the 1940s, ten environmental (non-occupational) cases of chronic beryllium

disease were identified and attributed to ambient air pollution from a local beryllium plant in Lorain, Ohio.[16] The furthest case detected by chest radiograph lived 0.75 mile from the beryllium plant.

While current exposures are lower, our ability to detect sensitization and early disease is much better. When the BeLPT was offered in modern occupational settings with less potential for exposure, investigators were surprised to find cases of beryllium sensitivity and CBD.

### 2.3.2 Current Medical Practice

When a primary care physician encounters a patient with a granulomatous lung disease, a pulmonary physician is typically consulted to search for the etiology. If no etiology is found and the clinical picture fits, a diagnosis of "sarcoidosis" is usually made. Because there is no specific test for sarcoidosis, the diagnosis depends on adequately excluding the other possible explanations.[16] In the absence of known occupational exposure, CBD is typically not considered in the differential diagnosis. The first CBD cases in the United States were initially thought to be sarcoidosis, creating what was believed to be an "epidemic of sarcoidosis." There is evidence in the peer reviewed literature that clinicians have continued to miss cases of CBD, typically mislabeling them as sarcoidosis.[17]

### 2.3.3 Identifying Beryllium Sensitization and Disease

A reliable test (*the BeLPT*) is now available to identify individuals who have become *sensitized to beryllium (BeS*). Stange et al. [2004] recently reviewed screening data for a large cohort of current and former Department of Energy (DOE) workers. They concluded that "...the BeLPT is efficacious in the surveillance of beryllium exposed individuals. The PPV of the BeLPT is comparable to other widely accepted tests." [18] This is especially true of confirmed results.[19]

To diagnose chronic beryllium disease, both an *immunologic sensitization* to beryllium and the presence of *granulomatous lung disease* [12, 13] must be documented. As is current medical practice, abnormal tests will be confirmed by additional testing. We will consider beryllium sensitivity to be confirmed after two abnormal BeLPT results, though other outcomes (e.g., one abnormal and one borderline, or three borderlines) are sufficient evidence to justify referral to a pulmonary specialist. In reality, the individual's clinical physician(s) must evaluate these test results along with the laboratory and clinical evidence obtained during medical evaluation to determine what diagnosis and followup is appropriate. We will defer to the clinician's diagnosis, if it is known.

### 2.3.4 Benefits of Participation

This plan provides testing for individuals who are concerned that past exposures may have caused them to become sensitized to beryllium. This testing should also provide some reassurance to those with normal test results. Individuals with abnormal results test will be asked to follow-up with their physicians or a pulmonary specialist of their choice.

While sarcoidosis is considered a medical diagnosis, it is more accurately described as a family of related granulomatous lung diseases. The BeLPT enables us to reliably diagnose CBD, which is a more specific and more informative diagnosis than sarcoidosis.[13] For example, the diagnosis of CBD tells the physician that:

a) exposure to beryllium caused the disease,

b) the disease is progressive [20],

c) the disease is unlikely to spontaneously resolve (sarcoidosis often does), and,

d) a clinical need for oral steroids probably implies lifetime therapy.

A specific diagnosis (CBD) also reinforces the need for long term medical follow-up. As with other serious lung diseases, patients can get preferential treatment for vaccinations against influenza and pneumonia and can be identified for early and aggressive interventions during respiratory infections. Knowing the etiology makes it possible to review potential exposure pathways and consider ways to separate the individual from exposure to beryllium. BeS and CBD result from immunologic hypersensitivity, which makes interruption of the exposure pathway an especially important public health intervention. The hypersensitivity mechanism is so variable among individuals that is difficult to establish a “safe” exposure level for susceptible persons.

## 2.4 Design and Location

This community service activity will provide testing for up to 200 people who are concerned that their past exposures may have resulted in sensitization to Be.

Facility employees are regularly tested for beryllium sensitivity and will not be included. However, household contacts of facility workers who are concerned about beryllium “take home” can be tested.

Because the local machine shops that work with beryllium alloys do not practice strict industrial hygiene or screen for beryllium sensitivity, their employees and household contacts are eligible to be tested. Sarcoidosis patients who are concerned about beryllium sensitivity and live in the Elmore area will also be offered testing.

## 2. 5 Activities

The goal of this activity is to provide an opportunity for up to 200 community members who are concerned about past exposure to be tested for Be sensitization. Those thought to benefit most from testing are listed in Table 1.

**2.5.1 Activity 1**. Inform community members with sarcoidosis about the availability of testing. The following actions support "Activity 1."

a) Obtain a list of local and referral physicians and ask them to inform their sarcoidosis patients of the opportunity for testing (see Appendix A).

b) Inform area sarcoidosis patients of this opportunity for testing through media outreach (radio "spots" and newspaper ads).

**2.5.2 Activity 2.** Inform the household contacts of facility workers, local machine shop workers, household contacts of local machinists, and those living within 1 ¼ mile of the plant about the availability of testing. The following *actions* support "Activity 2."

a) direct mailings to nearby residents with factsheets enclosed;

b) a media outreach program, and,

c) factsheets distributed at local machine shops.

**2.5.3 Activity 3.** Identify the first 200 volunteers who wish to be tested and fall into at least one of the four categories of interest. The following *actions* support "Activity 3."

a) conduct a brief telephone interview with interested individuals, and,

b) determine their eligibility to be tested.

These tasks will be performed by ATSDR staff.

**2.5.4 Activity 4**. Test eligible volunteers for beryllium sensitivity and interpret the test results. The following *actions* support "Activity 4."

a) Obtain informed consent and signed physician notification forms for the persons to be tested (Appendices D, E).

b) Collect and test blood specimens from eligible participants identified during Activities 1, 2, and 3.

c) Notify participants and their physicians (as authorized) of test results.

Those with a normal test will receive their final results.

We will arrange a second round of BeLPT testing for patients who need additional (confirmatory) testing. The recommendations after confirmatory testing is completed will include either (see Appendix K):

a) medical followup (by a pulmonary specialist, or by their family doctor); or,

b) no special recommendation (continue with routine medical care).

Medical diagnoses can only be made by an area physician providing clinical care. Medical evaluation can lead to the following diagnoses:

a) BeS;

b) CBD;

c) an illness unrelated to beryllium; or

d) no diagnosis.

### 2.6 Purpose

This public health activity will provide testing to individuals who are concerned about their potential exposure to beryllium. It may also provide useful information to the community. That is, a single case for someone known to be at risk (a local machinist or household contact) can serve as a "sentinel event," suggesting that others may also be at risk.

## 3.0 METHODS

This is a *voluntary testing program.* Outreach efforts will provide opportunities for self-identification. A brief questionnaire will determine eligibility.

Current plans are to obtain informed consent and draw blood specimens at the testing center or at the participant's home. If the machine shops permit and adequate space is available, we may be able to draw blood samples from the machinists at their workplace.

The tasks performed by the contractor will include scheduling, drawing and labeling blood samples, and shipping blood samples overnight to the testing laboratory or laboratories.

### 3.1. Biomedical Screening

ATSDR personnel have met with the community and proposed an environmental

investigation. Environmental sampling for Be is not currently planned. Instead, ATSDR will offer biomedical testing to people who are concerned about past exposure to beryllium.

ATSDR has conducted an availability session in Elmore, Ohio and has provided a 30-day period for public comments. An expert panel was held in Ottawa County on April 25, 2006 to explore unresolved issues. This document has been revised to consider the comments received during the public comment period and during the panel meeting.

3.1.1 Outreach

This toll free line was open during the time period for public comment. It will remain open to answer questions and assist community members who contact us wanting to be tested.

Outreach has also included:

a) sending letters and factsheets to local doctors, asking them to inform sarcoidosis patients about the opportunity to be tested;

b) sending letters and factsheets to people who live near the facility;

c) contacting local machine shops that contract to machine beryllium alloys to inform owners and workers about the testing; and,

d) media outreach, including placing ads in local newspapers to inform the public about the availability session.

We will now inform the community that we are going ahead with the testing. We will continue to answer questions and complete eligibility questionnaires for callers. Most callers will be informed of their eligibility status after completing the telephone interview.

Eligible persons who wish to be tested will then be contacted by telephone to schedule a time to sign consent forms (Appendix D) and physician notification forms (Appendix E), as well as to provide blood specimens.

3.1.2 Collecting, Handling, and Shipping Specimens

During the first round of testing, blood specimens (30 cc) will be collected and promptly shipped by overnight carrier to the National Jewish Hospital's Immunology Laboratory (see Appendix H).

For those needing followup testing, a second laboratory that performs the BeLPT will be selected. A second blood specimen (60 cc) will be collected from them,

split into two samples, and promptly shipped to the two testing laboratories in accordance with their specified procedures.

### 3.1.3 Interpreting Test Results

Researchers at the National Jewish Hospital in Denver, CO, did not find a single confirmed false positive among over 1000 unexposed individuals. They have stated in the public record that confirmed false positives occur *"rarely, if ever."* [21]

These results are consistent with the recent study by Stange et al. who found no *confirmed* abnormal results among 458 *unexposed* employees and new hires.[18] Further analysis of the information published by Stange et al. confirmed the low risk for false positive confirmation.[19] These results provide ample evidence of the specificity of a confirmed abnormal BeLPT.

For participants who agree and complete the authorization forms, the individual BeLPT test results will be shared with their personal physicians. Overall, the BeLPT results will be utilized as follows: two abnormals, an abnormal and a borderline, or three borderlines will be considered sufficient reason to encourage medical evaluation by a pulmonologist with expertise in beryllium-related health effects. The presence of respiratory symptoms will also influence the specific followup recommendations (Appendix K).

Clinical diagnoses of BeS or CBD will *not* be made or altered by ATSDR project personnel. The participant's doctor is responsible for planning the individual's clinical evaluation, making appropriate diagnoses, and recommending clinical follow-up and treatment as needed. ATSDR will not pay for any follow-up medical evaluations or treatment.

## 3.2 CURRENT TIMELINE -- CALENDAR YEAR

### 1st Quarter CY2006 (Done)

- ► Brief the Senator's office/DHHS/County Commissioners (March)
- ► Release the Protocol for Public Comment (March 31)

**2nd Quarter CY2006**

- ► Meet with the press and hold availability meeting (April 25) (Done)
- ► Mail letters to physicians and residents (April) (Done)
- ► Revise plan to respond to public comments (May) (Done)
- ► Notify community that we will implement the plan (June)
- ► Screen volunteers and computerize their information (June)
- ► Brief Senator and Ottawa County Commissioners (June)

**3rd Quarter**

- ► Notify and schedule eligible participants – **Contractor** (July)
- ► Begin actual testing and collect blood samples - **Contractor** (July)
- ► Provide results/cover letters to those tested and their doctors (August)
- ► Collect additional samples to confirm sensitivity – **Contractor** (August)
- ► Provide BeLPT results to those that required retesting. (September)
- ► Provide BeLPT retest results to doctors as requested. (September)

**4th Quarter**

- ► Write the community report (October)
- ► Obtain ATSDR clearance for community report (November)
- ► Meet with the community (December)

## 4.0 POPULATION

### 4.1 Eligibility Criteria

Please refer to *1.1.1 (Definitions),* and Appendices I, and J.

The individuals to be tested will come from the population of people who lived or worked in the Elmore, Ohio area but are not current or former employees of the beryllium processing facility. Participants must be adults (18 years of age or more), as normal values are not readily available for children. The criteria for testing are based on either a clear potential for exposure to beryllium, or the presence of a granulomatous disease that is clinically similar to CBD.

That is, eligibility for testing depends on the following:

1. ***Exposure-based Criteria*** – the individual has *(for at least 1 year)* ...

   a) lived near (within 1.25 miles) the facility;

**OR,**

   b) worked at one of the local shops that machine beryllium alloys;

**OR,**

   c) shared a household with a beryllium worker *(a worker at the facility, or from a local machine shop contracting to work with beryllium alloys).*

2. ***Disease-based Criteria*** -- a physician has diagnosed granulomatous lung disease without a clear etiology (sarcoidosis) AND prior to diagnosis:

   a) the individual met one of the Exposure-based Criteria ("1" above),

**OR,**

   b) lived or worked in the Elmore area *for at least 1 year.*

## 4.2 Estimated Number of Participants

ATSDR resources are available to test up to 200 people.

There are almost 70,000 adults (age 18 years or more) living within 15 miles of Elmore, Ohio (Appendix I). Using a prevalence estimate of 30 sarcoidosis diagnoses per 100,000 people, about 20 individuals with "sarcoidosis" are expected to live within 15 miles of the facility.

The machine shop located in Elmore, a shop that has worked extensively with beryllium alloys, has about 10 employees. We will offer to test these workers, and workers at another area machine shop with similar exposure potential from past work. Adult household contacts of workers from these machine shops or the facility are also eligible to be tested.

"*Nearby*" residents are adults who

   a) are 18 years or older; and,
   b) live within 1.25 miles of the facility.

There are 130 adults living within 1 mile, and we estimate that about 200 live within 1.25 miles. The background data needed to interpret BeLPT test results are not available for children.

**Table 1**

| Category | Estimated Numbers (Adults) *(n)* |
|---|---|
| **Sarcoidosis Cases** | 20 |
| **Machine Shop Employees** | 20 |
| **Adult Household Contacts of...** | |
| **Local Machinists** | 40 |
| **Facility Workers** | *Unknown* |
| **Nearby Adult Residents** | ~200 |

ATSDR does not know how many people will be interested in being tested but is able to test up to 200. As a community service project, the first 200 people from these categories who express interest in being tested and are eligible will be tested.

## 5.0 HUMAN SUBJECTS

Volunteers will come from the adult population, regardless of gender, race, or ethnicity. The BeLPT has been used primarily for adult workers and there is no reason to believe that the sensitivity or specificity will be different among adult community members who are eligible to be tested. The positive predictive value (PPV) depends on the outcome's prevalence in the group tested, which may be lower in groups with environmental exposure.

People with cognitive difficulties can also participate if their "legally authorized representative" (typically a spouse or parent) consents and can provide screening information for the participant.

## 5.1 Description of Risks and Benefits

We expect the risks for participation to be low. Blood collection (30 cc) could result in a small bruise. If follow-up testing is necessary, the follow-up blood collection will be 60 cc. It is possible that people could faint, but this is uncommon and the nurse or phlebotomist will have an established response plan for such situations. The questions on the survey are not expected to cause those tested any emotional discomfort; in any case, they may refuse to answer any questions that they do not want to answer.

All participants who provide a blood sample will receive a letter providing the results of their BeLPT blood test. If the initial BeLPT result is an abnormal or a borderline abnormal result, the participant will be notified by *phone* and by *registered letter*. A second round of testing will be offered (Appendix K). For uninterpretable results, the participant will be offered an opportunity to repeat the initial test.

This is a voluntary testing program. No money is available for testing beyond that described above. All participants with a confirmed abnormal BeLPT will be advised to contact their personal physician and to arrange follow-up with a pulmonary physician familiar with beryllium-related disease. Individuals will be responsible for the cost of their own follow-up medical care. No money is available for any follow-up medical care that is recommended.

## 5.2 Procedures for Informed Consent

This testing is offered as a clinical service to the community. It involves no more than minimal risk to participants. A written consent form is not needed to participate in the telephone interview. Informed consent will be obtained for blood collection and BeLPT testing.

ATSDR personnel will be available to answer any questions about what to expect, the risk, and the potential benefits to the best of their ability. After those who wish to be tested have signed the consent form, ATSDR will collect the form and the contractor will collect the blood specimen for testing.

An unsigned consent form will be given to each person tested. In some circumstances, the informed consent procedure, the interview, and the blood collection may occur at the participant's home or another location. This will occur if the participant is unable to come to the collection site or has a strong preference to provide the blood specimen at another location.

Investigators would like to confirm that participants have the same expectations as the investigators. To ensure that persons who consent to have their blood

tested are aware of the objectives of the program, each person will be asked if they are willing to answer a few questions about the blood screening and material written in the consent form. The questions they will be asked are included in Appendix L. If there are elements not understood the personnel administering the consent form will go over the item(s) with the subject to confirm comprehension and clarify the expectations for the blood screening.

## 5.3 Protection of Confidentiality

### 5.3.1 Protections

Each participant will receive a unique identifying number. The survey and consent materials include names, addresses, and telephone numbers; these documents will be kept in a locked file cabinet. Responses to the survey will be entered into an electronic database.

Blood samples that are sent to the laboratory will be labeled with a project identification number, but not with personal identifiers. Results from the laboratory will also be entered into the electronic database. Access to any electronic file containing identifying data will be password protected and restricted to personnel affiliated with the testing program.

The results may be published in a written report, or published in a scientific journal. Individual cases may be described, but no personal identifiers will be included and care will be taken to protect the identity of participants.

### 5.3.2 Exceptions

Other federal, state, and local public health personnel may be allowed to see the information if necessary to protect the participant's health, or to ensure the public's health. If a judge orders us to turn the information over to a court of law, we will comply.

# 6.0 DATA HANDLING AND ANALYSIS

## 6.1 Training

ATSDR project personnel will receive the phone calls and administer the survey to callers who wish to participate. Before beginning, the project leaders and other project personnel will meet to review and finalize the "on call" schedule and ensure consistency in administering the eligibility questionnaire and storing the information in a computer database. The project leader will meet with the personnel selected to administer the screening questionnaire, obtain informed consent, and ask for medical releases. A training session will take place to ensure that project administration has been understood and then practiced.

All components of specimen collection, handling, and shipping will be coordinated with the laboratories selected. Round 1 of testing will be done by the Specialty Laboratories in Santa Monica, California. For those persons who need addition testing (Round 2), split sample testing (2 labs) will be accomplished by adding the National Jewish Hospital in Denver. Contact information for the two laboratories is provided in Appendix H.

## 6.2 Data Handling

Participants will receive unique project identifation numbers after they complete the screening questionnaire and are found eligible. As they are collected, hard copies of this questionnaire, the consent forms, and the medical release forms will be kept in a locked file cabinet at ATSDR. Only the ATSDR project personnel, the ATSDR contractor, and other public health personnel assisting with the testing will have access to the personal identifiers of participants. The results obtained will be entered into the computer on a timely basis.

The database will be compared to hard copies for quality assurance. When data quality has been assured, paper copies of the survey instruments will be destroyed. Paper copies of consent and medical release documents will be maintained for a minimum of three years.

Blood samples that are sent for BeLPT testing will not be labeled with personal identifiers. Samples will be labeled with a unique project identification number that is linked to the participant's personal identifiers and questionnaire data. The ability to electronically link personal identifiers with survey information and test results will be maintained until ATSDR has completed work at this site. This is necessary initially to ensure proper notification of the participants and to ensure our ability to discuss the results with individuals and their physicians (as authorized).

Access to any electronic file containing identifying data will be password protected and restricted to project personnel. If necessary, we will share information with state or local public health personnel who need access to assist with the testing program or to protect public health.

## 6.3 Interpreting Results

### 6.3.1 Participants

To be eligible to participate, the individual must provide eligibility information and meet certain eligibility criteria. These criteria focus on either *exposure potential* or *disease diagnosis (sarcoidosis).*

6.3.2 Tentative Outcomes

The primary outcomes of interest are the BeLPT test results. The BeLPT results and reported symptoms will be used to group those tested as--

a) meeting the criteria to encourage referral to a medical specialist,

b) meeting the criterial for evaluation by their personal physician; or,

c) not meeting the criterial for special attention (i.e., continue routine care).

Consideration of their results and subsequent medical evaluation may lead their physician(s) to diagnose ...

1) *BeS* (confirmed sensitized to Be, only) ; OR,

2*)* *CBD* (confirmed sensitized to Be **AND** granulomatous lung disease); OR

3) not confirmed senitized to Be (another illness, or no illness).

Medical diagnoses and clinical care can only be made or altered by the individual's personal physician(s) .

## 7.0 DISSEMINATION, NOTIFICATION AND REPORTING OF RESULTS

Participants will be informed of the results of their blood tests. The scripts and draft letters that will be used are included in Appendicies F and G. A community report will be provided by ATSDR. A public meeting will be held to discuss the results and answer questions. Results may be published in the peer-reviewed literature.

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