Risk of chronic beryllium disease by HLA-DPB1 E69 genotype and beryllium exposure in nuclear workers

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Online Data Supplement

Exposure questionnaire development and administration

A work history/exposure questionnaire was developed using information from focus groups of RFETS workers. This questionnaire was administered by one of four trained interviewers, with industrial hygiene or exposure assessment experience, using an interview script and work history for each participant to establish start and end dates of each work assignment. Participants were asked to verify the start and end dates for each job assignment (i.e., machinist, chemical operator, electrician, etc.) along with an estimate of the average number of hours worked per week in the job. Calendar time and hours worked were used to establish an exposure time. The specific tasks (i.e., lathe, grind, plating, cleaning, etc.) performed for each job assignment were also recorded. Participants were asked to categorize each task in into one of seven exposure categories listed in order of decreasing qualitative exposure: 1) directly altering a beryllium part; 2) contact with beryllium waste materials; 3) contact with finished and cleaned beryllium parts; 4) work within 5 feet of a beryllium operation with no direct beryllium contact; 5) work in the same room as a beryllium operation with no direct beryllium contact; 6) work in the same building as a beryllium operation with no direct beryllium contact; or 7) no known beryllium exposure. For each of the tasks, the participant provided a percentage of time spent performing the task and a percentage of time spent performing the task with beryllium.

Task exposure estimates

From the exposure questionnaires, a total of 50 unique combinations of exposure category and task were identified (Table E1) consisting of 27 with direct beryllium exposure involving direct work with a beryllium part or with beryllium waste materials and 23 with indirect beryllium exposure where there was no direct work with beryllium or beryllium waste materials, but instead proximity to a beryllium operation. Based on published information(1, 2) and personal knowledge about beryllium production at RFETS, the 50 combinations were separated into one to three time periods of similar exposure based on installed controls and plant practices as shown in Table E1. For each of the unique combinations of exposure type, task, and time period that involved direct exposure to beryllium, the data sources listed below were searched for industrial hygiene data on the specific task or closely related tasks:

1. **RFETS historical data** consisted of approximately 1,800 samples compiled by researchers in the late 1990's constructing a multiple chemical job exposure matrix(3) in addition to a database of over 1,100 beryllium samples compiled from primary sources for this study. The data spans the years 1954 to 1996 and represents most of the major tasks at Rocky Flats. All of the data prior to 1984 was derived from high-volume, short-term air samples. Post-1984 data were derived from full-shift breathing zone samples of mostly machining tasks with a few shorter term samples of casting tasks.
2. **Unpublished RFETS machining operations pre- and post-control sampling report** described an analysis of 695 personal breathing zone samples collected from machinists in the primary beryllium machine shop at RFETS. The purpose of this report was to quantify average exposures for RFETS machinists before and after the installation of an upgraded low-volume, high-velocity ventilation system in 1986.
3. **Unpublished RFETS cleanup era data** consisted of beryllium sampling data from the clean-up, demolition, and decontamination of the facility's two major beryllium related buildings (444 and 865). These data consisted of over 8,000 personal samples spanning

the years 1999 to 2008 and provided unparalleled data on exposures for maintenance and cleaning tasks using modern control measures. These data were provided to study investigators after removal of all personally identifiable information by colleagues at Oak Ridge Associated Universities.

4. **Published RFETS summary data** were available from studies by Barnard et al.(1) and Viet et al.(2) including a summary analysis of a random sample of over 12,000 of the 500,000 high-volume, fixed airhead samples collected between 1960 and 1988 in the main RFETS beryllium machine shop. These data likely provide the best estimate of exposure for workers indirectly exposed to beryllium from proximity to beryllium machining tasks.
5. **Other unpublished Department of Energy site data** consisted of beryllium sampling data from the Y-12 facility in Oak Ridge, TN where similar beryllium tasks were conducted. This limited dataset contains approximately 1,800 personal breathing zone samples on a limited number of tasks and provides relevant beryllium exposure data for metallurgy, laboratory analysis, inspection, and plasma spray tasks.
6. **Published international data from another atomic weapons facility** were available for a facility in Cardiff, Wales which performed similar operations to RFETS from a study by Johnson et al.(4). These data consisted of yearly summaries of 217,000 personal beryllium samples by job task. While many of the job tasks at the Cardiff facility used different controls than similar job tasks at RFETS during the early years, the data were useful for establishing exposure estimates for specific tasks including casting after 1986, beryllium inspection, laboratory analysis, and maintenance.

7. **Beryllium precision machine shop data** consisted of beryllium a sampling dataset from a facility the Southeast U.S. spanning the years 1980 to 2008 with more than 6,340 samples of machining, inspection, deburring, administrative, and maintenance tasks that were compiled by the authors. Many of the job tasks at this facility were similar to those performed at RFETS. In fact, this facility fabricated some of the same beryllium components as were manufactured at RFETS. Analyses of portions of this dataset have been published by Kelleher et al.(5) and Madl et al.(6).
8. **Other relevant beryllium facility data** were available through unpublished literature and government documents. These data were primarily used for two infrequently performed operations, billet cutting and copper beryllium machining.

An arithmetic mean of the available exposure measurements was calculated for each combination of exposure type, task, and time period using the measurements from available data sources that were considered closest in time period and task composition based on the judgment of the authors. The source of the data used for each task is listed in Table E1. The arithmetic mean was calculated using one of three methods depending on the data available: 1) If less than six measurements were available or the data were determined to follow a normal distribution based on the D'Agostino-Pearson omnibus normality test, a simple average was calculated. 2) With six or more lognormally distributed measurements, the minimum variance unbiased estimate of the arithmetic mean was calculated using methods outlined in Gilbert (7) when no non-detectable values were present in the dataset, or using a maximum likelihood estimation method as described by Finkelstein and Verma (8) when there were non-detectable values in the dataset. 3) When only median values from summary data were available, an arithmetic mean was calculated using the relationships outlined in Strom and Stansbury (9) assuming the data followed a lognormal distribution and that the geometric standard deviation was 3 which is within the range described by Wambach (10) for frequently monitored high hazard agents. The arithmetic mean was chosen as an appropriate summary measure for each exposure type, task, and time period combination to allow the calculation of cumulative and lifetime weighted average concentrations.(11)

As very little relevant data were available for indirect beryllium exposure tasks, we used a conservative method for assigning average exposures to these tasks. Reported indirect exposures within 5 ft. of a beryllium task were assigned an average of 50% of the task, those in the same room 10% of the task, and those in the same building 1% of the task. While there are limited data to validate this method, Barnard et al.(1) identified that personal breathing zone samples were on average six to seven times greater than fixed airhead monitors from the same area and time period. This suggests that using a 50% reduction for exposures within 5 feet of direct beryllium operations is likely conservative. Approximately 12% of the indirect exposure tasks reported in the exposure questionnaires could not be linked to specific direct exposure tasks. For these situations, an average estimated from other indirect exposure tasks weighted by the amount of time the entire cohort spent in these tasks was used.

Participant exposure assessment

To summarize participants' varying beryllium exposure work histories, cumulative and lifetime weighted mean beryllium exposure were calculated in units of $\mu g/m^3$-years or $\mu g/m^3$, respectively. First, job specific exposure estimates were determined for each individual by multiplying the exposure estimate for the combination of exposure category, task, and time period in $\mu g/m^3$ by the percent of time worked with beryllium in that time period, the percent of time performing the task, the number of years spent in the job, and the average number of work hours per week divided by 40 hours. Cumulative exposure was calculated by summing all of the job specific exposures for an individual. Lifetime weighted mean exposure was calculated by dividing the cumulative exposure by the total number of years worked. For each participant, beryllium exposure and work time were included over a work history until the date of employment termination at RFETS or until the date of BeS or CBD diagnosis for the cases, whichever came first. The maximum task-based exposure in $\mu g/m^3$ for any exposure time period was used as a surrogate of short-term high exposure regardless of exposure time. Other exposure metrics used in our analyses were determined directly from the exposure questionnaires including the highest reported exposure category (e.g., directly altering beryllium part, contact with beryllium waste materials, etc.), the year of first beryllium exposure, work with beryllium oxide or as a beryllium machinist, and the percent of an individual's work time at RFETS spent directly or indirectly exposed to beryllium.

Statistical analysis

Two strategies for inclusion of genetic variables in logistic regression models were used: 1) carriage of any E69 allele, and 2) an allele specific risk model. The allele specific risk model used a set of classification variables coded as: 1) carriage of only E69 negative alleles; 2) carriage of a single copy of an *02 allele along with an E69 negative allele; 3) carriage of single E69 positive non-*02 allele along with an E69 negative allele; or 4) carriage of two E69 allele copies, one *02 allele and one E69 positive non-*02 allele. For this model, the first variable (E69-) was modeled as the reference. Also in this model, E69 homozygotes with two copies of either *02 alleles (n=10) or E69 positive non-*02 (n=3) were excluded from the analysis due to insufficient numbers to classify these genotypes in separate categories. Cumulative and lifetime weighted mean exposure variables were included in logistic regression models as continuous covariates both to reduce the occurrence of sparse classification cells and to increase power. A purposeful model building strategy(12) was used wherein all independent variables with univariate p-values less than 0.25 were evaluated in multiple logistic regression models which included one genetic variable specifying E69 status or genotype and one continuous exposure variable. A significance level of 0.05 was required for a variable to remain in the model. First-order interactions with significance levels at or below 0.1 were included in the final model. All demographic variables were tested in the final model for confounding and included in the model when their presence resulted in a at least a 10% change in any of the estimated regression coefficients. Based on significant differences in exposure between CBD and BeS cases, as well as between CBD cases and controls, CBD and BeS were modeled as separate outcomes. We included the following E69 genetic variables in our final logistic regression models: 1) carriage of only E69 negative alleles; 2) carriage of a single copy of an *02 allele along with an E69 negative allele; 3) carriage of single E69 positive non-*02 allele along with an E69 negative allele; or 4) carriage of two E69 allele copies, one *02 allele and one E69 positive non-*02 allele. E69 homozygotes with two copies of either *02 alleles or E69 positive non-*02 alleles were excluded from the analysis. Candidate exposure variables for logistic regression models included lifetime weighted average exposure, cumulative exposure, maximum task-based exposure, highest reported exposure category, year of first beryllium exposure, work with beryllium oxide or as a beryllium machinist, and the percent of work time spent directly or indirectly exposed to beryllium.

Table E1 – Task exposures by time period

Description	Time Period One*	Task Exposure Time Period One† (µg/m3)	Time Period Two*	Task Exposure Time Period Two† (µg/m3)	Time Period Three*	Task Exposure Time Period Three† (µg/m3)	Exposure Data Sources‡
Assembly/Inspection							
General assembly work with Be parts	'52-'05	0.13					7
Hand polishing or etching Be parts	'52-'85	1.0	'86-'05	0.14			7
Brazing/Welding Be parts	'52-'85	1.32	'86-'05	0.7			1
Inspection or handling of Be parts	'52-'85	0.71	'86-'05	0.15			6
Work within 5 feet of Be inspection operations§	'52-'85	0.36	'86-'05	0.075			6‖
Work in same room as Be inspection operations§	'52-'85	0.07	'86-'05	0.015			6‖
Work in same building as Be inspection operations§	'52-'85	0.007	'86-'05	0.0015			6‖
Machining							
Cutting Be with a band saw	'52-'05	1.78					8
Machining Be parts (mill, lathe, bore)	'52-'74	2.56	'75-'85	1.19	'86-'05	0.052	2
Hand grinding of Be parts	'52-'05	0.56					1
Machine grinding Be parts	'52-'74	3.16	'75-'05	0.56			7
Machining BeCu parts	'52-'05	0.09					8
Work within 5 feet of a Be machining operation§	'52-'74	1.28	'75-'85	0.6	'86-'05	0.026	2‖
Work in same room as a Be machining operation§	'52-'74	0.35	'75-'85	0.16	'86-'05	0.007	4
Work in same building as a Be machining operation§	'52-'74	0.035	'75-'85	0.016	'86-'05	0.0007	4‖
Foundry							
Be casting and mold breakout (old foundry,444)	'52-'85	73.0	'86-'05	2.0			1, 6
Be casting and mold breakout (new foundry, 865)	'52-'05	2.0					6
Work within 5 feet of Be casting (old foundry, 444)§	'52-'85	36.0	'86-'05	1.0			1‖, 6‖
Work within 5 feet of Be casting (new foundry, 865)§	'52-'05	1					6‖
Work in same room as Be casting (old foundry, 444)§	'52-'85	7.3	'86-'05	0.1			1‖, 6‖
Work in same room as Be casting (new foundry, 865)§	'52-'05	0.2					6‖

*Specifies the time period of similar exposure for the task. Tasks did not necessarily occur in every year in the time period.
†Specifies the arithmetic mean of the exposure for the task and time period combination
‡Data sources used to establish exposure estimates for each time period and task combination – see methods section for numbers.
§For these tasks, there was only indirect exposure to beryllium.
‖Specifies source of base data, actual exposure estimates were extrapolated based on the method outlined in the methods section.

Table E1 (continued)– Task exposures by time period

Description	Time Period One[*]	Task Exposure Time Period One[†] (µg/m3)	Time Period Two[*]	Task Exposure Time Period Two[†] (µg/m3)	Time Period Three[*]	Task Exposure Time Period Three[†] (µg/m3)	Exposure Data Sources[‡]
Forming							
Hot pressing of Be parts	’52-‘05	1.03					1
Rolling Be parts (sheet rolling)	’52-‘05	0.18					1
Cutting Be using a shear	’52-‘05	1.28					1
Annealing/Heat treating Be parts	’52-‘05	0.2					1, 8
Work within 5 feet of Be rolling/pressing[§]	’52-‘05	0.3					1[‖]
Work in same room as Be rolling/pressing[§]	’52-‘05	0.06					1[‖]
Work in same building as a Be rolling/pressing[§]	’52-‘05	0.006					1[‖]
Laboratory							
Metallurgical testing of Be parts	’52-‘05	0.16					5
Laboratory analysis of Be samples	’52-‘85	0.26	’86-‘05	0.13			6
Work within 5 feet of Be laboratory operation[§]	’52-‘05	0.08					5[‖]
Work in same room as a Be laboratory operation[§]	’52-‘05	0.016					5[‖]
Work in same building as Be laboratory operation[§]	’52-‘05	0.002					5[‖]
Treating/Finishing							
Plating/Chemical milling/Etching beryllium parts	’52-‘05	0.32					7
Operating metal spray/plasma machine with Be	’52-‘05	0.52					5
Grit blasting or sand blasting Be parts	’52-‘05	0.3					1
Work within 5 feet of Be plating/chem... Milling[§]	’52-‘05	0.16					7[‖]
Work in same room as a Be plating/chem... Milling[§]	’52-‘05	0.03					7[‖]
Work in same building as a Be plating/chem.. Milling[§]	’52-‘05	0.003					7[‖]

[*]Specifies the time period of similar exposure for the task. Tasks did not necessarily occur in every year in the time period.
[†]Specifies the arithmetic mean of the exposure for the task and time period combination
[‡]Data sources used to establish exposure estimates for each time period and task combination – see methods section for numbers.
[§]For these tasks, there was only indirect exposure to beryllium.
[‖]Specifies source of base data, actual exposure estimates were extrapolated based on the method outlined in the methods section.

Table E1 (continued)– Task exposures by time period

Description	Time Period One*	Task Exposure Time Period One† (μg/m3)	Time Period Two*	Task Exposure Time Period Two† (μg/m3)	Time Period Three*	Task Exposure Time Period Three† (μg/m3)	Exposure Data Sources‡
Maintenance and D&D							
Cleaning Be contaminated machines/surfaces	’52-‘85	4.5	‘86-‘94	2.25	‘95-‘05	0.05	1
Maintenance on Be contaminated machines/equipment	’52-‘85	1.0	‘86-‘94	0.18	‘95-‘05	0.04	7, 6, 3
Filter replacement/testing on Be contaminated systems	‘52-‘05	23.9					1
Work in same building as a Maint/D&D operation§	’52-‘85	0.045	‘86-‘94	0.023	‘95-‘05	0.0005	3‖
Waste							
Washing Be contaminated laundry	‘52-‘05	0.3					1
Collecting Be waste materials (chip collecting)	’52-‘85	23.9	’86-‘05	3.3			1, 8
Crushing Be parts/shapes	’52-‘85	36.4	’86-‘05	3.3			1
Be waste packaging/re-packaging	’52-‘85	0.6	’86-‘05	0.31			3
Miscellaneous							
Oversight within 5 feet of unspecified Be activities§	’52-‘74	0.93	‘75-‘85	0.42	‘86-‘05	0.06	Wt Avg**
Oversight in same room as unspecified Be activities§	’52-‘74	0.18	‘75-‘85	0.075	’86-‘05	0.015	Wt Avg**
Oversight in same bldg as unspecified Be activities§	’52-‘74	0.026	‘75-‘85	0.012	‘86-‘05	0.001	Wt Avg**

*Specifies the time period of similar exposure for the task. Tasks did not necessarily occur in every year in the time period.
†Specifies the arithmetic mean of the exposure for the task and time period combination
‡Data sources used to establish exposure estimates for each time period and task combination – see methods section for numbers.
§For these tasks, there was only indirect exposure to beryllium.
‖Specifies source of base data from numbering in methods section, actual exposure estimates were extrapolated based on the method outlined in the methods section.
**Weighted averages of other equivalent operations as outlined in the methods section

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