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Specialists in Occupational & Environmental Health

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Deputy Director
Agency for Toxic Substances and Disease Registry
US Department of Health and Human Services
Atlanta, GA 30333

Dear Dr. Sinks:

I am writing at the request of Mr. Steve Arndt, County Commissioner of Ottawa County, Ohio to provide comments on the 03/31/06 *Public Comment Release* of Testing for Beryllium Sensitization, A Community Service in Elmore, OH ('Plan').

My comments reflect both my review of the documents that ATSDR has made available and also discussions about this project during meetings on 03/24/06 (in the office of Senator Michael DeWine) and on 04/25/06 (several meetings in Ottawa County).

1. The Plan proposes to test five categories of Ottawa County residents:

   Sarcoidosis Cases
   Machine Shop Employees
   Household Contacts of Local Machinists
   Household Contacts of Brush Wellman (BW) Workers
   Nearby Adult Residents

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From the standpoint of the proposed testing, these five categories can be seen as falling into three different testing paradigms:

Diagnostic testing: A well-established database indicates that chronic beryllium disease (CBD) may be misdiagnosed as sarcoidosis, and there is also evidence that BeLPT can help discriminate between those two diseases.

BeLPT serves a diagnostic function in sarcoidosis patients.

Workplace-related medical surveillance: A well-established database indicates that prevalence rates of beryllium sensitization (BeS) and CBD are significantly increased in beryllium-exposed workers. There is also evidence that BeS and

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and CBD have occurred in the household contacts of beryllium-exposed workers. Use of BeLPT in the context of workplace medical surveillance for beryllium-exposed workers is generally well-established. BeLPT is not routinely used for household contacts, but based on a small number of reported examples of BeS or CBD in contacts it is possible that such individuals might be at significant increased risk for disease.

Although it is not clear that such workers and their household contacts fall into the traditional areas of ATSDR mandate (e.g., CERCLA waste sites), there are data to suggest that they might meet the traditional level of concern for ATSDR medical monitoring programs as described in *Final Criteria for Determining the Appropriateness of a Medical Monitoring Program under CERCLA*:

> "the periodic medical testing to screen people at significant increased risk for disease" (1), p. 38840.

BeLPT serves a workplace-related medical surveillance function in machine shop employees (assuming that those workers are exposed to beryllium-containing metals) and household contacts of beryllium exposed workers.

Medical screening: The Plan proposes to use BeLPT to screen asymptomatic individuals identified solely on the basis of the location of their residences in Ottawa County. There is no established database indicating an increased risk of BeS or CBD in Ottawa County residents who have not been employed at a beryllium facility or who were household contacts of such employees. Likewise, there is apparently no evidence of an increased risk of BeS or CBD in those characterized solely by proximity of their residences to the BW Elmore facility. Moreover, your statements repeatedly affirmed that ATSDR knows of no BeS or CBD cases in Ottawa County residents who were neither employed at a beryllium facility nor household contacts of such employees.

Thus there is apparently no empirical basis to propose that 'Nearby Adult Residents' represent a group "at significant increased risk for disease". Accordingly, this group falls outside of traditional ATSDR screening activities.

More importantly, there is essentially no published basis for use of the BeLPT as a screening test in asymptomatic persons defined solely by place or residence and who are not "at significant increased risk for disease". There is no basis to suggest that BeLPT serves an appropriate function for screening such individuals.

With respect to those identified as "Nearby Adult Residents", ATSDR proposes to use a diagnostic and workplace surveillance test for medical screening in the general population. The relatively extensive BeLPT database does not consider or address its use as a general screening test. For that reason, this test would not meet criteria promulgated by the US Preventive Services Task Force for adoption of medical screening tests (2-4). For example, the sensitivity, specificity, positive predictive value and negative predictive value of the test in the general population are unknown. In other words, use of BeLPT in the general population has never been validated.

Accordingly, such use of BeLPT in an asymptomatic population defined solely on the basis of their places of residence can not be seen as the use of a validated screening test for purposes of "service". It should properly be seen as either a feasibility study or an experiment.

2. Besides the more general lack of validation and basis for use of BeLPT in the general population, the Plan proposes a novel set of interpretive criteria for defining BeS that have not been previously validated in any population.

As discussed at the Expert Panel convened by ATSDR earlier this week, "beryllium sensitivity" should not be defined on the basis of one abnormal and one borderline BeLPT, as is proposed in the Plan. Contrary to the statements in the Plan, that criterion is <u>not</u> "current medical practice" [1].

The Plan also relies on a recently published study by Middleton et al. (5), which proposed testing algorithms similar to those proposed in the Plan. In turn, the Middleton algorithms, which defined BeS as either 2 abnormal BeLPTs or one abnormal and one borderline BeLPT, derived from work earlier published by
Stange et al (6). However, Stange et al. excluded borderline tests in their analyses:

> "The 1902 BeLPT results that were borderline-abnormal, unsatisfactory, or uninterpretable were excluded from the analyses." (6)

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[1]. The Plan cites only a single reference in support of that criterion (7), itself a methodologically problematic study. That study did not compare outcomes according to its two criteria of "confirmed abnormal BeLPT", so it is not possible to evaluate the novel vs. traditional criteria. Moreover, the authors essentially ignored their criteria: "Table IV show the distribution of single abnormal tests by trade; the number of confirmed abnormals is too small to present this way". Five workers were identified as CBD, but the specific basis for that diagnosis was described for only four, of whom one more likely suffered from hard metal disease ("giant cells on lung biopsy and a lymphocytosis on BAL"). On the basis of respiratory evaluations, "no statistically significant differences were detected comparing workers with and without an abnormal BeLPT". In other words, the study provides no information about the novel criterion or its usefulness in the evaluation of beryllium exposed individuals.

Accordingly, it is difficult to understand the conclusions of the Middleton et al. report and their relevance to the Plan is not apparent. I presume that the Plan is not intended to validate the Middleton algorithms, which otherwise have not been validated and therefore should not be used in a screening program.

In summary, I find the criteria proposed for defining beryllium sensitization are mischaracterized and have not been validated. I also note that none of those at this week's Expert Panel agreed with the Plan's definition of beryllium sensitization and none have used such a definition in their published reports.

Accordingly, I urge ATSDR to revise the plan to use only the standard criteria for defining beryllium sensitization (i.e., two abnormal tests).

3. Because the accumulated BeLPT database does not address its use in the asymptomatic general population and because the Plan proposes the use of novel criteria for defining BeS, I am concerned that those who undergo testing and their physicians will be unable to usefully interpret test results. For example, it will not be possible to inform them of their risks of future disease. By contrast, the corresponding database for sarcoidosis cases, machining workers and household contacts is at least more robust.

Uncertainty about the meaningfulness of results will especially impact those who are in the "Nearby Adult Residents" category. I strongly encourage ATSDR to prepare informational materials for those individuals and their physicians that clearly indicate that the meaningfulness of their test is unclear and that the risks of disease seen in beryllium-exposed workers with positive BeLPTs probably overstates the corresponding risks in community-exposed individuals. It would be a disservice to cause them to feel unnecessary and unjustified anxiety about their future well being.

I raise this particular concern because the Plan, to the extent that it discusses the predictive value of BeLPT and the prognosis of BeS and/or CBD, relies solely on the experience of exposed workers. But such workplace studies indicate that test performance and individual prognosis is seemingly linked to the level and nature of exposure; the performance of BeLPT and its predictive value for CBD in highly exposed beryllium workers differs meaningfully from its performance and value in those with minimal workplace exposures.

To support my statement, I present below several observations by Welch et al. (7), which I cite because it was relied upon by the Plan; other studies provide similar support:

> "We would expect that the predictive ability of the BeLPT will decline as it is used in populations with less intense exposure to beryllium."

> "Results presented here from screening construction workers also suggest that the dose of beryllium may affect development of CBD more than sensitization. Biologically, the dose to the lung must be an important determinant of the risk of CBD..."

That study found a low prevalence of CBD and documented that BeLPT had a low PPV for CBD. Reasonably, they proposed that the low prevalence and the low PPV reflected relatively low levels of exposures (notwithstanding that their subjects worked at beryllium facilities), and they raised concerns that the PPV of the test declines as exposure levels decline.

This has profound implications for the residents of Ottawa County who might be tested solely for reason of the proximity of their residences to the BW facility and in whom exposure levels would reasonably be assumed to be substantially lower than those of the workers in Welch et al. The implication of Welch et al. is that the PPV of BeLPT will likely be significantly smaller in ambient exposed individuals than in exposed workers. Accordingly, the workplace BeLPT database does not serve as an appropriate basis for informing individuals from the general population.

I strongly urge ATSDR to revise its Plan to indicate that statements regarding the performance of BeLPT testing and statements regarding the prognosis of BeS and/or CBD derive solely from studies of occupationally exposed beryllium workers and that such data are unlikely to apply to asymptomatic members of the general population (without a history of sarcoidosis, employment in beryllium facilities, or household contacts of such workers).

4. Section 2.6 of the Plan states that as one Purpose of the activity, "It may also provide useful information to the community." It is interesting to consider the meaning of that statement.

That might mean that it would be "useful ... to the community" to know of previously unrecognized cases of BeS among Machine shop employees and in the household contacts. I agree that such information might be interesting and useful, but its value "to the community" would be relatively limited. Likewise, a finding of CBD cases previously misdiagnosed as sarcoidosis would be interesting, but not of particular usefulness "to the community".

Rather, it seems likely that ATSDR means that it would be "useful information to the community" if testing finds a greater than expected prevalence of BeS in 'Nearby Adult Residents'. Such information can only be obtained by aggregating the testing data. Such

aggregation raises a number of methodological issues that are not adequately addressed in the Plan.

First, testing results from 'Nearby Adult Residents' should be clearly distinguished from the results of those in recognized higher-risk categories (e.g., machine shop workers and household contacts). Grouping them together would exemplify selection bias that would make the data invalid for inferences concerning community ambient risks.

Second, accurate exposure histories must be obtained from 'Nearby Adult Residents' in order to ensure that none should be included in a higher-risk group. However, that may prove difficult because many individuals have little or no specific or general knowledge of beryllium and their historical exposures. For example, Welch et al. observed such difficulties even at DOE worksites (7):

> "In our population, the minority of workers had any knowledge of beryllium, let alone potential work tasks or building in which exposure to beryllium could have taken place. Consequently, we concluded that we could not use worker recollection of beryllium exposure as a tool to triage workers into exposed and unexposed groups."

Accordingly, ATSDR should either aggressively investigate historical exposure backgrounds of individuals with positive or borderline BeLPT, or statements should be made in any report indicating the uncertainty of individual exposure histories.

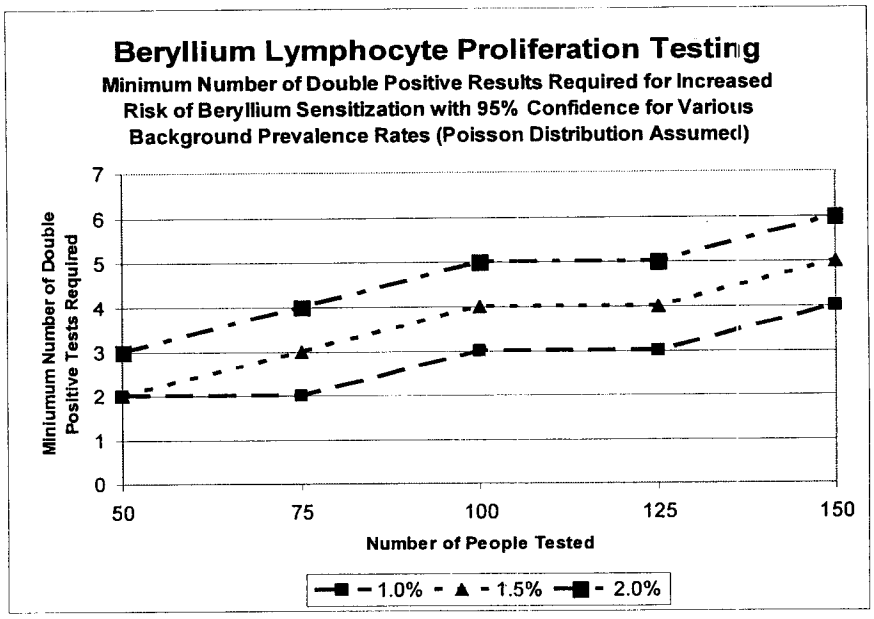
Third, accurate determination of individual residencies will be critical because the plan specifically focuses on only a small number of 'Nearby Adult Residents' who live within 1.25 miles of the plant. Inclusion of others, regardless of their BeLPT status, would make the results uninterpretable.

Fourth, even if the first two points above are adequately addressed, it may be impossible to interpret aggregated data because there is insufficient information regarding the expected background rate of BeS in the general population.

As discussed at the Expert Panel meeting, some studies (e.g., Stange et al. (6)) found no confirmed positive BeLPT in new hires, while others (e.g., Yoshida et al. (8); Deubner presentation of BW data) report rates of 1-2% among new hires. It is unreasonable to suggest that there is no background rate although the cause (e.g., ambient exposure vs. unrecognized high-level exposure) may be knowable. Thus, the critical issue is not whether there are any confirmed positive BeLPTs among 'Nearby Adult Residents", but whether there are too many.

Without knowledge of expected background rates, it will not be possible to determine whether a small number of positive tests among 'Nearby Adult Residents' is "too many". As we have previously discussed, I would have preferred that ATSDR properly undertake efforts to establish or control for such a background rate, either by direct determination or by means of an appropriate control group in some other community.

Lacking such data that would have provided a biological basis for interpreting test results, I suggest that test data from 'Nearby Adult Residents' be interpreted in terms of statistical significance. I have provided below a series of power plots, indicating in light of the number of 'Nearby Adult Residents' tested, the numbers of positive tests that would be required to achieve statistical significance assuming that there is a background rate and that the occurrence is best described by a Poisson distribution. In the figure below, I have calculated for tested populations of 50, 75, 100, 125 or 150 individuals and for background rates of 1%, 1.5% and 2%.



Fifth, notwithstanding the above four points, it is imperative to note that if only a small number of 'Nearby Adult Residents' are tested, the significance of a small number of positives would still be uninterpretable. For example, if there were a single confirmed positive BeLPT from among, say, 25 volunteer Residents, the meaning of that finding would remain ambiguous even if it were statistically significant.

In summary, I urge ATSDR to revise the Plan to explicitly outline its intentions to deal with these methodological issues before, rather than after testing has been performed. I

also urge ATSDR to include appropriate statements in the Plan indicating the limitations of these data interpretations.

I hope that you find the above comments to be useful. I continue to be concerned that the Plan proposes a study that is likely to provide uninterpretable data that will cause unnecessary concerns among the residents of Ottawa County and that will offer little if any benefit to tested individuals.

Yours truly,

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2. Guide to Clinical Preventive Services: Report of the US Preventive Services Task Force. Baltimore: Williams & Wilkins, 1996.

3. Harris RP, Helfand M, Woolf SH, et al: Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 20 (suppl 3):21-35, 2001.

4. Gray JAM: Evidence-based Healthcare. How to make health policy and management decisions. Edinburgh: Churchhill Livingston, 2001.

5. Middleton DC, Lewin MD, Kowalski PJ, et al: The BeLPT: algorithms and implications. Am J Ind Med 49:36-44, 2006.

6. Stange AW, Furman FJ, Hilmas DE: The beryllium lymphocyte proliferation test: Relevant issues in beryllium health surveillance. Am J Ind Med 46:453-462, 2004.

7. Welch L, Ringen K, Bingham E, et al: Screening for beryllium disease among construction trade workers at Department of Energy nuclear sites. Am J Ind Med 46:207-218, 2004.

8. Yoshida T, Shima S, Nagaoka K, et al: A study on the beryllium lymphocyte transformation test and the beryllium levels in working environment. Ind Health 35:374-379, 1997.