Summary

On April 25, 2006, ATSDR convened an expert panel to address important questions that had been raised about the ATSDR plan, "Testing for Beryllium Sensitization, A Community Service in Elmore, Ohio."

Based on the panel's input, the plan was revised in the following ways:

a) the definition of "confirmed beryllium sensitization" was changed to 2 abnormal BeLPT results;
b) any case of confirmed sensitization in the groups known to be most at risk (exposed machinists, household contacts of beryllium workers) will be considered a sentinel event;
c) a respiratory questionnaire was added;
d) the schema for testing and follow-up recommendations was revised;
e) the rate of confirmed beryllium sensitization identified among nearby residents (within 1.25 miles of the Brush Wellman facility) will be compared to an assumed background prevalence of 1%.

Selected Panelists

Seven experts participated in the panel discussion and Dr. Tom Sinks (ATSDR) served as the moderator. ATSDR invited a number of these experts and provided an opportunity for Brush Wellman, the Ottawa County Commissioners, and to each select a participant.

The experts invited to participate were:

a) Dr. Jonathan Borak, Associate Clinical Professor of Medicine, Epidemiology, and Public Health, Yale University, Consultant for Ottawa County.
b) Dr. David Deubner, Vice President, Occupational and Environmental Medicine, Corporate Medical Director, Brush Wellman, Inc.
c) Dr. Raed Dweik, Pulmonology, the Cleveland Clinic;
d) Dr. Kathleen Fagan, Environmental and Occupational Medicine, Case Western University, Board Member, Ohio Citizens Action;
e) Dr. Lisa Maier*, Director, Occupational & Environmental Pulmonary Medicine Practice, National Jewish Medical and Research Center
f) Dr. Dan Middleton, Medical Epidemiologist, Division of Health Studies, Agency for Toxic Substances and Disease Registry
g) Dr. Milton Rossman, Professor of Medicine, University of Pennsylvania Medical Center

* *Dr. Lisa Maier could not attend, but provided electronic input.*

Charge to the Panel (see Attachment 1)
The panel was charged with addressing two important issues :

1. What confirms sensitization?
2. What results should lead to additional public health activities?

ISSUE 1. What confirms sensitization? (see Attachment 2)
The panel members suggested various criteria for "confirmed sensitization," including:

a) 1 abnormal (1 panelist);
b) 1 abnormal and 1 borderline (3 panelists); or,
c) 2 abnormals (3 panelists).

The plan was revised to define *confirmed beryllium sensitization* as two abnormal BeLPTs. This is the most conservative definition of sensitization offered for consideration.

In addition, panel members suggested criteria for referral to a pulmonary specialist familiar with chronic beryllium disease.

These criteria included:

a) 1 abnormal (3 panelists); and,
b) 1 abnormal and 1 borderline (4 panelists).

The plan was revised so that persons with 1 abnormal and 1 borderline will be encouraged to see a specialist, but will not be labeled as having "confirmed" sensitization.

ISSUE 2. What results should lead to additional public health activities?
The expert panel that met in Ottawa County specifically discussed the possibility of follow-up for both individuals and for the community. All the experts indicated that recommendations for individuals or the community could vary depending upon the test results. The experts were concerned that only providing results to patients and primary care providers would not allow appropriate recommendations for follow-up to be made.

Most panelists agreed that a confirmed positive test for someone already known to be at risk (i.e., an exposed machine shop worker, or household contact of any beryllium worker) should be treated as a sentinel event. In other words, targeted recommendations for follow-up might be needed.

There was less agreement about how to interpret confirmed positives among nearby residents, a group thought to be at less risk. Different views were expressed about the existence of a background rate of confirmed beryllium sensitization and the implications for interpreting results from the nearby residents.

The highest background rate suggested for persons without work-related exposure was 0.9% (Attachment 3). Dr. Borak proposed a graph (Attachment 4) for statistically determining excess confirmed positive tests, based on assumed background positive rates. For comparison purposes, ATSDR agreed to assume a background rate for confirmed sensitization of 1% for residents living within 1.25 miles of the Brush Wellman facility.

Attachment 1. Charge to the Expert Panel

Prior to the expert panel meeting on April 25, 2006, the following issues were provided to panel members for consideration.

ISSUE I. What confirms sensitization?

We plan to screen each person tested with one blood BeLPT and follow-up abnormal or borderline results with a sample split to 2 labs. Please fill in the boxes under "Interpretation" and "Recommend Referral" with a "Yes" or a "No." Explain as necessary.

Test Results	Interpretation	Recommendation
If 3 tests are done and the results include:	**Confirmed Sensitization (Yes/No)**	**Recommend Referral (Yes/No)**
1 Borderline		
2 Borderlines		
3 Borderlines		
1 Borderline and 1 Abnormal		
2 Abnormals		

ISSUE II. What results in a subgroup (or overall) should lead to additional public health activities or interventions?

Note that volunteers who are tested will come from one of the following ***subgroups*** --

a) nearby residents (within 1.25 miles of the Brush Wellman facility)

b) local machinists who machine beryllium alloys

c) household contacts of local machinists who machine beryllium alloys

d) household contacts of Brush Wellman workers

e) area sarcoidosis patients.

The individuals tested will be those from the subgroup(s) above who ask to be tested.

Some examples of possible future ***actions*** include:

a) none

b) environmental sampling – limited vs. community sampling

c) blood tests – additional community service testing or a research study

d) sarcoidosis patients – case-series investigation

e) other interventions – e.g., community education, physician education

The maximum number to be tested overall is N=200 and the numbers in each subgroup are unknown.

How many confirmed abnormals in each ***subgroup*** and ***overall*** would lead you to recommend 1) no further action, 2) limited follow-up of individuals, or 3) further community evaluation.

Subgroup's Potential Exposure	**No Further Action**	**Limited Follow-up of Individuals** *(Specify)*	**Further Community Evaluation** *(Specify)*
Residents Nearby (1.25 miles)			
Local Machinists (Be alloys)			
HH Contacts (Local Machinists)			
HH Contacts (Brush Wellman)			
Area Sarcoidosis Patients			

Comments _____

_____

_____

Use additional sheets as needed.

Attachment 2. Revised Proposal for Individual Follow-up Recommendations

Action	Criteria*
Confirm Sensitization	2 AB
Recommend Specialist Evaluation	2 AB
	1 AB + 1 BL
	3 BL
	(1 AB or 2 BL) and Symptomatic
Recommend Primary Care Visit	(1 AB or 2 BL) and Asymptomatic
	(1 BL or 1 NL) and Symptomatic
Copy to Medical Record	(1 BL or 1 NL) and Asymptomatic

* In situations where symptom status matters, it is listed.

Attachment 3. New Hire Testing by Brush Wellman

Brush Wellman new hire testing analysis by ChemRisk, independent scientists

CR given entire new hire database by BWI 1999 through mid 2005

CR audited database

CR produced the following report

New hires tested when beginning work	539	100 %
New hires with a positive BeLPT	13	2.4 %
New hires with a confirmed positive BeLPT	8	1.5 %
New hires without discernable prior beryllium exposure	5	0.9 %

Interpretation of community persons testing positive

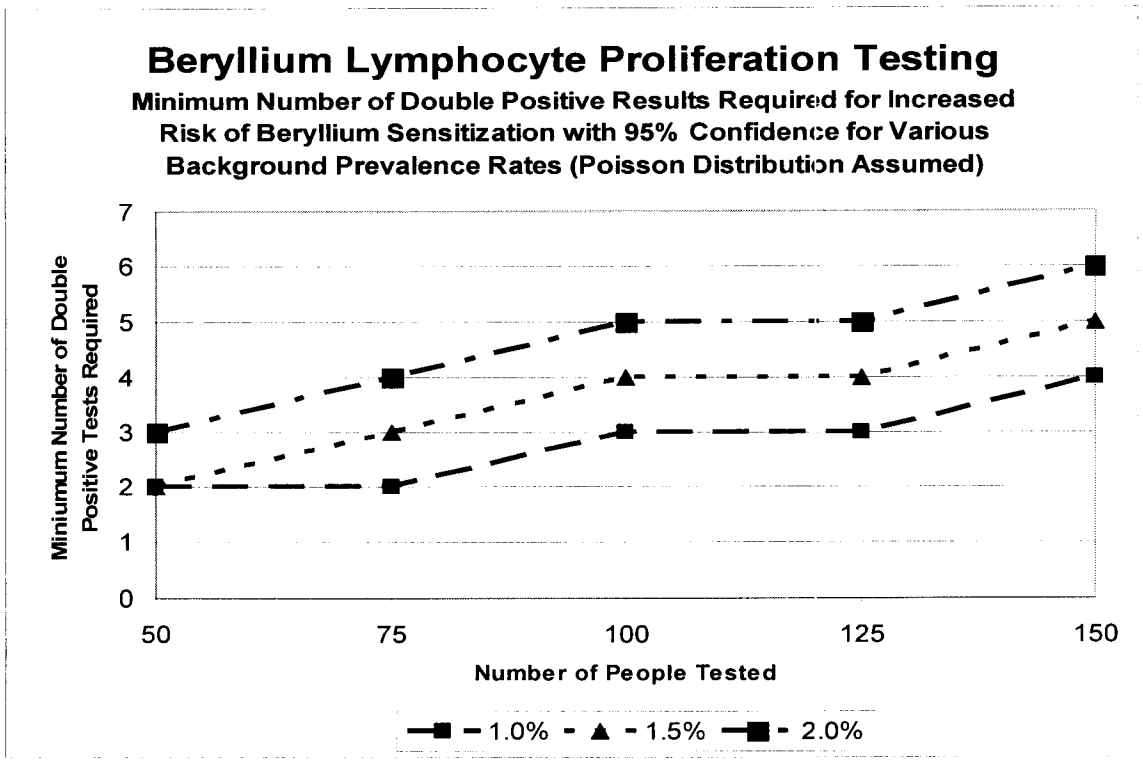
Interpretation of BeLPTs requires that each person be categorized with respect to validated measures of each of the following prior to testing.

a) Beryllium worker, current or prior
b) Family contact of beryllium worker
c) Exposed to beryllium manufacturing "drag out"
Examples: beryllium worker, equipment, articles
d) Exposed to non-beryllium manufacturing beryllium source
Examples: processing of bauxite, coal
e) Exposed to "ambient" beryllium (air, water) from beryllium manufacturing
f) Exposed to "ambient" beryllium from non-beryllium manufacturing beryllium source

Test results are interpreted by relating the outcome (BeLPT positive vs. negative or confirmed positive vs. unconfirmed positive/negative) to the joint effect of the exposure categories, probably using linear logistic regression

Note
Provided by Dr. David Deubner during expert panel of April 25th, 2006.

Attachment 4. Number of Confirmed Abnormals for Increased Risk



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Note
Provided by Dr. Jonathan Borak during expert panel of April 25th, 2006.

Panelists' Comments

Panelist A

Background Rates
Panelist A mentioned that Yoshida published a report of a background level of sensitized persons and that there was unpublished data on a group of Alcoa new hires.

Panelist A was concerned about aggregating the test results. The concern was that confirmed abnormals from a group at higher risk could be interpreted as showing that the community was at risk from plant emissions. This panelist believes that natural occurring beryllium can result in sensitization.

Community Screening
Panelist A stated that the BeLPT is not validated in the general population and does not meet USPSTF requirements for a screening test. It should be validated before using it in a community.

Even if a single BL (borderline) occurs in the community, we should give it to the individual's physician.

Interpreting Group Results
Panelist A gave out a handout – some background level associated curves (e.g., 1%, 2%) were used to model the number of persons with beryllium sensitivity that would be considered elevated for various n's tested ($p < 0.05$).

The panelist said that we should restate the question – i.e., what is the fewest number of positives among nearby residents that would be statistically significant?

Panelist A was most concerned about the risk of a false inference about the community.

ATSDR has 5 categories
In some ATSDR categories (e.g., machinist, household contact, sarcoidosis patient), even one case should be treated seriously. These categories should not be summed and applied to the nearby residents, who are not known to be at risk.

The BeLPT at Brush Wellman

Brush Wellman started using the BeLPT surveys in the early 1990s, performed surveys every few years through the late 1990s. The rates of positivity did not change between BeLPT surveys. Brush Wellman uses BeLPT as a check on hygiene controls.

Background Sensitization / Interpretation

Panelist B argued there is *"circular reasoning"* in DOE work - *"because new hires are negative must not be exposed – because positive must have been exposed."*

He provided data on background rates of confirmed positives for new hires –
5 confirmed positives of 539 with no known Be exposure. New hires are exposed by working between first and second test.

There is cycling between positive and negative among employees at Brush Wellman. Variability in immuno-responsiveness to beryllium exposure is a fact.

Panelist B does not agree that two positives during testing means excess exposure.

This panelist stated that they did not use the term "false positive" and did not use the BeLPT for screening. The panelist stated that what Brush Wellman does with the BeLPT is surveillance. He said that referral for bronchoscopy and biopsy is also part of surveillance. Split-samples are used to increase sensitivity by 25 to 30%.

Purpose of Testing

- Benefits administration (they offer a exit "package' to confirmed positives)

- Surveillance

- Individual referral of employees is based on single positive w/symptoms for medical evaluation by pulmonologists -- for surveillance).

Brush Wellman has referred employees for evaluation who have symptoms consistent with CBD, but are consistently negative on the BeLPT.

BeLPT testing has a capacity for psychological harm. Panelist B is against its use for screening. There is no benefit for those w/o symptoms.

Referral

Panelist B does not believe that borderlines should be used for decision-making.
He believes that referral should be based on exposure and symptoms.

This panelist suggested caution when referring to family physicians – they may not be familiar with beryllium-related health issues.

He does not think automatic referral is good medicine and noted that employees w/ abnormal results (w/o symptoms) can get angry when referral does not lead to action.

Panelist B stated that referral should be based on all the information about exposure, symptoms, and test results, as he has seen persons with symptoms who had no positive BeLPT tests.

Q - Would I recommend environmental sampling for cases? It depends –
A - ...if the individual was exposed was 25 year ago – NO.

Labs

Lab results vary over time. The two ways of looking at lab stability are with

a) split testing, and
b) follow-up BAL BeLPT (bronchoalveolar fluid).

Brush Wellman has had good experience using Specialty Labs.

Panelist B stated that he has previously worked with concerned local residents to ensure a balanced medical evaluation.

General Thoughts

This could spin out of control. The panelist talked about a DOE study in Las Vegas – BeS was attributed exposure to carpeting in an office building

The panelist said that we must do as much work up front before testing. It is important to take into account multiple exposure categories – that is, how will you decide ranking? If there is more than one pathway, which exposure caused the beryllium sensitization?

Background Rates of Sensitization

Panelist C stated that there is no gold standard for beryllium sensitization.
He assumes that there is no background rate for sensitization to beryllium.

Community Use of BeLPT

This Panelist said there is no way of knowing if the BeLPT will function as well in the community setting as it does for beryllium workers.

He assumes that persons who volunteer are interested in knowing results – suggested benefit for early referral.

Interpretation

The panelist said that a single BL requires retesting. Individuals with borderline results need to be retested until they are either positive or negative.

He said that the action taken for various numbers of confirmed abnormals will depend on one's perspective, and must take into account the exposure history of the index case. Any one positive case in the categories listed should be considered an index case for that group and pursued accordingly.

Panelist C suggested that the power calculations by Panelist A may take into account background rates that may not actually exist. Until demonstrated otherwise, one should still consider that there is no beryllium sensitization in the general population.

Questionnaire

Panelist D said that the questionnaire would be useful, but probably not essential. This panelist was not sure that it would significantly change the recommendation.

If a questionnaire is used, we should recommend follow-up for positive answers to a health questionnaire, independent of the lab results -- which is why the questionnaire may actually make things more complicated

This panelist recommended giving everyone who participates information for their physician -- including how to interpret the test results.

Referral

Panelist D recommends that those tested should see their own doctor who can then refer them on to a specialist if necessary. We should give them and their doctor a list of referral possibilities.

One issue is how strongly to recommend referral. This panelist recommends referral for sensitization (2 abnormals) and borderline sensitization (1 abnormal and 1 borderline). In these cases, the panelist believes in strongly recommending follow-up/referral.

Community-Based Actions

A cluster would require follow-up. In most cases, 1 confirmed abnormal would raise concern about the group of interest.

Panelist E commented about criteria for referral and identification of beryllium sensitization. These recommendations are…

Refer someone with three borderlines for specialist evaluation.

Refer someone with one abnormal and one borderline for specialist evaluation.

One abnormal and one borderline provide sufficient evidence of sensitization.

Panelist F

Panelist F noted that the definition of sensitization varies somewhat, but that most physicians do recommend evaluations by a specialist after "1 abnormal and 1 borderline."

A table was provided showing a number of reports in the peer reviewed literature where testing unexposed groups resulted in no confirmed abnormals.*

Note: exposure among nearby residents in the Tallevast community may be more properly considered "unknown" than "absent;" even so, the nearby residents were clearly the group at the *lowest* risk (among those tested: ex-workers, their household contacts, and nearby residents). The outcomes seen were also consistent with that interpretation.

*References

Stange AW, Furman FJ, Hilmas DE. *The beryllium lymphocyte proliferation test: relevant issues in beryllium health surveillance.* American Journal of Industrial Medicine 2004; 46:453-462.

ATSDR. Exposure Investigation Report. Former American Beryllium Site in Tallevast, Manatee County, FL. EPA Facility ID: FLD004100731. March 20, 2006.

Muller-Quernheim J, Gaede K, Fireman E, Zissel G. *Diagnoses of chronic beryllium disease within cohorts of sarcoidosis patients. ERJ Express 2006; doi: 10.1183/09031936.06.00112205*

Variability

Panelist G noted that steroid and aspirin may negatively affect test results, and transient exposures may illicit a transient response.

We need to obtain information about signs and symptoms from participants.

This panelist stated that testing depends on the purpose, whether it is for surveillance (trying to accumulate information about the prevalence of disease in the community) or for screening (trying to detect disease in individuals).

Referral

Individuals who are exposed to beryllium and develop cough and shortness of breath should always be referred for specialist evaluation.

Persons with beryllium sensitization (BeS) but no symptoms should have periodic follow-up (e.g., PFT/x-ray).

Panelist G felt that a single borderline requires retesting. Part of the decision for referral is based on clinical situation. A borderline and a positive BeLPT should require referral to a pulmonary doctor, but does not fully meet the criteria for confirmed sensitization.

Education

Panelist G pointed out need for education and full disclosure a priori – that is, borderline and indeterminate results can be expected to occur at times. People need to know that and how they will be handled.

1 positive in 50 (2 percent) would be statistically significant and suggest more testing. This panelist had an experience with a community that was ultimately shown to have a high rate of sensitization to beryllium – but the first 10 tested were initially negative, because the sample was insufficient. There are really two questions here:

1. If evidence of beryllium sensitization is detected, how many positives would constitute a number greater than expected? This is the basis of the graph handed out.

2. The other question is, assuming that there is increased beryllium sensitization in the community, is: how many individuals do I need to test to be sure that I haven't missed it because by chance I just happened to test individuals who were negative?