Associations of metrics of peak inhalation exposure and skin exposure indices with beryllium sensitization at a beryllium manufacturing facility

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Supplemental Information

Metrics of Peak and Skin Exposure

Data Sources

Quantitative exposure data used to create the peak inhalation and skin metrics came from three sources: 1) a targeted comprehensive (baseline) air sampling campaign conducted in 1999 by the company, 2) ongoing task and process surveillance (historical) air monitoring conducted by the company throughout the study period (1994-1999), and 3) a sampling campaign of air, gloves and surface wipe measurements of representative jobs conducted jointly by NIOSH and the company in 2007. The baseline sampling was conducted over three months in 1999 and collected 4,022 full-shift personal samples from 269 production and non-production jobs that represented most jobs at the facility. On average, 15 air samples were collected from each job for durations ranging from 140-877 minutes (median=421, with 99% <508 minutes); details of the sampling and analysis methods have been described previously (Virji et al., 2011). The company conducted task and process surveillance monitoring by collecting task samples (sample type=BZ) from tasks known to have high beryllium exposure, and general area process samples (sample type=GA) from all process locations (Kolanz et al., 2001). All samples were identified by a location code, followed by specific task or process codes. The BZ samples were short-duration samples typically taken by holding the sampler near the source or in the breathing zone of the worker for durations <15 minutes (samples ranged from 1-480 minutes, with >99% under 60 minutes). The GA samples were taken at fixed locations, often but not always within several feet of the worker, for durations of up to 24 hours (samples limited to 1 minute to 5.5 days – for

administrative locations, with >95% under 24 hrs.). Details of the GA and BZ sample collection and analyses and their historical use are provided elsewhere (Kolanz et al., 2001). A total of n=79,639 measurements (77,046 or 96.7% GA and 2,593 or 3.3% BZ data) were available for the years 1994-1999, and were collected from production and non-production locations. The exposure sampling campaign conducted jointly by NIOSH and the company in 2007 included cotton glove sampling as a relative index of historical skin exposure (Armstrong et al., 2014). A total of 323 cotton glove samples were taken from 138 workers from representative jobs in the production and non-production departments for multiple 2-hour periods over a work week. Cotton glove samples were worn over the skin-protective nitrile gloves, required at the time of this campaign, to simulate historical conditions when protective gloves were not used, and the sampling results were expressed as beryllium loading in µg/hour.

Inhalation peak metrics from baseline air monitoring data

The baseline data are suitable for describing the typical exposure distribution for jobs, but are less likely to capture any irregular events or upset conditions within the short sampling campaign period (Deubner, 2013). Data from the baseline sampling were summarized for each job and used to create quantitative metrics of peak inhalation exposure. The derived summary baseline metrics for each job (denoted with a subscript "b") are described in Supplementary Table S1, and included for example, the lognormal based 95th percentile point estimate ($P95_b$), percent of measurements exceeding 2 µg/m^3 ($Pcnt_b$ >2). The baseline exposure metrics were assigned to jobs held by the study participants regardless of the time period during which the job was performed because historical correction factors could not be developed for such point estimates of the upper tail of the distribution. Depending on the number of jobs held during the study period, the multiple values of each metric were summarized by selecting the highest value as the peak value. The location, year and duration of the peak job for each metric was also noted.

Inhalation peak metrics from historical air sampling data

The historical exposure data are more likely to capture exposures associated with process upset conditions or non-routine tasks as they were collected regularly over the entire study period. Historical air sampling data were available for 86 locations, in each of which there were 1-18 (median=2) BZ task codes and 1-16 (median=3) GA process codes, for a total of 484 unique location-task/process strata, for which the number of samples collected ranged from 1-6,344 per strata. Summary statistics were calculated for strata with 2 or more measurements (denoted with a subscript "h") and are described in Supplementary Table S1, e.g., the maximum measured concentration (Max_h), lognormal based 95th percentile point estimate ($P95_h$). However, data were not available for all the location-task/process strata when these were further sub-divided by year and quarter. For the strata with missing or fewer than 2 measurements, a data summarization approach was used that successively went from finer classification (location-task/process in a year-quarter) to broader classification (ever in a location). Exposure estimates were assigned to work histories in multiple steps successively until all cells were filled starting with: location-task/process in a quarter (cumulative % of cell assignment: 20%), location-task/process in a year (cumulative: 39%), location-task/process from a previous or following year (cumulative: 59%), location-sample type in a quarter (cumulative: 75%), location-sample type in a year (cumulative: 75%), location-sample type from a previous or following year (cumulative: 85%), location in a quarter (cumulative: 87%), location in a year (cumulative: 88%), location from a previous or following year (cumulative: 89%), and from anytime in a location-task/process (cumulative: 99%), location-sample type (cumulative: 100%) and location (cumulative: 100%). In addition, maintenance and decontamination workers who were present in many production areas but did not perform the specific tasks in those locations were assigned only the process (sample type=GA) codes for those locations. The multiple values of each metric arising from the different locations and time periods (year and quarter) where the work was performed were summarized for each worker by selecting the highest value as the

peak. The location, year and duration of the highest value were noted. These historical metrics are different from the baseline metric as they include short-term peaks (from BZ data), were assessed continuously over the work history and summary statistics were calculated over a short time period (quarter).

Peak metrics based on company records of upset conditions

Monthly reports and/or quarterly summaries of exposures and events were available for production locations throughout the study period from 1994 to 1999. These reports were reviewed and information was extracted for each location and quarter, on the number of occurrences of specific events such as: leaks and upset conditions described as events such as furnace fuming or leaks in hoses (Leaks); major spills described by events such as fire, blown furnaces and breakage of barrels or packages containing beryllium resulting in spills (Spills); and instances of evacuations when workers had to vacate their work area due to fire, explosions, spills, etc. (Evacuations). The number of events were assigned to the work histories based on location, year and quarter, and the highest and the sum of the events were selected for each worker as the peak (during a quarter) and total number of events in a location (Supplementary Table S1). Locations in the production areas that were not mentioned in the reports and locations in non-production areas were assigned 0 for number of events. The number of events metrics were categorized as none for 0, and low or high group based on the median of the non-zero number of events.

Peak metrics based on self-reports from questionnaire responses

As summarized in Supplementary Table S1, workers answered questions on the survey questionnaire on the number of times they participated in shutdown maintenance, experienced high exposure due to an accident, and whether they ever performed decontamination of work areas, materials and products leaving the plant, or cleanup after spills. These events were coded as 1 if they occurred or 0

if they did not occur or were not answered. The number of events were categorized as none for 0, and low or high groups based on the median of the non-zero number of events. The occurrence and number of events were assigned to each participant.

Skin Symptoms based on self-reports from questionnaire responses

The survey questionnaire also included questions on rashes related to work in a specific process (pebbles plant) where beryllium was present in a soluble salt form, rashes related to work anywhere else in the plant, skin ulcers related to work anywhere in the plant, the first and latest year of the skin problems and the number of times the problem occurred during their tenure. These events were coded as 1 if they occurred or 0 if they did not occur or were not answered. The number of events were categorized as none for 0, and low or high groups based on the median of the non-zero number of events. The occurrence and number of events were assigned to each participant. An assumption was made that the symptoms persisted from the date of first onset to the date of most recent event and all processes worked in during this period were assigned positive for skin symptoms.

Skin exposure metrics based on a recent exposure survey

Glove sampling data were summarized by selecting the mean and the maximum associated with a job as indices of skin exposure, and were assigned to jobs in workers' work histories. Historical jobs that were no longer performed during exposure monitoring (which took place in 2007) were assigned glove loading values of similar jobs by a panel of experts familiar with the jobs performed. The profile of each worker's glove loading over all jobs performed during their work tenure was summarized by selecting the highest mean or maximum glove loading values as peak metrics (Supplementary Table S1).

Additional metrics and summary measures

Additional metrics reflecting the duration of time (in years) in the highest exposure jobs were calculated to evaluate the utility of duration metrics in predicting BeS. To summarize the multiple values

for each of the metrics as a single value per metric for each worker, the highest value from each worker's work history was selected as a measure of peak exposure as described above. None of the duration metrics as a measure of time spent in jobs or locations with highest exposures were associated with BeS.

To further evaluate the influence of the timing of exposure, each worker's work history was restricted to the first year (first 4 quarters) and the values for the quantitative peak metrics, i.e., $P95_b$, $P95_h$, Avg_b, Avg_h, Max_b, and Max_h were selected from this restricted work history (hereto referred to as first-year metrics). The first-year metrics were not associated with BeS but were significantly associated with skin symptoms (data not shown).

Statistical Analysis

Hierarchical Clustering

Hierarchical clustering was done which creates a single variable of groups of participants who share similar exposure profiles across the different inhalation and skin exposure metrics (i.e., input variables). In this case, 16 exposure metrics were used as input variables. The inputs were standardized to minimize the effect of scale and outliers. Each participant began as an individual cluster. Ward's linkage method and Euclidean distance measure were used to estimate the similarity of input variables between clusters, and then to combine two most similar clusters at each step until all clusters belonged to one single cluster, forming a cluster tree (Friesen et al., 2015). A plot of the dendrogram is generated, which is a tree diagram illustrating the hierarchical clustering pattern.

Supplementary Table S1: Descriptions of the exposure metrics generated from multiple sources of data and information.

Name	Exposure metrics definition
Quantitative peak metrics derived from the 1999 baseline survey (denoted by subscript b), corresponding metrics derived from the 1994-1999 historical surveillance (denoted by subscript h), and metrics of skin exposure derived from the 2007 survey.	
$P95_b$, Avg_b, Max_b, $Pcnt_b>2$, GSD_b, $FYP95_b$, $FYAvg_b$, $FYMax_b$, $FYPcnt_b>2$, $FYGSD_b$, $LDP95_b$, $LDAvg_b$, $LDMax_b$, $LDPcnt_b>2$, $LDGSD_b$, $DurP95_b$, $DurAvg_b$, $DurMax_b$, $DurPcnt_b>2$, $ExP95_b$, $ExAvg_b$, $ExMax_b$, $ExPcnt_b>2$. $P95_h$, Avg_h, Max_h, $Pcnt_h>2$, GSD_h, $FYP95_h$, $FYAvg_h$, $FYMax_h$, $FYPcnt_h>2$, $FYGSD_h$, $LDP95_h$, $LDAvg_h$, $LDMax_h$, $LDPcnt_h>2$, $LDGSD_h$, $DurP95_h$, $DurAvg_h$, $DurMax_h$, $DurPcnt_h>2$, $ExP95_h$, $ExAvg_h$, $ExMax_h$, $ExPcnt_h>2$.	Lognormal based 95th percentile point estimate, average, and maximum (in $\mu g/m^3$), percent of measurements (%) exceeding 2 $\mu g/m^3$, and geometric standard deviation for the highest exposure job over the whole work history as well as over the first year (prefix FY), exposure associated with the longest duration (prefix LD) jobs, the duration of the highest exposure (prefix Dur), and indicator variables for intensity metrics exceeding 2 $\mu g/m^3$ or 5% (prefix Ex) from the baseline survey and the historical surveillance data.
$Glove_{Max}$, $Glove_{Avg}$	The maximum and average beryllium mass loading on glove samples (μg/hr).
Peak metrics derived from company records from 1994-1999 of upset conditions, and self-reports of high exposures or exposure events in 1999 questionnaire survey.	
Leaks, Evacuations, Spills	The number of leaks and upsets events, evacuations and major spills reported in the quarterly reports between 1994 and 1999 for locations. This was summarized as the total number of events at the location experienced by a worker, categorized into three groups, the lowest group had no recorded events while the intermediate and high groups were separated based on the median of the non-zero number of events.
Exposure score, $Accidental_{Exp}$, $Decontaminate_{Ar}$, $Decontaminate_{Pd}$, $Shutdown_{Maint}$.	Self-reported exposure score, ranging from 1 (none), 2 (minimal), 3 (moderate) to 4 (heavy); number of times a worker reported accidental high level of exposure to beryllium; ever performed decontamination of an area or cleanup of beryllium spills coded at 0 (no) and 1 (yes) or materials leaving the company coded at 0 (no) and 1 (yes); number of times a worker reported participating in shutdown maintenance.

Supplementary Table S2: Selected questions for the questionnaire used for assessing skin symptoms and to create surrogates of peak exposure intensity.

5	Skin Reactions	
5A	Have you ever had a rash or skin problem related to the fluoride or pebble area(s)? If yes	Yes_____ No_____ Don't know_____
5A1	In what year did this first occur?	19__
5A2	In what year did this most recently happen?	19__
5A3	How many times in this interval did you have a rash or skin problem related to the fluoride or pebble area?	____ times
5B	Have you ever had a rash or skin problem related to other work at Brush Wellman? If yes	Yes_____ No_____ Don't know_____
5B1	In what year did this first happen?	19__
5B2	In what year did this most recently happen?	19__
5B3	How many times in this interval did you have a rash or skin problem related to other work (other than the fluoride or pebbles areas) at Brush Wellman?	____ times
5C	Have you ever had ulcers or small craters in the skin while working at Brush Wellman? If yes	Yes_____ No_____ Don't know_____
5C1	In what year did this first happen?	19__
5C2	In what year did this most recently happen?	19__
5C3	How many times in this interval did you have ulcers or small craters in your skin?	____ times
10A	Have you ever done shutdown maintenance?	Yes_____ No_____
	IF YES TO 10A, ASK QUESTIONS B, C AND D. IF NO, CHECK DOES NOT APPLY IN QUESTIONS B, C AND D AND GO TO QUESTION 11.	
10B	How many times?	_____ Does not apply
10C	When did you first do shutdown maintenance?	_____ Does not apply
10D	When did you last do shutdown maintenance?	_____ Does not apply
11A	Which of the following decontamination or clean-up tasks have you done?	
11A1	Area cleaning?	Yes_____ No_____
11A2	Beryllium materials spill clean-up?	Yes_____ No_____
11A3	Decontamination of materials or equipment leaving the plant.	Yes_____ No_____
12A	Have you ever been involved in an incident that may have resulted in high beryllium exposure?	Yes_____ No_____ Don't know_____
	IF YES TO 12A, COMPLETE THE FOLLOWING: IF NO TO 12 A, GO TO QUESTION 13.	
12B	Describe the incident which you believe may have resulted in your highest beryllium exposure: type of incident, how many times it has happened, and the years this first and last occurred and whether your were wearing a respirator. (Yes = 1, No = 2, At Times but not always = 3) Times Occurred _____First year 19____Last Year 19____Respirator Worn _____	Incident description
13	How would you classify your overall exposure to beryllium at the company? None _____, Casual or Minimal _____, Moderate _____, Heavy _____	

Supplementary Table S3: Ranges of correlation (Spearman) across the different types of continuous, count and score peak metrics.

	Baseline Intensity	Historical Intensity	Baseline 1st Year	Baseline Longest Job	Baseline Duration	Historical Duration	Historical Events	Self-reports	Gloves
	0.73-0.96	0.62-0.94	0.70-0.97	0.65-0.99	0.82-0.95	0.18-0.67	0.87-0.94	0.18-0.42	0.96
Historical Intensity	0.47, 0.72								
Baseline 1st Year	0.65, 0.94	0.39, 0.68							
Baseline Longest Job	0.48, 0.76	0.22, 0.64	0.50, 0.77						
Baseline Duration	-0.36, -0.24	-0.10, -0.02	-0.36, -0.23	-0.09, 0.003					
Historical Duration	-0.57, 0.07	-0.68, -0.08	-0.54, 0.05	-0.48, 0.05	0.05, 0.35				
Historical Events	0.38, 0.64	0.52, 0.76	0.29, 0.59	0.20, 0.57	0.05, 0.10	-0.49, -0.01			
Self-reports	0.20, 0.53	0.17, 0.48	0.17, 0.53	0.20, 0.53	-0.16, 0.12	-0.36, 0.06	0.22, 0.42		
Gloves	0.52, 0.76	0.32, 0.50	0.54, 0.76	0.41, 0.65	-0.15, -0.23	-0.40, 0.002	0.38, 0.48	0.27, 0.47	

Spearman correlation presented below the diagonal across the different types of continuous, count and score peak metrics, and within a class of metrics in the first row.

Supplementary Table S4: Simplified summary of the clusters by input and other variables not used in clustering

Rank	Cluster	Salt	Glove	Baseline Air	Historical Air	Rcorded Events	Self-Reported Events	BeS	Skin Symptoms
1	C4	H	H	M	M	M	H	H	H
2	C7	0/L	H	H	M/H	M	M/H	H	H
3	C6	L	M	M	H	H	H	M	M
4	C5	0	L	L	M	H	M/H	M	M
5	C3	0	L	M	M	M/L	M/H	M	M
6	C2	0	L	L	L	L	H	M	L
7	C1	0	L	L	L	L	L	0	L

H=high; M=medium, L=low; 0=absent

Supplementary Table S5: Prevalence ratios for BeS associated with exposure metrics reported in Figure 1.

Exposure Metric	PR	95% CI	AIC	β/SE
Baseline Metrics				
$P95_b$ (μg/m^3)	1.214	1.006-1.465	169.9	2.0
$Pcnt_b$>2μg/m^3 (%)	1.005	0.985-1.025	173.6	0.5
Avg_b (μg/m^3)	1.258	1.016-1.556	169.6	2.1
Max_b (μg/m^3)	1.258	1.022-1.547	169.2	2.2
GSD_b	1.130	0.929-1.375	172.6	1.2
Historical Metrics				
$P95_h$ (μg/m^3)	1.077	0.922-1.259	173.0	0.9
$Pcnt_h$>2μg/m^3 (%)	1.004	0.995-1.014	173.2	0.9
Avg_h (μg/m^3)	1.127	0.932-1.364	172.4	1.2
Max_h (μg/m^3)	1.268	1.044-1.540	166.7	2.4
GSD_h	1.018	0.959-1.079	173.6	0.6
Process Material				
Beryllium Salt	3.581	1.738-7.382	164.6	3.5
Historical Events				
Evacuations 2 vs. 1	1.487	0.579-3.819	172.7	0.8
3 vs. 1	2.189	0.935-5.123		1.8
Leaks 2 vs. 1	0.992	0.354-2.785	171.9	-0.01
3 vs. 1	2.151	0.962-4.807		1.9
Spills 2 vs. 1	1.436	0.548-3.760	173.9	0.7
3 vs. 1	1.811	0.790-4.150		1.4
Any Events 2 vs. 1	1.015	0.362-2.849	171.9	0.03
3 vs. 1	2.167	0.970-4.844		1.9
Skin Metrics				
$Glove_{Max}$ (μg/hr)	1.107	0.969-1.265	171.5	1.5
$Glove_{Avg}$ (μg/hr)	1.178	1.001-1.387	169.7	2.0
Self-Reports				
Accidents	0.977	0.461-2.069	173.9	-0.06
Decontaminate Products	2.044	0.991-4.217	170.3	1.9
Decontaminate Area	1.926	0.601-6.173	172.4	1.1
Shutdown Maintenance	1.963	0.885-4.355	170.9	1.7
Skin Symptoms	3.429	1.625-7.232	163.0	3.2

All the exposure intensity metrics were log-transformed.

Supplementary Table S6: Prevalence ratios for BeS associated with exposure metrics in the first-year of employment.

Exposure Metric	PR	95%CI	AIC	β/SE
Baseline Metrics				
$FYP95_b$ (μg/m^3)	1.126	0.913-1.388	172.6	1.1
$FYPcnt_b$>2μg/m^3 (%)	0.988	0.958-1.018	173.1	-0.8
$FYAvg_b$ (μg/m^3)	1.171	0.920-1.490	172.2	1.3
$FYMax_b$ (μg/m^3)	1.164	0.933-1.453	172.0	1.3
Historical Metrics				
$FYP95_h$ (μg/m^3)	1.000	0.827-1.209	173.9	0.0
$FYPcnt_h$>2μg/m^3 (%)	0.999	0.987-1.011	173.8	-0.2
$FYAvg_h$ (μg/m^3)	1.020	0.813-1.279	173.8	0.2
$FYMax_h$ (μg/m^3)	1.093	0.924-1.292	172.8	1.0
Historical Events				
Evacuations 2 vs. 1	1.099	0.453-2.664	175.8	0.2
3 vs. 1	1.167	0.482-2.822		0.3
Leaks 2 vs. 1	0.993	0.390-2.528	175.2	0.0
3 vs. 1	1.385	0.596-3.220		0.8
Spills 2 vs. 1	1.913	0.836-4.379	172.8	1.5
3 vs. 1	0.729	0.252-2.109		-0.6
Any Events 2 vs. 1	1.141	0.471-2.765	175.7	0.3
3 vs. 1	1.231	0.509-2.977		0.5
Skin Metrics				
$Glove_{Max}$	1.094	0.960-1.246	172.0	1.3
$Glove_{Avg}$	1.119	0.961-1.303	171.7	1.5

All the exposure intensity metrics were log-transformed.

Supplementary Table S7: Prevalence ratios for BeS associated with exposure metrics for the longest duration job.

Exposure Metric	PR	95% CI	AIC	β/SE
Baseline Metrics				
$LDP95_b$ (μg/m^3)	1.158	0.908-1.476	172.5	1.2
$LDPcnt_b$>2μg/m^3 (%)	0.977	0.926-1.032	173.0	-0.8
$LDAvg_b$ (μg/m^3)	1.211	0.916-1.601	172.0	1.3
$LDMax_b$ (μg/m^3)	1.180	0.923-1.508	172.1	1.3
Historical Metrics				
$LDP95_h$ (μg/m^3)	1.241	1.002-1.536	170.2	2.0
$LDPcnt_h$>2μg/m^3 (%)	1.001	0.970-1.032	173.9	0.0
$LDAvg_h$ (μg/m^3)	1.238	0.955-1.604	171.5	1.6
$LDMax_h$ (μg/m^3)	1.162	0.989-1.366	170.6	1.8
Skin Metrics				
$Glove_{Max}$	1.103	0.965-1.261	171.8	1.4
$Glove_{Avg}$	1.121	0.955-1.315	171.9	1.4

All the exposure intensity metrics were log-transformed.

Supplementary Table S8: Prevalence ratios for BeS associated with the duration of the highest exposure for each intensity metric.

Exposure Metric	PR	95%CI	AIC	β/SE
Baseline Metrics				
$DurP95_b$ (Yrs)	0.830	0.525-1.313	173.2	-0.8
$DurPcnt_b$>2μg/m^3 (Yrs)	0.945	0.619-1.442	173.8	-0.3
$DurAvg_b$ (Yrs)	0.797	0.483-1.316	173.0	-0.9
$DurMax_b$ (Yrs)	0.759	0.455-1.269	172.6	-1.1
Historical Metrics				
$DurP95_h$ (Yrs)	0.994	0.423-2.337	173.9	0.0
$DurPcnt_h$>2μg/m^3 (Yrs)	0.225	0.040-1.262	165.6	-1.7
$DurAvg_h$ (Yrs)	0.605	0.081-4.539	173.5	-0.5
$DurMax_h$ (Yrs)	0.253	0.011-6.047	172.3	-0.8

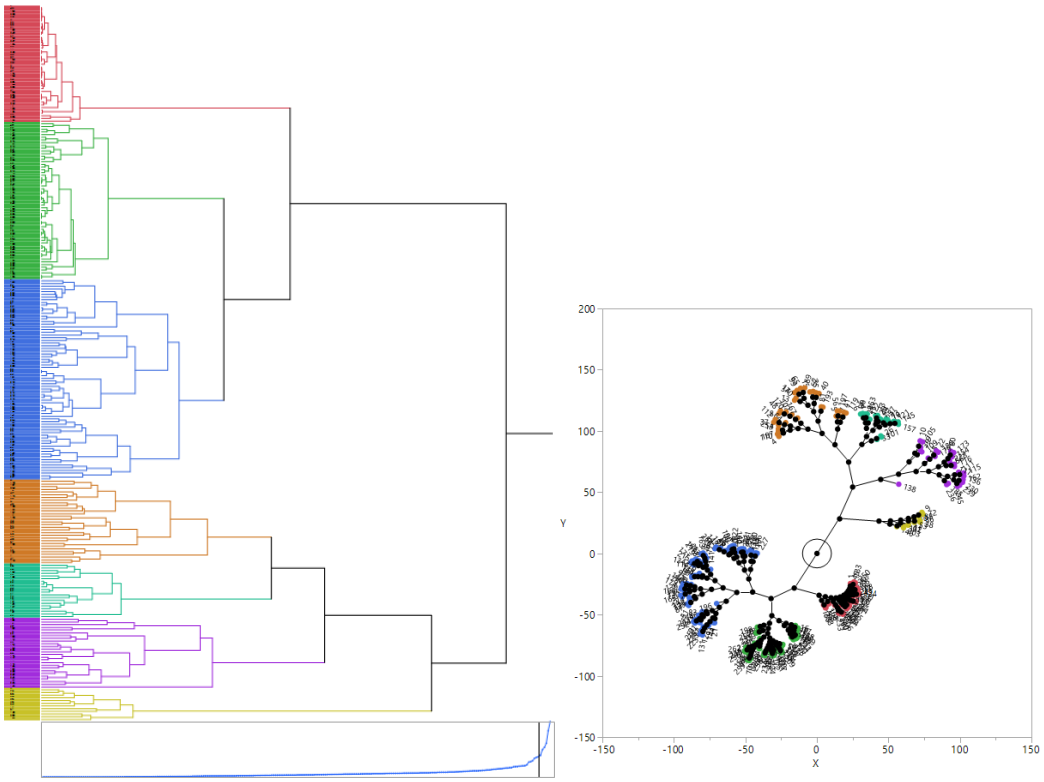
All the exposure duration metrics are in years.

Supplementary Table S9: prevalence of BeS by combination of Air, Skin and Salt variables.

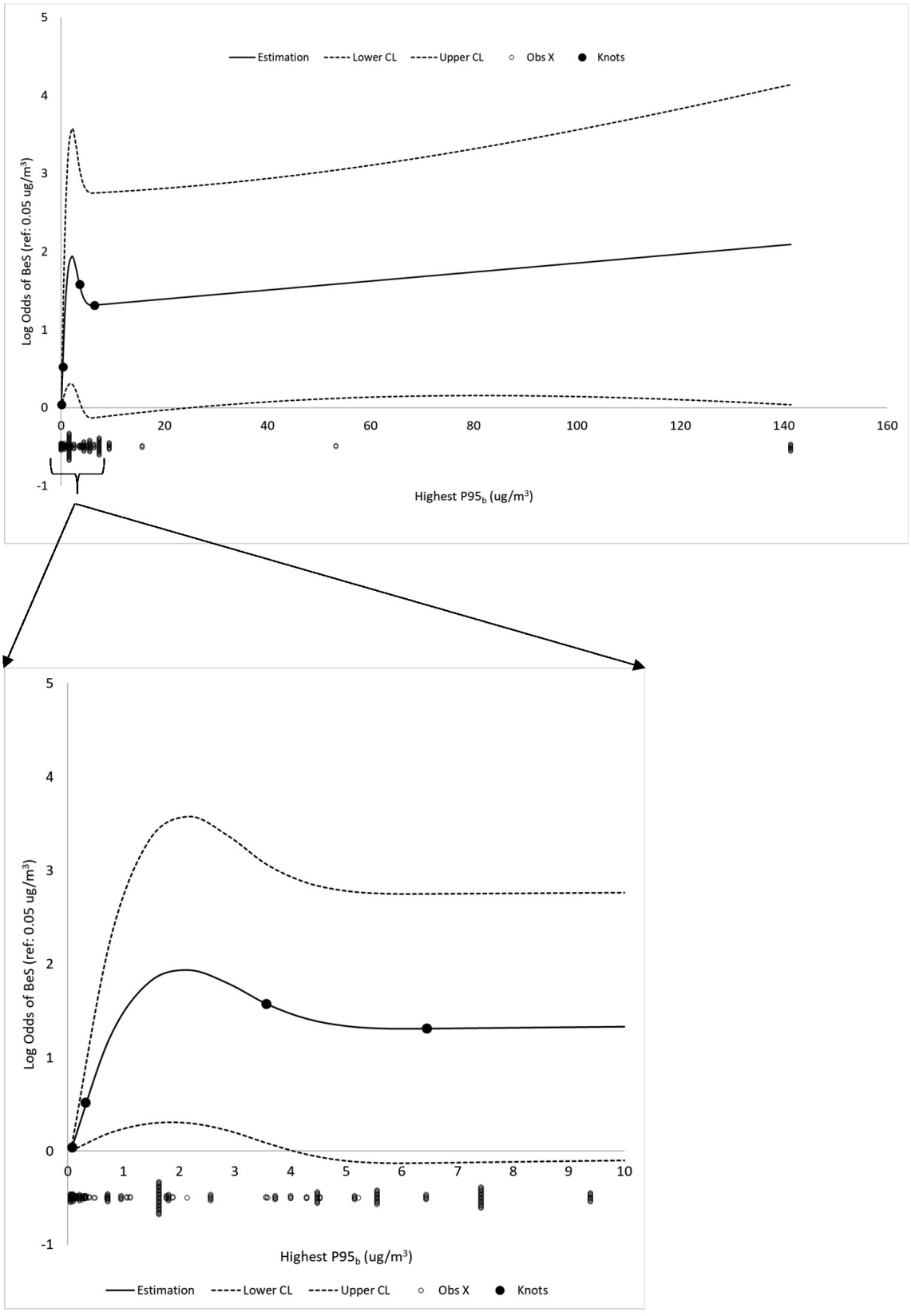
		Baseline Air		Historical Air	
#	Variable/Level	N	BeS N (%)	N	BeS N (%)
0	Air=0, Glove=0, Salt=0	98	7 (7.1)	71	4 (5.6)
1	Air=0, Glove=0, Salt=1	-	-	-	-
2	Air=0, Glove=1, Salt=0	34	3 (8.8)	30	3 (10.0)
3	Air=1, Glove=0, Salt=0	33	3 (9.1)	60	6 (10.0)
4	Air=1, Glove=0, Salt=1	-	-	-	-
5	Air=1, Glove=1, Salt=0	65	4 (6.2)	69	4 (5.8)
6	Air=0, Glove=1, Salt=1	2	1 (50.0)	3	1 (33.3)
7	Air=1, Glove=1, Salt=1	32	8 (25.0)	31	8 (25.8)
#	Variable/Level	N	BeS N (%)	N	BeS N (%)
0&2	Air=0, Salt=0/1, Glove=0/1	98	7 (7.1)	71	4 (5.6)
3&5	Air=1, Salt=0/1, Glove=0/1	132	10 (7.6)	159	13 (8.2)
6&7	Air=0/1, Salt=1, Glove=1	34	9 (26.5)	34	9 (26.5)

Air=The fraction of baseline mesurements > 2 $\mu g/m^3$ exceeding 5% ($ExPcnt_b>2$) or historical mesurements > 2 $\mu g/m^3$ exceeding 5% ($ExPcnt_h>2$); Glove= beryllium glove levels above the median ($Glove_{Avg}$); Salt=presence or absence of material containing beryllium salts.

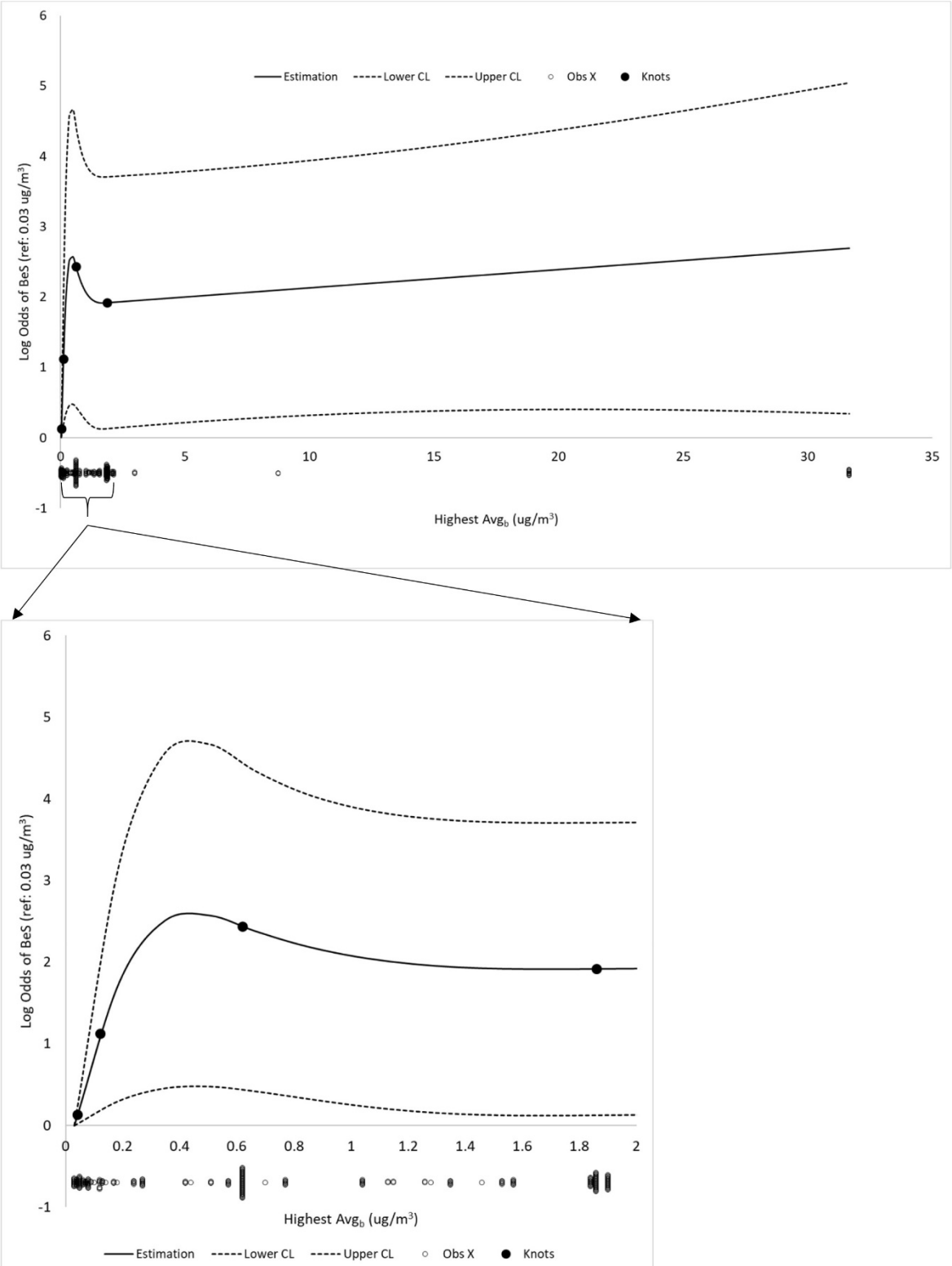
Supplementary Figure S1: Dendrogram and constellation plot showing hierarchical clustering of participants into seven cluster groups. Clusters are indicated by different colors. For example, all the participants in cluster 1 (indicated by the red band on the left most side of the plot) had the similar exposure profile across all exposure metrics.



Supplementary Figure S2: Restricted cubic splines showing the relationship between BeS and the baseline 95th percentile exposure.



Supplementary Figure S3: Restricted cubic splines showing the relationship between BeS and highest baseline average exposure.



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