DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

June 12, 2006

Jonathan Borak, M.D.
Yale University
234 Church Street
New Haven, Connecticut 06510

Dear Dr. Borak:

The purpose of this letter is to provide the Agency for Toxic Substances and Disease Registry's (ATSDR's) response to your letter of April 28, 2006, which included your comments on our "Testing for Beryllium Sensitization, A Community Service in Elmore, Ohio" plan.

In your letter, you question whether testing household contacts and "Nearby Adult Residents" falls within the ATSDR mandate. As both groups are part of the exposed community, they are included under this plan. As you are aware, this is a one time screening, and therefore is neither medical monitoring nor surveillance.

You question the appropriateness of the BeLPT in this setting. This test has been widely used for diagnostic testing and for exposure-related testing by both government agencies and industry. You referred to the United States Preventive Services Task Force (USPSTF) guidelines. We have not recommended screening the general population by primary care providers, the intended audience for such guidelines. We have offered to test potentially exposed individuals who wish to be tested because they are concerned about past beryllium exposures. The potential beryllium exposure to each category is based upon documented environmental releases of beryllium into the nearby community from the Brush-Wellman facility, and the well documented relationships between chronic beryllium disease, household contacts of beryllium workers, and sarcoidosis.

You stated that the sensitivity and specificity of the BeLPT were unknown. We note that summary estimates of the sensitivity and specificity of the BeLPT across four commercial laboratories have been published by Stange et al. [2004]. As there is no true "gold standard" for comparison, Stange relied on the premise that after a few rounds of testing, true abnormals will be repeated and false abnormals will not. This same logic is the basis routinely used for *clinical confirmation testing* – i.e., the concept that one abnormal might be a false positive, but after two abnormals the individual is considered sensitized. These estimates are the most broad-based and credible estimates of BeLPT parameters to date.

You state that occupational data are unlikely to apply to asymptomatic members of the general population (without a history of sarcoidosis, employment in beryllium facilities, or being household contacts of such workers). We agree that data on the BeLPT collected on exposed individuals is not likely to apply to the unexposed general population. ATSDR considers all of

those eligible for testing to have had the potential to be exposed to beryllium released from the Brush-Wellman, Elmore plant. We do not know the prevalence of sensitization within or between the four categories of eligibility and the current plan will not provide such estimates.

You question the interpretive criteria for the screening. Some physicians, including one panel member, believe that the BeLPT is so specific that it does not need to be confirmed to establish sensitization. The article you cite (Welsh et al. 2004) clearly states that one abnormal and one borderline are sufficient evidence of sensitization (as are two abnormals). Even so, we have revised the ATSDR testing plan to define sensitization as two abnormal tests. We will make clear that other findings (one abnormal and one borderline, or three borderlines) also merit referral for medical evaluation as recommended at the expert panel meeting you attended.

ATSDR is using the BeLPT to determine if eligible individuals have been exposed to beryllium in sufficient amount to cause sensitization. The accuracy of the test for predicting clinical or sub-clinical chronic beryllium disease is not the focus of this effort. Nevertheless, because individuals who have become sensitized should be referred for clinical follow-up, ATSDR will recommend that individual participants seek follow-up care as recommended by the members of the expert panel meeting which you attended. The final diagnosis must be made by a physician who knows the patient's history and has completed an appropriate clinical evaluation.

You state that accurate determination of individual residencies will be critical. We will administer screening questions to everyone who seeks testing to try to validate exposure assignments. We will be matching the names and addresses of persons who identify themselves as nearby residents with commercially available data to help ensure that they do live in the residential area near the facility. We are also exploring other ways to validate the information we collect.

Participants will be assigned to each exposure category in which they are eligible. Analysis of summary results will rank the potential exposure pathways in a hierarchical fashion. In this manner, we will consider the "household contact" pathway to be a more likely source of exposure than a "nearby resident" pathway for a confirmed abnormal individual who lives within 1¼ mile of the facility and was also the household contact of a former beryllium-exposed worker. This approach addresses your concern about the possibility of overstating the risk from less significant pathways.

You state it may be impossible to interpret aggregated data because there is insufficient information regarding the expected background rate of BeS in the general population. The evidence for background cases of beryllium sensitization in the general (unexposed) population is uneven and contradictory. Dr. Deubner (Brush Wellman) has reported to us (unpublished data) that he found confirmed abnormal results for 5 persons who did not have occupational exposure among over 500 new hires tested. Yoshida et al. [1997] reported finding 2 individuals with elevated stimulation indices (SI's) among 159 unexposed workers, but did not

report confirmation testing. The rate reported (2 abnormals / 159 tested) appears to be the false positive rate for single tests and is consistent with that reported by other researchers [Stange et al. 2004]. When testing new hires and unexposed employees, other investigators have found no confirmed abnormals [Stange et al. 2004]. If there is a background rate for beryllium sensitization in the general population, it is very low. In this investigation, we will assume (for comparison purposes) a background rate of 1%.

Again, thank you for your comments. We appreciate the interest shown in our testing plan for the Elmore community. Should you have additional comments or concerns, please do not hesitate to contact me.

Sincerely,

Thomas Sinks

Thomas Sinks, Ph.D.
Deputy Director, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry

References

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