From: David_Deubner@brushwellman.com
Sent: Thursday, April 06, 2006 4:50 PM
To: Middleton, Dan
Cc: Kowalski, Peter J.; Daniel_Skoch@beminc.com;
Marc_Kolanz@brushwellman.com; Michael_Kent@brushwellman.com
Subject: Re: FW: ATSDR Testing for Beryllium Sensitization Plan

Attachments: testingplan.pdf

Dear Dan,

I apologize for not responding immediately to your e-mails but have been
traveling and want to give a considered response. I am looking forward to
meeting with you the morning of April 25 in the Elmore area.

You have asked me about two issues, the Brush Wellman Inc (BWI) protocols for
use of the BeBLPT and the interpretation of the BeBLPT.

Protocols:

Brush Wellman uses the BeBLPT in two modes, "medical diagnostic" and "medical
surveillance". It does not use the BeBLPT for "medical screening".
Brush Wellman uses classic preventive medicine definitions of the above terms.
Brush Wellman does not use the term "monitoring", as this is used casually,
often to cover a combination of goals better classified as surveillance,
screening, or a combination.

As far as the test itself, Brush Wellman via the Beryllium Industries Scientific
Advisory Committee, supported Dr. Fred Miller's work in convening the 5 US
laboratories (Oak Ridge and developing a consensus standard for performance of
the BeBLPT. We continue to use this standard, and have concerns that subsequent
modifications by the DOE and individual laboratories have been made without
demonstration of improved performance relative to the standard.

Medical Diagnosis:

The BeBLPT is used in medical diagnosis when there is clinical suspicion that a
person may have or be developing clinical chronic beryllium disease (cCBD), due
to development in a person with potential beryllium exposure, relevant symptoms,
diagnosis of adult onset asthma or other respiratory disease possibly confused
with chronic beryllium disease (CBD), significant PFT decrease in FEV1 and or
FVC, or relevant chest x-ray changes, specifically ground glass change,
enlargement of lymph nodes, prominent peripheral nodules, or fine scattered
nodularity. The major clinical benefit of diagnosis of cCBD is avoidance of or
correction misdiagnosis of some other disease, and avoidance of treatment for
that disease that would be inappropriate for cCBD. There is no proven long term
medical benefit of treatment of cCBD, so making the diagnosis itself is of
doubtful medical benefit per se. It is not at all clear, given the devastating
side effects of long term treatment with prednisone or other "prednisone
sparing" drugs such as methotrexate, that the net effect of long term treatment
of cCBD is not harmful.

Because of the known inter-laboratory and intra-laboratory (test to test in the
same person at different times) variability in the BeBLPT, we test at two
laboratories with a split sample. It is not infrequent to observe that some
persons test consistently positive at one lab and negative at another.

Testing at two laboratories increases the rate of a positive test by 25-33%. When clinical suspicion is high, we do repeat testing at at least two laboratories, and may do it a third time, possibly varying the lab choices from the original two. Although it is stated in the literature that CBD is relatively frequently BeBLPT negative, this perception is based on practice with one test at one lab. In our experience, persons who have had six tests, two labs x 3, without a positive test, rarely have CBD, and we no longer send people in this situation to bronchoscopy, but elect to wait and watch and possibly retest with the BeBLPT in 6 months or a year.

Sub-protocols include repeating uninterpretable or borderline tests at the same lab. Positive tests lead to repeat up to two times at two labs.
Persons with a single positive test are labeled "unconfirmed positive".
Persons with two positive tests, irrespective of time or lab, are labeled "confirmed positive" and are considered "beryllium sensitized" (BeS).
However, both categories (unconfirmed and confirmed positives) with beryllium exposure are referred for further evaluation, including bronchoscopy with lavage (cell differential count and BeBALLPT) and biopsy (granuloma). Persons with positive BeBALLPT but not granulomas are labeled "beryllium lung sensitized", a category containing relatively few people.

Persons with either [two positive BeBLPTs or a positive BeBALLPT] and granulomas seen on biopsy are considered to be diagnosed with CBD. We do not diagnose CBD in the absence of granulomas. We characterize persons diagnosed with CBD using the AMA Classes of Respiratory Impairment guide.

We have similar benefits for persons with lung sensitization and CBD under the BWI CBD benefits policy and may combine the categories for the purposes of analysis. The terms clinical and sub-clinical are used a) as concepts and b) to differentiate on the basis of status at onset of the clinical investigation, i.e. clinical suspicion of CBD vs. follow-up of a positive surveillance BeBLPT in a worker considered otherwise well.

One of the additional problems with testing at only one lab is that we have observed, at periods of time, systematic variation in a laboratory's performance such that sensitivity for CBD declines. The laboratory experiencing a decline in sensitivity for CBD may be producing a higher rate of positive tests (our most frequent experience) or a lower rate.

Medical surveillance:

BWI conducts medical surveillance with the BeBLPT according to the classic model, with a specific purpose and a commitment to analysis and application of the information for a public health benefit. In doing so BWI does not assume medical benefit will accrue to the individual being tested. In fact, it is lack of evidence that BeBLPT testing has medical benefit for the otherwise well worker or ex-worker that we do not conduct medical screening with the BeBLPT.

BWI has performed two types of medical surveillance using the BeBLPT, facility cross sectional prevalence survey surveillance and serial incidence surveillance. The purpose of the surveys, conducted in the years 1992 to 2001, was to develop information that was relevant to the development of an enhanced preventive model. The purpose of the serial testing, conducted 1999 to the present, was to develop information of the impact of an enhanced preventive model on reducing the rate of new positive tests in newly hired workers as well as to better understand the pattern of test results over time in previously hired workers.

In the surveys in general we have used an initial test protocol of a split sample analyzed at two labs. Split sampling was originated by Dr. Tom Markham for the purpose of developing information on laboratory variation, but when the increased yield (see above) became apparent, it was continued as the surveys incorporated the value of finding the most positives in a short time, even though there was a diminished positive/cost ratio.

Sub-protocols include repeating uninterpretable or borderline tests at the same lab. Positive tests lead to repeat up to two times at two labs.
Persons with a single positive test are labeled "unconfirmed positive".
Persons with two positive tests, irrespective of time or lab, are labeled "confirmed positive" and are considered "beryllium sensitized" (BeS).
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We have similar benefits for persons with lung sensitization and CBD under the BWI CBD benefits policy and may combine the categories for the purposes of analysis. The terms clinical and sub-clinical are used a) as concepts and b) to differentiate on the basis of status at onset of the clinical investigation, i.e. clinical suspicion of CBD vs. follow-up of a positive surveillance BeBLPT in a worker considered otherwise well. As an example, in our 1999 Elmore plant survey, of 30 persons diagnosed as CBD in the survey, 3 individuals were considered clinically suspicious at the time of the survey (two with recent sub-acute onset of symptoms and PFT changes were by coincidence being evaluated at the time of the survey initiation, and so were included, and one had been previously offered but had declined evaluation including bronchoscopy because of progressive decline in lung function). These three were considered clinical and the other 27 sub-clinical.

In the serial testing our purpose was to compare incidence of positive BeBLPTs with previously observed prevalence, so the design was to use single tests at the laboratory which had the best stability of performance over time, which was the only laboratory used by BWI (the 4 excluding Oak Ridge) not observed to have a clinically observable period of decreased sensitivity for CBD. We consider the results of this testing as an "Index" of BeS, not a determination of BeS, a theme which will be picked up below under "interpretation".

Interpretation:

The interpretation of BeBLPT results in individuals and populations depends on four factors

1)   Views on the natural history of sensitization to beryllium (BeS)
2)   Views on laboratory performance of the BeBLPT
3)   Views on the relationship between the BeBLPT and BeS.
4)   Views on the relationship between the BeBLPT and CBD

My views on the natural history of sensitization to beryllium (BeS)

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 BeBLPT (Yoshida, BWI unpublished data). 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 BeBLPT results were used to identify beryllium exposure (Stange 2001, Welch 2004) so any population with positive BeBLPTs was by definition exposed, and any unexposed population by definition did not have positive BeBLPTs. The reason for beryllium immunologic responsiveness in the general population is unknown, and it may either be an immunologic cross reaction, a response to environmental beryllium (nearly ubiquitous in soil and bio-concentrated in plants, including foodstuffs), or an artifact of HLA receptor-beryllium-normal protein interaction. What ever the reason, the patch test and the BeBLPT responses, when positive in the general population, are indistinguishable from the response in a beryllium exposed worker.

When a worker enters for the first time a workplace where exposure may induce sensitization, sensitization becomes manifest in the first weeks to months of work (Shima, Henneberger, Schuller, Cummings). Sensitization is never lost, but may be variably detectable. Sensitization occurs as a result of both skin (proven) and lung (assumed) exposure to beryllium, and possibly as a result of gastro-intestinal tract exposure as well.

Note: The relationship between BeS and subclinical CBD (sCBD) and clinical CBD (cCBD) is distinct and conditional on exposure. In persons without either direct or indirect over exposure to an industrial beryllium source, CBD would be diagnosed only when there is chance co-existence of a positive BeBLPT (1-2% in the general population) and an otherwise not classifiable granulomatous lung disease (e.g. sarcoidosis). In populations with significant beryllium work exposure, rates of granulomas in lungs of persons with positive BeBLPTs are 10-15% (BWI data) in the first two years of employment and rise to the 60 – 100% range by 5 years of employment (BWI data and literature). However, this is a reflection of surveys dealing primarily, by definition, with sCBD, the prevalence of which is independent of time worked from 5 to 35 years of employment, but with a rapidly increasing cumulative incidence with repeat surveillance. In contrast, cCBD incidence accumulates steadily with time worked from initial employment through 40 years, with no characteristic latency.

My views on laboratory performance of the BeBLPT

In spite of assertions that laboratory performance has improved (Stange), no evidence was been advanced to support this and my ongoing experience contradicts this notion, as we continue to observe frequent discrepancies between lab results on split samples as well as on retests at the same labs. No lab has demonstrated recently improved sensitivity and specificity and most labs have demonstrated importantly variable performance at periods of time. This latter observation creates the requirement for detailed and continuous monitoring of laboratory performance, and a high level of concern that unusual patterns may reflect deviant performance.

The best way to monitor laboratory performance is via continuous use of split samples to 2 labs with comparison of the rates of positivity, the degree of correlation, and the relation to subsequent demonstration of granulomas. Deviant performance can be confidently diagnosed with the combination of a) differential

rate of positivity, b) lowered correlation between labs, and c) lower rates of sensitivity for granulomas in one lab compared to the other.

There are probably three reasons for variability in laboratory performance, these being modulation of the number of Be-sensitive lymphocytes in the blood at any point in time, different serum sources, and other variations in laboratory procedure or materials (e.g. bacterially contaminated serums).

The problem with inter-laboratory variability, and the variability of laboratory performance over time, it that it makes it very problematic to compare groups tested by different laboratories or the same laboratory at different points in time. For testing of important hypotheses, groups should be tested simultaneously at the same la or labs.

My views on the relationship between the BeBLPT and BeS

Compared to the beryllium patch test, the BeBLPT is an insensitive test for BeS. The sensitivity is most certainly less than 50% (Bobka) and probably in the 20-30% range, based on 1) comparison rates of positivity from the patch test and the BeBLPT in populations with relatively high exposures, and the observation that prevalence of BeBLPT positivity is flat with time worked after employment year 1 to year 35 at a rate 1/3 that observed in workers at 4-8 months employment (6% compared to 18%) and 1/3 the 10 year cumulative incidence (6% compared to 20%).

The BeBLPT should be viewed as a measure of beryllium sensitivity "strength" or "up-regulation" which waxes and wanes daily and over longer periods. On average in the sensitized person the BeBLPT will be positive not more that 1/3 of the time with a range from 0% to 100%. This waxing and waning of "up-regulation" explains both the observation of the occasional person going from double positives to double negatives on split samples separated by weeks, and from negative to positive and positive to negative over longer periods of time. The prevalence-cumulative incidence relationship described above is consistent both with temporary disease model and with a temporary positive manifestation model. I think it biologically unlikely that BeS appears and disappears in beryllium workers, and more plausible that the BeBLPT is measuring temporary shifts in the regulation of BeS, just as a Hi-Lo blood pressure cuff might measure temporary shifts in blood pressure regulation.

It appears that at the time of the primary immune response (initial sensitization) in the first few months of work the beryllium immune response is relatively up-regulated, which accounts for the consistently higher high prevalence of BeBLPT in months 4-8 of employment. Thereafter the BeS is relatively down regulated and variable such that at a point in time few sensitized people have positive BeBLPTs and prevalence is flat with time worked. Continued testing over time reveals the same prevalence, and lack of relationship to time worked, but catches different people in the up-regulation phase so cumulative incidence rises rapidly despite constant lower prevalence.

This means that for individuals tested at a point of time the BeBLPT is a poor indication of BeS, and certainly a negative test cannot be interpreted as indicating a persons is not sensitized (unless the prevalence of BeS is low, in which case no test and a negative test have similar negative predictive values).

For populations and research there are several implications for this. The BeBLPT is useful as an indicator of relative sensitization rates in worker groups if the sensitivity of the test for BeS is relatively constant. In fact the major result of BeBLPT research is the demonstration that groups distinguished by work history have different rates of BeBLPT positivity.

However, the high rate of misclassification of BeS persons as BeBLPT negative severely limits the efficacy of analytic epidemiology in which BeBLPT positive individuals are compared to BeBLPT negative individuals for some specific exposure variable. In fact, all the survey epidemiology has been extremely disappointing in terms of its ability to demonstrate statistically significant relationships between BeBLPT positivity and specific factors or exposure variables. This is consistent with the concept that rates of BeBLPT may be proportional to the underlying rates of BeS, but there is substantial misclassification (~70-80%) of BeS individuals into the BeBLPT non-positive category and subsequent bias of statistical relationships toward the null.

My views on the relationship between the BeBLPT and CBD

Since BeS prevalence rates may be high (to 100% by the patch test) and cCBD rates are low (lifetime cumulative incidence ~ 2 %) there is a lot going on between sensitization and cCBD. 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 BeBLPT positivity, suggesting sCBD may be a waxing and waning disease as well, analogous to subclinical sarcoidosis.

The problem is that we see sCBD only through the "window' of the positive BeBLPT. However, anecdotal evidence of low rates of granulomas in persons bronchoscoped without positive BeBLPTs that perhaps granulomas do form and regress as the BeS is up and down regulated and the BeBLPT becomes positive and negative.

In definitely beryllium exposed persons the positive predictive value of the positive BeBLPT 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 BeBLPT positivity (~3%). The most likely hypothesis to explain this combination of lower PPV and low BeBLPT rates in the DOE populations is that the PPV is low in populations with low BeBLPT positive prevalence because the BeBLPT positive prevalence is a combination of a relatively few (1-2%) persons with positive BeBLPTs due to beryllium exposure at work and of the persons with the population background rate (1-2%) of BeBLPT positivity. The persons with background positive BeBLPTs dilute the PPV.

Interpretation

Taking the views expressed above into account, how are positive and negative BeBLPTs in individuals, and the positive BeBLPT rate in populations to be interpreted.

First, the problem is not qualitatively different in beryllium workers vs. persons in the community, although the data may be quantitatively different and the considerations different. They form a continuum as workplace exposures are lowered and community exposures are increased.

In the workplace, when the rates are high compared to the community background rate, say 6%, it is likely that an individual with a positive BeBLPT has that positive BeBLPT as a result of workplace exposure, but as rates decrease, it becomes a larger consideration that the individual may have a positive BeBLPT due to one or more of the following:
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
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.

 Looking at the BeBLPT results in the community, one would have the same considerations to go through to assign a source to the positivity. Key here is prospective valid determination of any of the specific exposure potentials in order to avoid recall bias once people know their BeBLPT status. Anyone using the BeBLPT in the community who wishes to interpret it should be using prospectively a tested data gathering instrument and an algorithm that distinguishes these categories.

The meaning, in terms of the relationship of the BeBLPT to BeS, would be expected to be similar, as the estimate of the sensitivity of the BeBLPT for BeS overlaps in both the community background (1-2%/4-5% = 25-40%) and workplace (20-30%).

In terms of positive predictive value for CBD, as far as we know, community granulomatous disease is not associated with BeS, beyond random coincidence so, as in the DOE example above, the PPV might be expected to be a weighted average of the % of the BeBLPT positive who were industrially induced (times 0.6) with the % who were background positives (times 0.0).

As far as rates are concerned, a major issue is alpha and beta error. With low expected rates, 1-6%, in small populations there is substantial opportunity for both sources of error, and even one random positive in a small group can produce a large, alarming percentage. With small populations, one or two positives will

not produce statistically significant results however arranged, frustrating interpretation.

Finally, interpretation depends on stable laboratory performance. All groups should be tested in the same time period and with samples split to two labs.

The meaning of negative BeBLPTs is largely a function of the BeS prevalence. If the prevalence of BeS is background, 4-5%, a negative is likely to be correct (96-97%) and very close to a non-test (95%). However, if the prevalence of BeS is high, a large fraction of the negatives will be incorrect reflections of BeS status.

One factor I have not gone into in detail is the issue of the meaning of a single positive test in someone who has been tested repeatedly, and the meaning of two positive tests. In beryllium workers, it is clear that the rate of granulomas in persons with a single positive test is not highly different from the person who has two positives. Now it is true that the rate of granulomas is a bit higher the more consistently a person tests positive and the strength of the positive test (magnitude of the highest SI). This is consistent with the regulation concept, consistent positives and large SIs being a reflection of degree of up-regulations. However, one interpretation of the PPV of single positive tests is that single positives tend to occur when a BeS person's up-regulation is waning and he/she is entering a down regulation phase, but timely bronchoscopy catches the granulomas before they regress.

The single positive BeBLPT in a truly BeS person has to be distinguished from a positive BeBLPT resulting from random variation or a misperformed or misreported test in a BeS negative person. The former is a true positive test from the BeS point of view, but the latter is a false positive.

Dismissal of all single positive tests in beryllium workers as "false" positives is clearly a mistake, which is why we use the terminology "unconfirmed positive".

In a single positive test in a member of the community, the same considerations apply, and the probabilities derive from the prevalence of BeS, the sensitivity of the test for BeS, and the rate of false positives.

However, since community members with background beryllium immunologic responsivity do not, in general, have associated granulomas, so unless the patch test is used as a more sensitive test for BeS, there is no way to distinguish a true single positive from a false single positive.

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I hope the above is helpful.

With regards,

David

David C. Deubner MD MPH
VP Occupational and Environmental Medicine Brush Wellman Inc 14710 West Portage River South Road Elmore OH 43416-9502
Phone: 419-862-4391
Cell Phone: 419-346-3357
FAX: 419-862-4591
E-mail: David_Deubner@brushwellman.com