Applied Occupational and Environmental Hygiene
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uaoh20

Ultrafine Beryllium Number Concentration as a Possible Metric for Chronic Beryllium Disease Risk

Michael A. McCawley [a] , Michael S. Kent [b] & Michael T. Berakis [a]

[a] Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, West Virginia

[b] Brush Wellman, Inc., Elmore, Ohio

Available online: 30 Nov 2010

To cite this article: Michael A. McCawley, Michael S. Kent & Michael T. Berakis (2001): Ultrafine Beryllium Number Concentration as a Possible Metric for Chronic Beryllium Disease Risk, Applied Occupational and Environmental Hygiene, 16:5, 631-638

To link to this article: http://dx.doi.org/10.1080/10473220120812

Applied Occupational and Environmental Hygiene
Volume 16(5): 631–638, 2001

1047-322X/01 $12.00 + .00

Ultrafine Beryllium Number Concentration as a Possible Metric for Chronic Beryllium Disease Risk

Michael A. McCawley,[1] Michael S. Kent,[2] and Michael T. Berakis[1]
[1]Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, West Virginia; [2]Brush Wellman, Inc., Elmore, Ohio

Beryllium is a lightweight metal which causes a chronic granulomatous lung disease among workers who become sensitized to it. Recent research has shown a persistence of the disease despite efforts at control with mean exposures below the Occupational Safety and Health Administration (OSHA) occupational exposure limit of 2 $\mu g/m^3$. Results of our current research confirm a previous finding in certain plants that particle number concentrations are higher in areas where historical estimate of risk showed a high risk of disease despite relatively lower mass concentrations. By providing side-by-side measurements of both particle number and mass, this research adds support to the proposal that particle number rather than particle mass may be more reflective of target organ dose and subsequently a more appropriate measure of exposure for chronic beryllium disease. Our evidence also shows that particle mass exposure measurements and particle number exposure measurements were not correlated.

Keywords Beryllium, Chronic Beryllium Disease, Beryllium Sensitization, Lung Deposition, Particle Size, Occupational Exposure, Ultrafine Aerosol

Beryllium is a lightweight metal which causes a chronic granulomatous lung disease among the occupationally exposed population who become sensitized to it. The disease may be fatal in severe cases. Sensitization can be detected with a beryllium-specific lymphocyte proliferation test, which is used in the industry as a screening tool.(1) Sensitized workers, identified through workplace screening programs, undergo clinical diagnostic tests including lung lavage and transbronchial lung biopsy to determine whether they have beryllium disease. The proportion of sensitized workers who have beryllium disease at initial clinical evaluation has varied from 41–100 percent in different workplaces.(2) Sensitized workers often develop beryllium disease with follow-up, but whether all sensitized workers will eventually develop beryllium disease is unknown. Additionally, there are some non-exposed (or not able to document exposure) workers who have a positive BeLPT and the test may be difficult to interpret.

The processes under investigation in this research are located in two different facilities, one in Elmore, Ohio, and the other in Reading, Pennsylvania. Processes in the Elmore facility include the magnesium reduction of beryllium hydroxide ($Be(OH)_2$), the form which the ore is in after extraction; vacuum casting which removes any remaining slag and magnesium from the reduction process; manufacturing of BeO powder for use in ceramics; and alloy production, primarily of beryllium-copper which covers the associated steps of forming the alloy into a desired shape by rolling, cutting or extrusion. The Reading plant only reprocesses materials received from the Elmore plant to more specific tolerances and sizes at customer request. Specific sites that were sampled represent steps within the above processes.

The research described in this article is part of an effort that has included confidential medical interviews, screening for beryllium sensitization with the blood lymphocyte proliferation test, clinical evaluation of abnormals with bronchoalveolar lavage and transbronchial lung biopsy, development of a job exposure matrix with historical exposure measurements, and genetic marker characterization linked to the epidemiologic data.

Prior surveillance efforts established that particular processes conferred substantial increased risk of beryllium sensitization and disease. Machinists in a ceramics plant were previously found to have a sensitization rate of 14.3 percent compared to a 1.2 percent rate among other employees,(3) as well as the highest historical exposure. In the Elmore plant, the highest risk process had modest historical indices of exposure in comparison to lower risk processes. The discrepancy at this one plant between exposure and health outcome suggested that gravimetric measurements of total beryllium were likely a poor marker of biologic risk of granulomatous disease, which might be more closely associated with some other measure of exposure that better represents alveolar deposition.

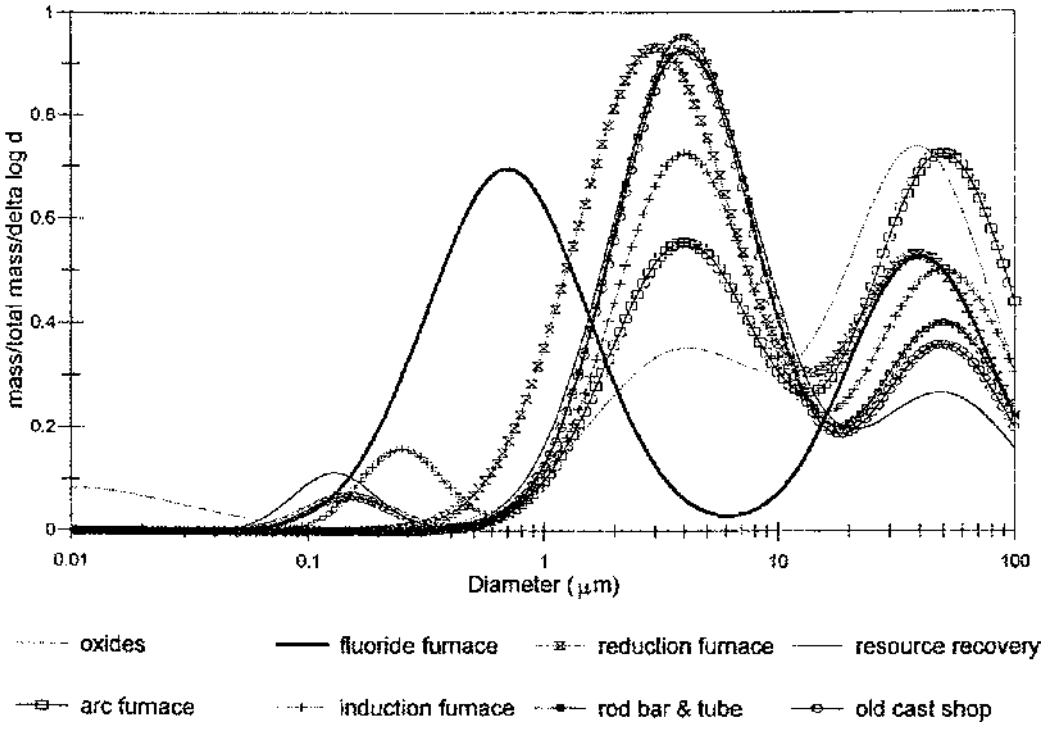

FIGURE 1

Beryllium mass distributions from the Elmore plant were fitted to a multimodal lognormal distribution function. The ordinate axis is the normalized frequency function. Size distributions graphed this way exhibit the same integrated area regardless of the actual total mass collected. The area under any mode is proportional to the fraction of mass in that mode. Five of the eight distributions have a recognizable submicrometer mode. For the fluoride furnace, the majority of the mass of the beryllium particles is contained in this submicrometer mode.

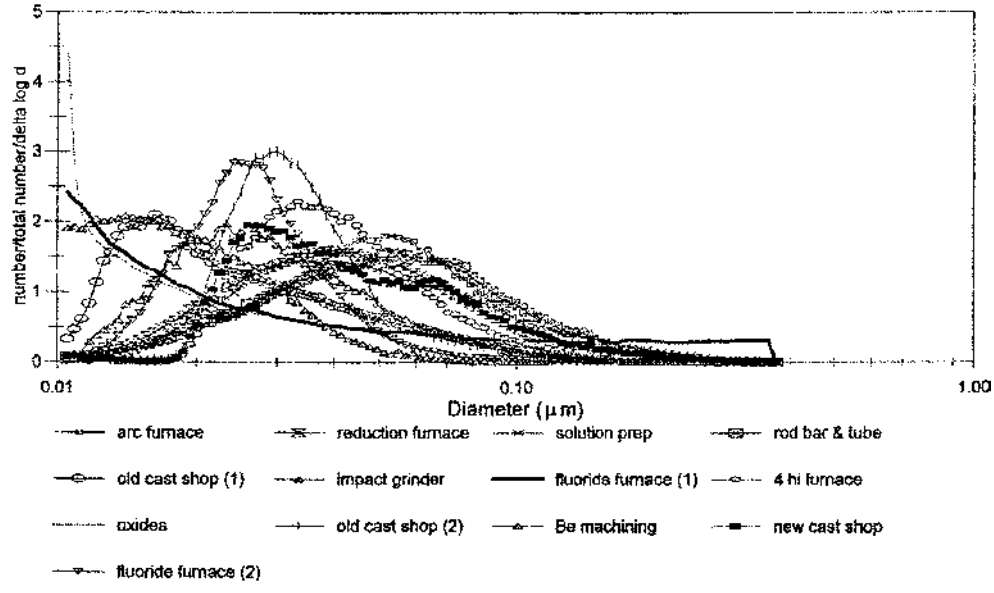

FIGURE 2

Particle number distributions from the Elmore plant were obtained from the raw data without curve fitting. As with Figure 1 the distributions were plotted as a normalized frequency function. Curve fitting, not shown here, demonstrated that the majority of these curves were a single mode lognormal distribution with geometric means ranging from 0.019 μm to 0.065 μm, with geometric standard deviation slightly less than 2.

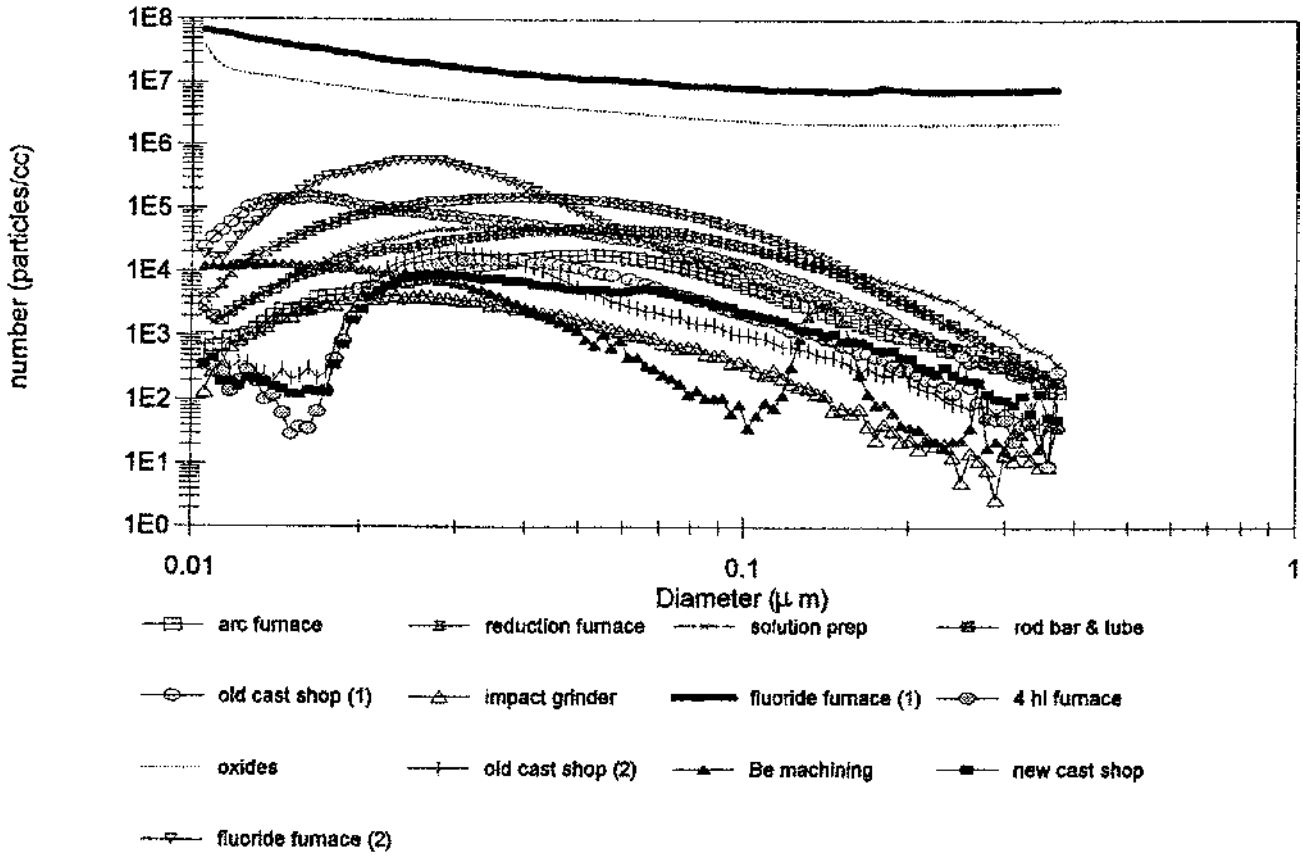

FIGURE 3

The same distributions shown in Figure 2 were graphed as a function of the actual number concentration. This shows the wide range of particle number concentrations and demonstrates the exceptionally high concentrations found when the fluoride furnace was fuming [fluoride furnace (1)] and when fuming was brought under control [fluoride furnace (2)]. The concentration is reduced three orders of magnitude when fuming is controlled but is still slightly higher than the other processes. The oxides are in the same area as the fluoride furnace and the concentration of particles seen in that area is believed to be due to generation from the fluoride furnace.

It has been proposed[4] that the number concentration of particles may be related to the risk of chronic beryllium disease. No direct measures of particle number concentration and size were previously available. The data presented here are on side by side measurements of both mass and particle number. By directly confirming the presence of high concentrations of ultrafine particles in areas where there is a known high risk of chronic beryllium disease (CBD), this research adds support to the previously stated hypothesis that the more appropriate exposure metric reflective of target organ dose is the ultrafine (<0.1 μm) component of the beryllium measured as number of particles per volume of air.

METHODS

Area size distribution measurements of mass were taken using a microorifice uniform deposit impactor (MOUDI) (MSP, Minneapolis, MN). The MOUDI uses a reduced pressure to overcome the fluid mechanic restrictions of ambient pressure impactors. By lowering the pressure within the impactor, it is possible to obtain particle sizing down to 0.05 μm (aerodynamic diameter) with conventional vacuum pumps. The MOUDI has ten stages with cut points ranging from 0.05 to 10 μm. A grease coated mixed cellulose ester (MCE) substrate was used to collect impacted particles.

Beryllium collected on MCE substrates was quantified using flame atomic absorption spectroscopy or atomic absorption spectroscopy with graphite fumace. Flame atomic absorption spectroscopy has a limit of detection of approximately 0.01 μg per sample.[5] Atomic absorption with graphite furnace is the more sensitive, though more time-consuming, method with a limit of detection of 0.005 μg per sample.[6] The graphite fumace technique was used only for those samples falling below the limit of quantification of the atomic absorption method. Gravimetric analysis of the material collected could not be determined because the MCE substrates are not weight stable.

To determine general area particle number concentration and size distribution we used a Submicrometer Particle Sizer (SMPS) (TSI, Minneapolis, MN). The instrument is a combination of

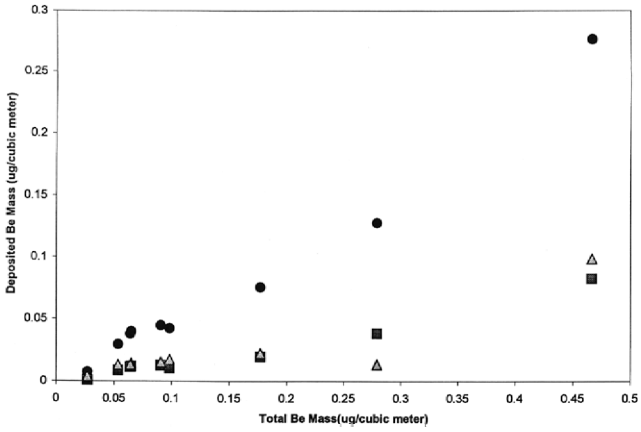

FIGURE 4

The beryllium mass distributions in Figure 1 were used to determine the fractional regional deposition amounts. The fractions plotted were total lung deposition (●), tracheobronchial deposition (■), and alveolar deposition (▲). This shows that all the fractions were in constant proportion to the total mass.

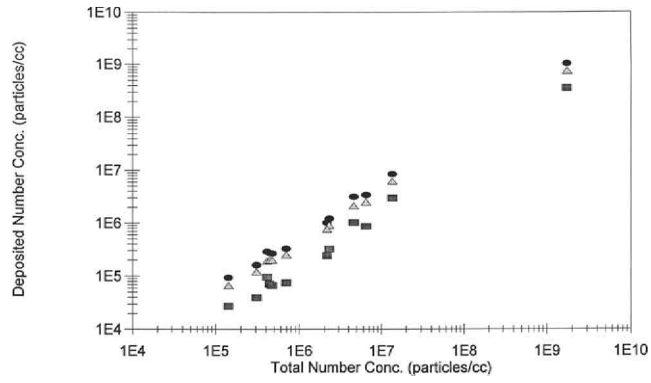

FIGURE 5

The particle number distributions in Figure 2 were used to determine the fractional regional deposition amounts. The fractions plotted were total lung deposition (●), tracheobronchial deposition (■), and alveolar deposition (▲). This shows that all the fractions were in constant proportion to the total number.

electrical mobility analyzer and condensation particle counter. Particles are sized by their mobility in an electrical field. Their mobility is also related to their diffusional ability. Particles sized this way can be considered classified by their thermodynamic diameter. Two particles have the same thermodynamic diameter if they have the same diffusion coefficient. This differs from aerodynamic diameter in that thermodynamic diameter and, for that matter, diffusion are independent of particle density. Particles were sized into 100 size categories between 0.4 and 0.01 μm. Although the instrument is capable of scanning the entire size range in a few minutes, data were averaged over 60 minute periods.

Lognormal distribution functions were fitted to the particle size distribution histograms to determine the geometric mean and geometric standard deviation.[7] These functions were then integrated with respect to the lung deposition functions[8] to obtain estimates of the deposited dose. To simulate work conditions, a value of 1.45 liters for a tidal volume with a breathing rate of 15 per minute and a functional residual capacity of 3.3 liters for mouth breathing were chosen.[9]

RESULTS

Figures 1 and 2 show the size distributions from the metal and alloys manufacturing operations at the Elmore plant. These size distributions were normalized for easier comparison by dividing frequency by the total mass and total number of particles, respectively, Both MOUDI and SMPS collected size distributions were available from the metals/alloys operation showing a wide variety of size distributions. Although ultrafine aerosols should and do dominate the particle number size distributions, even the mass distributions from the MOUDI were weighted heavily with ultrafines for several processes (Figure 1). SMPS measurements emphasized the smaller particles in the number distribution (Figure 2). Also revealed were particle number concentrations in excess of 1 billion/cm^3 in oxides and fluoride furnace areas.

Though not as apparent in the total count normalized graph, the nonnormalized distributions (Figure 3) in those areas show particle concentrations exceeding all others by at least two orders of magnitude. This caused an overload in the SMPS resulting in the unusually exponential looking distributions. Total beryllium and deposited beryllium mass were correlated (Figure 4) as were total and deposited particle number (Figure 5). Particle number size distributions for a beryllium alloy operation in Reading, PA (Figure 6) show a similarity to Figure 2. Though number concentrations for the Reading plant were orders of magnitude lower, it is important to note that the Elmore plant is not alone in having ultrafine particle size distributions.

Results shown here are similar to a previous study done in the Elmore plant's metal/alloys operation.[4] A comparison of the beryllium mass size distribution histograms between the two studies in Figures 7a–d show only minor differences in the distributions taken a number of months apart.

DISCUSSION

It has been proposed by Kent et al.,[4] who used estimates of the particle size distribution calculated from the mass size distribution, that it may be the particle number rather than the mass of beryllium that is in some part responsible for the health effect, chronic beryllium disease. This is a credible hypothesis to explore since decreasing particle size result in increased surface area per unit mass which may enhance toxicity and decrease clearance in the lung.[10] Particles of this size would, therefore, be retained for longer periods and also be capable of penetrating the pulmonary epithelium, thus making them

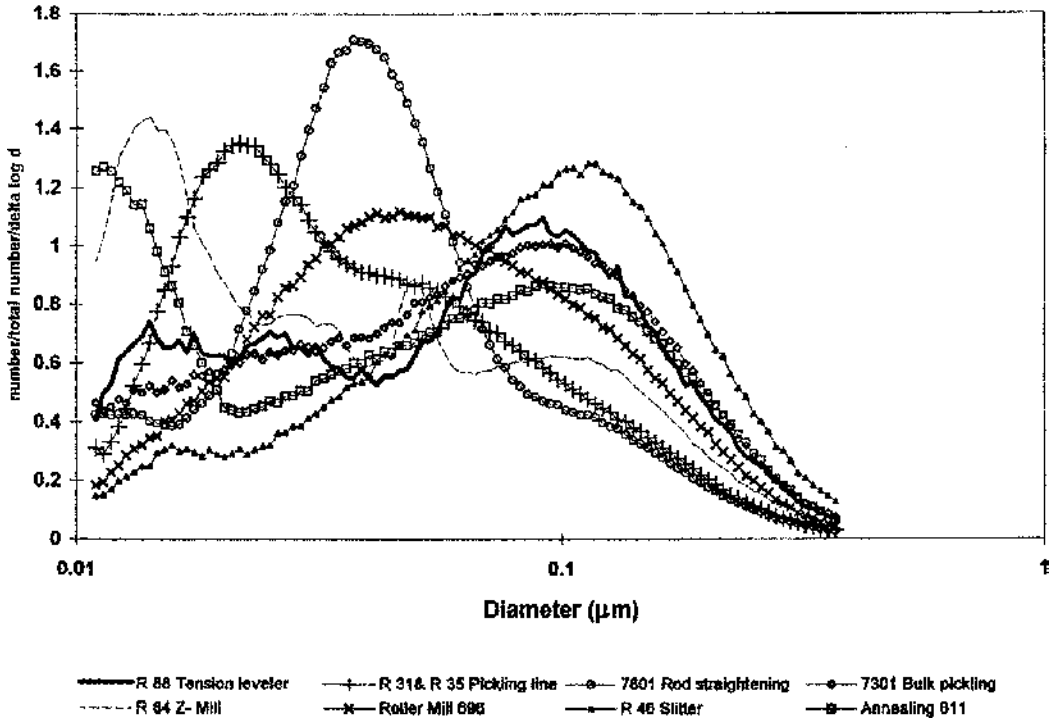

FIGURE 6

Particle number size distributions for the Reading plant show a similarity to the first plant studied, shown in Figure 2. The frequency function is the same as that described in Figure 2. Copper beryllium was being processed during the sampling period. Each of the distributions represents a different kind of equipment used to process sheets, rods, or bars of the copper beryllium alloy to attain their final customer specification.

available for retention in the interstitium. Ambient air studies have also indicated that particle number concentrations of ultrafine aerosols may be responsible for increased mortality in the general population.[11,12] Direct confirmation of the particle number concentrations found by Kent would support the dose metric side of the argument. During the investigation simultaneous measurements of both mass and number size distributions were made and confirmed the finding that certain areas of the metal/alloys operation had particle number concentrations that were disproportionately higher than other areas.

In support of the other part of the dose-response relationship, we found higher particle number concentrations in the area of the plant where the oxide and fluoride furnaces are located (Table I). This area is currently under restrictions to nonessential personnel because of a higher potential health hazard. The area was documented in a previous epidemiology study[2] as the greatest health hazard area in the plant because of the determined higher risk of sensitization and disease for workers who had been in this area. Total beryllium measurements, taken at least quarterly, agreed with the measurements in Table I and did not show this area to have the highest mass concentration of beryllium. Why, then, is there a higher risk in this area?

Part of the answer could be that particle number concentrations around the fluoride furnace area exceeded by at least two orders of magnitude the number concentrations in other areas. We found that there was no correlation between any measure of particle mass dose and particle number dose (Figure 8), so particle mass did not predict the increased particle number exposures.

Past studies[13] have also paid little attention to the role of lung deposition and the weighting given to various particle sizes. Even a study considering particle size[14] has looked only at the effect of respirable penetration efficiency, which is not necessarily the same as deposited dose. Below 0.5 μm, deposition in the lung rises rapidly due to increased diffusion (Figure 9).[8] As

TABLE I

Point estimates of total beryllium mass concentration and particle number concentration in Elmore beryllium metal and alloys plant

Area	Beryllium mass concentration ($\mu g/m^3$)	Number concentration (10^6 particles/cc)
Fluoride furnace	0.027	1,739
Reduction furnace	0.054	6.5
Arc furnace	0.177	0.7
Rod, Bar & Tube Shop	0.064	2.2
Old cast shop (during pour)	0.466	4.6
Old cast shop (between pours)	0.098	0.4

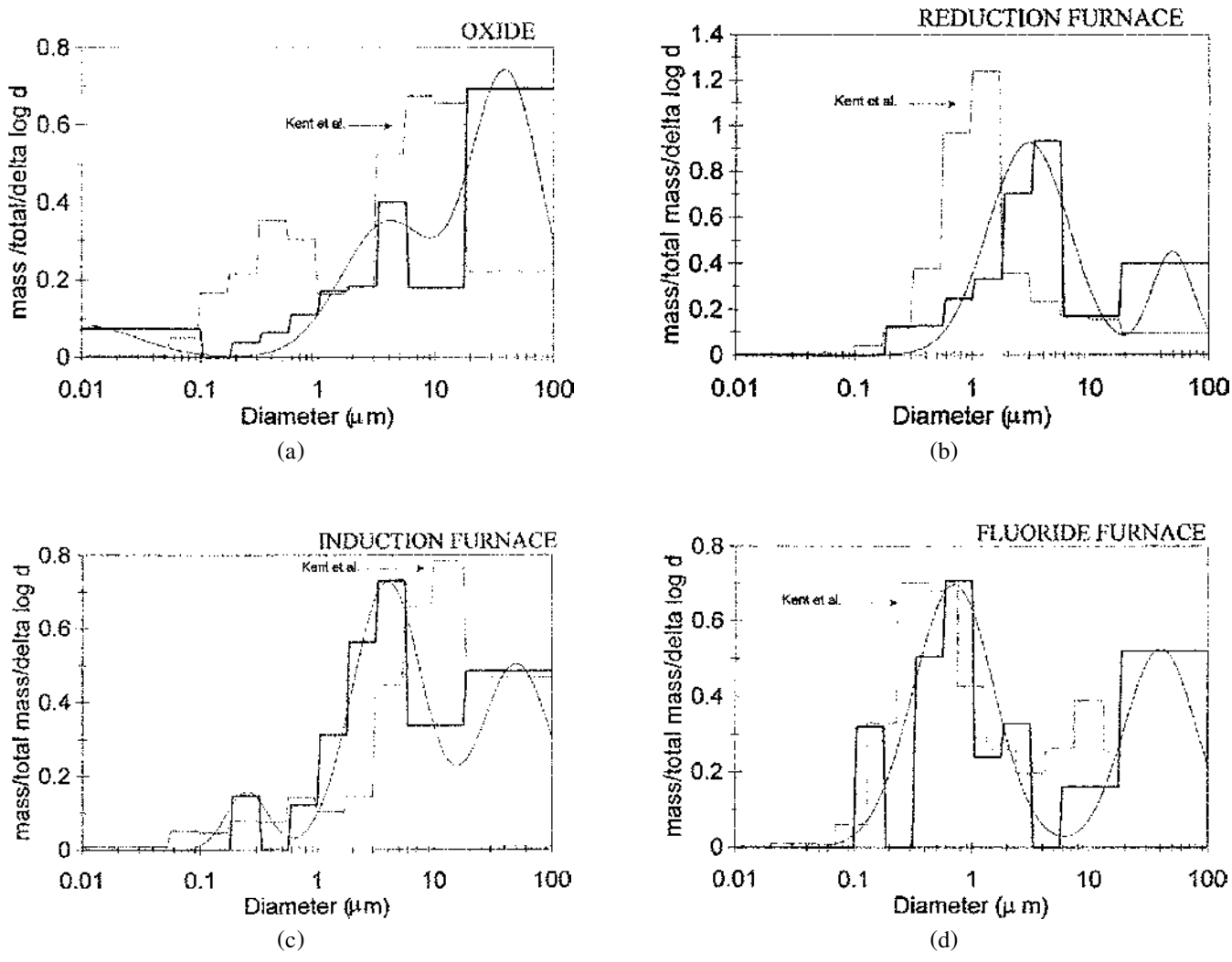

FIGURE 7

The Elmore data from the current study described in this article can be compared to a previous study at Elmore by Kent et al.[4] Figure 7a is the oxide area with the dark line histogram data from the current study, the dotted line histogram from Kent et al. And the lighter curve the lognomal distribution that was fitted to the histogram for this study. Figure 7b is the same arrangement of data for the reduction furnace area. Figure 7c is for the induction furnace area, and Figure 7d for the fluoride furnace, again with the same arrangement of data. The lognormal distribution curves are the same as those in Figure 1.

particle size changes, so too does the difference between a measures of exposure (whether total or respirable) and deposition (Figure 10).

Below 1 μm there is no difference, in fact, between respirable and total dust measurements since both weight the probability of exposure to those particle sizes at 100 percent and thereby equally conceal the actual dose.[15] If the particle size distributions were constant across operations, these total dust measurements might be as good a measure as any other. Variability in the size distribution can, thereby, change the dose without the exposure measured by a respirable sampler changing. That is, the total submicrometer dust concentration can remain constant even though the actual dose changes when the size distribution is changed.

As an example, note the two points on the graph in Figure 10 representing two different hypothetical size distributions. Note that for the upper point on the graph, representing a particle size distribution with a geometric mean of 0.4 ϒm and a geometric standard deviation of 2, the difference between respirable or total dust exposure measurements and the actual dose is almost fivefold. For the second point, with the geometric mean decreasing to 0.1 ϒm (and the geometric standard deviation remaining the same) the difference changes to less than three-and-a-half-fold, which actually reflects an increased deposition and increased dose. The differential in the two doses is 150 percent in this example even if the total concentration remains steady. That differential in dose is due entirely to the change in median particle size.

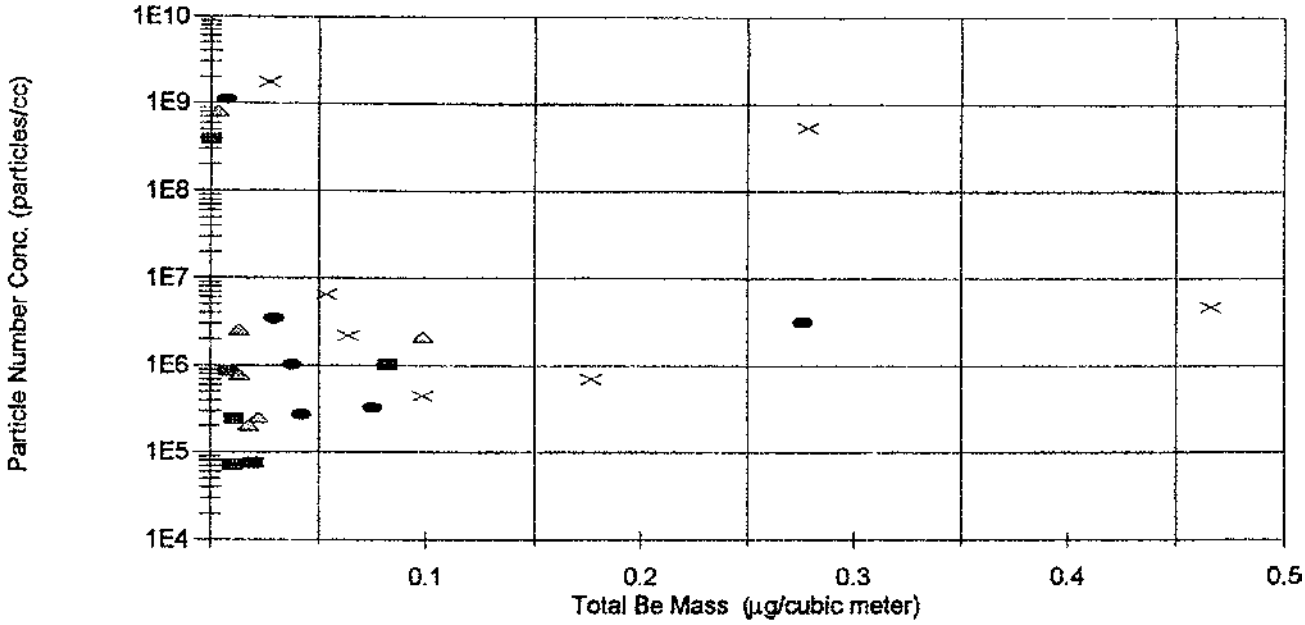

FIGURE 8

A comparison of the calculated fraction for the beryllium mass and particle number concentration data in Table I shows no discernible relation between the two by any fractional metric of deposition or of total number to total mass. As in Figures 4 and 5 the fractions plotted were total lung deposition (●), tracheobronchial deposition (■), alveolar deposition (▲), and trial mass (×).

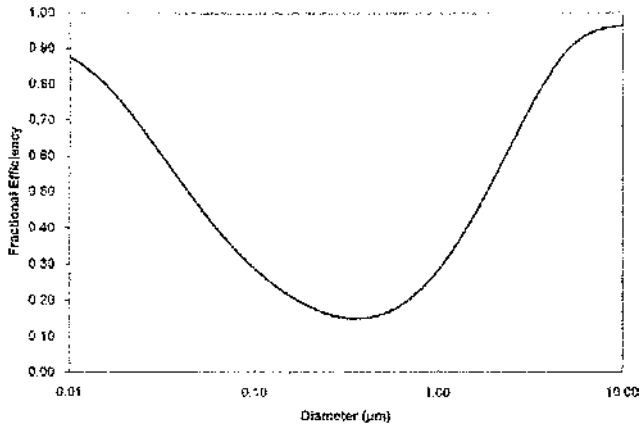

FIGURE 9

The fractional deposition of particles in the lung is mostly a function of three mechanisms—impaction, sedimentation, and diffusion. For particles sizes less than 0.5 μm the mechanism is predominantly diffusion, resulting in increased deposition with decreasing particle size. Though the curve varies slightly with changes in tidal volume and breathing frequency, the shape of the curve, shown here for a tidal volume of 1.45 liters and a frequency of 15 breaths per minute,[8] remains similar.

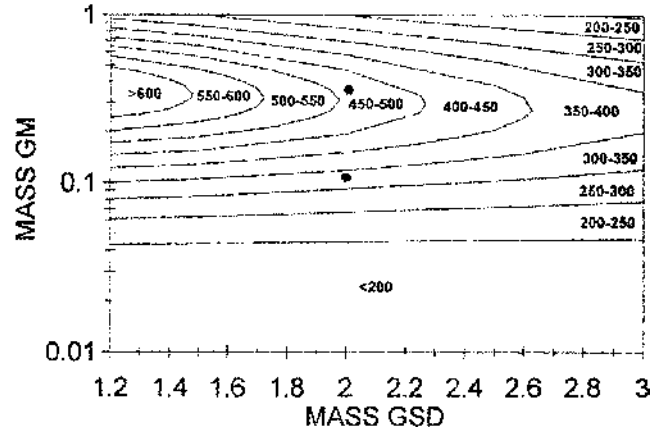

FIGURE 10

The result of not accounting for deposition when sampling either total or respirable beryllium as a function of geometric mean (GM) and geometric standard deviation (GSD) can be estimated from this figure. The two points on the graph are examples explained in the text showing the effect of a change in particle size. The numbers within the isopleths are the percent difference between the total or respirable fraction and the total lung deposition fraction.

CONCLUSIONS

Since there have been recent recommendations to reduce the beryllium standard[16] it is important to note that any steps taken to reduce exposure may need to take particle size into account. If controls reduce total mass but increase the fraction and number of particles less than 0.5 μm, the actual effect on dose may be the opposite of what is expected. As particle size decreases below 0.5 μm, deposition, which is directly related to dose, increases rapidly. This could offset gains in reduction of total mass. If particle number proves to be the metric of interest, this scenario is even more extreme. Reduction of mass resulting in a shift in particle size may also result in an increase of particle number along with an increase in deposition. Therefore, any effort at control of beryllium should also include measurements of the particle size distribution both before and after controls are used as well as some estimation of the deposition fraction.

REFERENCES

1. Rossman, M.; Jones-Williams, W.: Immunopathogenesis of Chronic Beryllium Disease. In: Beryllium: Biomedical and Environmental Aspects, M.D. Rossman; O.P. Preuss; M.B. Powers, Eds., pp. 167–176. Williams & Wilkins, Baltimore (1991).
2. Kreiss, K.; Mroz, M.M.; Zhen, B.; et al.: Risks of Beryllium Disease Related to Work Processes at a Metal, Alloy, and Oxide Production Plant. Occup Environ Med 54:605–612 (1997).
3. Kreiss, K.; Mroz, M.M.; Newman, L.S.; et al.: Machining Risk of Beryllium Disease and Sensitization with Median Exposures below 2 μg/m^3. Am J Indust Med 30:16–25 (1996).
4. Kent, M.S.; Robins, T.G.; Madl, A.K.: Is Total Mass or Mass of Alveolar-Deposited Airborne Particles of Beryllium a Better Predictor of the Prevalence of Disease? A Preliminary Study of a Beryllium Processing Facility. Appl Occup Environ Hyg, this issue (2001).
5. National Institute for Occupational Safety and Health (NIOSH): Method 7300—Elements by ICP, DHHS(NIOSH) Pub. No. 94–113. NIOSH, Cincinnati, OH (1994).
6. National Institute for Occupational Safety and Health (NIOSH): Method 7102—Beryllium, DHHS(NIOSH) Pub. No. 94–113. NIOSH, Cincinnati, OH (1994).
7. Hewett, P.; McCawley, M.: A Microcomputer Spreadsheet Technique for Analyzing Multimodal SizeDistributions. Appl Occup Environ Hyg 6:865–871 (1991).
8. Stahlhofen, W.; Rudolf, G.; James, A.C.: Intercomparison of Experimental Regional Aerosol Deposition Data. J Aerosol Med 2(3):285–308 (1989).
9. Jones, C.O.; Gauld, S.; Burley, J.F.; Rickmann, A.M.: Personal Differences in the Breathing Patterns and Volumes and Dust Intakes of Working Miners. Final Report on CEC Contract 7246-12/8/002, Edinburgh, Scotland. Report No. TM/81/11 (1981). Institute of Occupational Medicine.
10. Ferin, J.; Oberdorster, G.; Penney, D.P.; Soderholm, S.C.; Gelein, R.; Piper, H.C.: Increased Pulmonary Toxicity of Ultrafine Particles? 1. Particle Clearance, Translocation, Morphology. J Aerosol Sci 21:381–384 (1990).
11. Oberdorster, G.; Gelein, R.M.; Ferin, J.; Weiss, B.: Association of Particulate Air Pollution and Acute Mortality: Involvement of Ultrafine Particles? Inhal Toxicol 7:111–124 (1995).
12. Peters, A.; Wichmann, E.; Tuch, T.; Heinrich, J.; Heyder, J.: Respiratory Effects Are Associated with the Number of Ultrafine Particles. Am J Respir Care Med 155:1376–1383 (1997).
13. Eisenbud, M.: The Standard for Control of Chronic Beryllium Disease. Appl Occup Environ Hyg 13(1):25–31 (1998).
14. Martyny, J.W.; Hoover, M.D.; Mroz, M.; et al.: Aerosol Generated During Beryllium Machining. J Occup Environ Med 42(1):8–18 (2000).
15. Hewett, P.: Limitations in the Use of Particle Size-Selective Sampling Criteria in Occupational Epidemiology. Appl Occup Environ Hyg 6(4):290–300 (1991).
16. Wambach, P.F.; Tuggle, R.M.: Development of an Eight-Hour Occupational Exposure Limit for Beryllium. Appl Occup Environ Hyg 15(7):581–587 (2000).