DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

June 12, 2006

David Deubner, M.D., M.P.H.
14710 W. Portage River south Road
Elmore, Ohio 43416-9502

Dear Dr. Deubner:

Thank you for your email of April 6, 2006. We are responding to issues raised in your email and relating them to the ATSDR's plan for testing for beryllium sensitization in Elmore, Ohio. We are also again requesting the survey instrument used by Brush Wellman for its workforce.

You raise several issues, among them the use of prednisone for clinical treatment. Treatment is not a part of the ATSDR plan. Even so, we feel the decision of when prednisone is justified and how much is needed must remain a clinical issue to be resolved between the doctor and patient. We would hope that clinicians would be judicious and use the minimum amount needed to produce the desired effect.

You indicated that the testing that Brush Wellman offers to its workers is considered surveillance. The Brush Wellman plan contains the elements typically seen in workplace medical screening. That is: a) workers are tested for an outcome associated with the exposure, b) abnormal results lead to medical evaluation, and c) test results and clinical findings can qualify the worker for exposure-related job changes.

You state that "compared to the beryllium patch test, the BeLPT is an insensitive test for BeS." As you are aware, the patch test is not generally used in the United States because of concern that it may induce sensitization where none previously existed, or it may cause a serious or fatal anaphylaxis in someone already sensitized.

You state that "the single positive BeLPT in a truly BeS person has to be distinguished from a positive BeLPT resulting from random variation or a misperformed or misreported test in a BeS negative person." A single positive that is never confirmed (despite serial attempts) is possibly consistent with a "false positive." A second abnormal test is considered by essentially everyone who uses the test including Brush Wellman as "confirmation" of true beryllium sensitization.

The sensitivity and specificity of the BeLPT have been estimated by Stange et al. [2004]. While it is true that Stange et al. did not have a true gold standard for comparison, they were able to rely on the premise that after a few rounds of testing, true abnormals will be repeated and false abnormals will not. This same logic is used by Brush Wellman and others for *clinical confirmation testing* – i.e., that one abnormal might be a false positive, but after two you can

believe the individual is truly sensitized to beryllium. This practical approach has led to useful estimates of BeLPT characteristics, both for single tests and for testing algorithms.

You also state that "the prevalence of immunologic responsivity (delayed hypersensitivity) to beryllium in the general population is 4-5% as detected by the beryllium patch test (Shima, Bobka) and 1-2% as detected by the BeLPT (Yoshida, BWI unpublished data)."
From our reading of the report, Yoshida does not mention confirmation testing, so the 1-2% appears to reflect the usual false positive rate (not confirmed abnormals). However, we note that among persons not occupationally exposed, Brush Wellman has reported less than 1% confirmed abnormal (sensitized) among new hires. If there is a background rate for confirmed abnormals among individuals without work-related exposure, it can be expected to lie between 0% and 1%. For comparison purposes, we will assume that a background rate of approximately 1% exists in this community.

You state that '"...the DOE data that asserts that double positives are unknown in unexposed populations is biased due to selection derived from circular reasoning. The DOE has both presented at meetings and published the fact that the BeLPT results were used to identify beryllium exposure (Stange 2001, Welch 2004) so any population with positive BeLPTs was by definition exposed, and any unexposed population by definition did not have positive BeLPTs." As you know, Stange et al. [2004] reported testing over 450 unexposed individuals and finding no confirmed abnormal results. While you express concern about circular reasoning in categorizing and testing DOE employees, this concern cannot logically extend to the approximately 300 new hires tested by DOE – with no confirmed abnormals (0%).

You list several concerns about the manner in which individuals could be exposed including: "1) beryllium exposure associated with employment in another workplace,
2) the background rate of beryllium responsivity due to beryllium in the natural environment in soil and naturally bio-concentrated in plants and plant products, or an immunologic crossover reaction, 3) beryllium exposure as a result of localized contamination due to "drag-out" from an industrial source, and 4) ambient beryllium in the community due to release through air or water from an industrial source, e.g. manufacturing or recycling of beryllium products, or processing materials naturally containing beryllium, such as coal, or bauxite." As you know we are assuming a background rate of 1% in the testing in Elmore. If potential causes unrelated to Brush Wellman's releases in this community are taken into consideration, we believe they would be accommodated in the 1% background rate we are using for comparison. Also, we have not said that we could definitively determine the significant exposure routes for any individual.

You state that "in definitely beryllium exposed persons the positive predictive value of the positive BeLPT for granulomas on biopsy is high (60-100%). In the DOE, however, the PPV is much lower in many populations (~20-30%) that also have relatively low rates of BeLPT positivity (~3%)." Middleton, Lewin, and Kowalski [2006] estimated that the positive predictive value for true sensitization for the algorithm proposed would be 93% if the

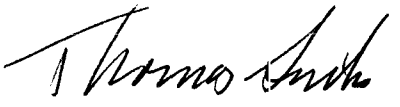
prevalence of sensitization is 2%. While the predictive value of a positive test does decrease with decreases in the prevalence of sensitization, this finding can be predicted from an increase in the ratio of false abnormals to true abnormals. We don't believe that it adds to the evidence for a background rate of confirmed abnormals.

The predictive value negative will also be very high for normal tests, given that sensitization is a rare outcome. Having a normal test does not prove that the person is not sensitized to beryllium. Approximately one- third of those sensitized may have normal test. The benefit to those who test negative is reassurance that they likely are not sensitized. If the prevalence of sensitization is as high as 3% or as low as 1%, the likelihood of a false negative test would be 1% or 0.3%. In other words, less than one in 100 people with a normal result truly have beryllium sensitization. This is clearly adequate to provide reassurance to most people.

You state that "CBD is probably similar to pulmonary sarcoidosis in that most disease is sub-clinical and progressive clinically significant disease is a limited proportion of the whole spectrum. With repeated surveillance cumulative rates of sCBD in our population have reached 12% (life table). The prevalence-cumulative incidence relationship for sCBD is identical to that for BeLPT positivity, suggesting sCBD may be a waxing and waning disease as well, analogous to subclinical sarcoidosis." We do not know what percentage of subclinical cases of CBD identified today can be expected to progress to significant clinical disease. We do know that physiologic parameters can be significantly impacted before the symptoms cause an individual to seek care. While (by definition) CBD at the clinical level is more advanced than is CBD at the subclinical level, all levels of CBD have some negative effect on the individuals physiology and state of health. In addition, some proportion of individuals with subclinical disease will progress to debilitating clinical disease.

We appreciate the opportunity to respond to your comments. If you wish to discuss these issues further, please contact me at 404-498-0004 or Dr. Dan Middleton at 404-498-0565.

Sincerely,



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