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Critique of Van Dyke et al (2011) study of beryllium exposed workers at Rocky Flats

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Pursuant to the request of the Beryllium Science & Technology Association, an expert analysis of the VanDyke et al. (2011) study was conducted for consideration by the German UAIII Committee in its assessment of beryllium (Be) metal. This critique focuses on issues that are specifically related to use of the Van Dyke et al. (2011) data for quantitative risk assessment.

Background

VanDyke et al. (2011) conducted a case-control study that assessed HLA-DPB1 E69 (a glutamic acid at position 69) genotype in 386 current and former workers of the Rocky Flats Environmental Technology Site (RFETS) with exposure to beryllium. Specific E69 genotypes (i.e., E69 homozygotes and non-*02 E69 carriers) were hypothesized to have increased odds of beryllium sensitization (BeS) and chronic beryllium disease (CBD). In the study, 70 individuals with BeS, 61 CBD cases, and 255 control subjects were evaluated. Of those with BeS, 17 individuals were not evaluated further for the presence of CBD. The study included a quantitative risk assessment (regression modeling) of CBD related to lifetime-weighted average exposure (LWE) for covariates such as age, race/ethnicity, gender, smoking status, year of hire, and E69 genotype.

Executive Summary

Specific comments regarding the use of Van Dyke et al. (2011) for quantitative risk assessment are summarized below.

Multiple Logistic Regression Modeling of Risk

> The authors report a significant risk of CBD with LWE and cumulative exposure. However, the findings are not statistically significant under proper statistical analysis. The authors separated the data into quartiles and

reported significance tests focused on specific quartiles. Splitting the data into quartiles multiplies the number of tests by four, and the p-values should be interpreted with a Bonferroni correction factor of four, but this was not performed. If this correction is included, CBD risk is not significantly correlated with either cumulative exposure or LWE.

A better way to conduct the analysis would be to treat exposure as the continuous variable and use the other variable as the independent variable in an analysis that treats control, BeS, or CBD status as the outcome—either a multinomial logistic regression, if the intent is to view disease status as purely categorical, or polytomous ordinal logistic regression, if the intent is to treat disease status as a rank-ordered outcome.

Because CBD requires Be exposure, the authors should also have constrained the multiple regression model to essentially zero CBD risk at zero exposure. With the unconstrained regression model that was used, the predicted risk of CBD at zero LWE exposure ranges from 1 to 8% for individuals with genotypes ranging from those with the average composite genotype (average of population studied) to those who are most sensitive (E69 homozygotes). This is not a reasonable outcome for a condition such as CBD that requires exposure, and the more appropriate approach would be to develop a custom model that constrains the lower bound of the exposure-response curve such that at zero exposure, the risk is as practically close to zero as possible. Modeling results for the dose metric of cumulative exposure were not presented, but these comments would also apply to cumulative dose as a dose metric.

The authors could not fit BeS to conventional multiple logistic regression models with any exposure metric, even controlling for genetic variables shown to be associated with a significant increased risk of BeS. Although the exposure-response for BeS has not been demonstrated in many studies, the recent study by Schuler et al. (2011) found a significant exposure-response for BeS by quartiles of exposure using two related dose metrics (highest job exposure worked and mean exposure). The advantage of the Schuler et al. (2011) study data is that exposure reconstruction relied on a very robust exposure data base, minimizing misclassification of exposures. Van Dyke et al. (2011) study's inability to identify a BeS dose-response is likely due to failure of the exposure reconstruction and limited industrial hygiene monitoring data.

Due to the fairly small number of subjects enrolled in the study and even smaller number of subjects carrying any E69 allele, 95% confidence intervals (CIs) were for odds ratios by beryllium exposure and HLA-DPB1 E69 genotype for the risk of developing CBD were wide. Wide 95% CIs indicate uncertainties about the effect measure and the need for additional data to confirm the findings. In fact, there is not statistically significant difference

(confidence intervals overlap) between risk for the least sensitive genotype ($E69^{-}$) at a LWE of 2 $\mu g/m^3$ and that for the most sensitive genotype (E69 homozygote) at a LWE of 1.0 $\mu g/m^3$ (Table 7 of Van Dyke et al. 2011). Further, when comparing confidence intervals for odds ratio with exposure ranging from 0.02 to 2 $\mu g/m^3$ for each H69 variant (with the exception of $E69^{-}$) there is no significant difference across that entire 100-fold exposure range. Thus, confidence in the exposure-response modeling, by genotypic variant is low.

Exposure Reconstruction

Accurate characterization of exposure is critical for health risk assessment. In VanDyke et al. (2011), the exposure assessment is based on a relatively limited data set that does not characterize the variability of personal exposures, and because most of the data were derived from Fixed Air Head (FAH) general area air sampling measurements, it is expected that the exposure estimates significantly underestimate personal exposures. Only FAH measurements were available for most of the exposure time period—1952 through 1984. Exposure estimates from FAH sampling were much lower than personal exposure measurements resulting in an underestimation of exposure for most of the evaluation period. Further, exposure estimates were highly generalized. For approximately one-half of the exposure category/task combinations, a single value represented exposure for a time period spanning over 50 years (e.g., exposure is assumed to be 0.13 $\mu g/m^3$ for all individuals and exposure periods with the job description of "General assembly work with Be parts" that occurred from 1952 to 2005). Exposure estimates were not specific to individuals, or even to RFETS, and relied on data from other facilities and operations. Significant refinement of the job-exposure matrix is needed, if possible given the limitations of the hygiene data, to make the exposure reconstruction more accurate and precise.

Finally with regard to the exposure reconstruction, it is important to note that LWE should not be considered an exposure measure that is representative of the individual daily exposures, e.g. an 8-hour time-weighted Occupational Exposure Limit (OEL). Thus, the risk at a LWE of 0.2 $\mu g/m^3$ is not equivalent to risk at an 8-hr OEL of 0.2 $\mu g/m^3$ for an occupational lifetime. This is because the LWE includes periods of zero exposure, and thus, risk of CBD at daily worker exposures of 0.2 $\mu g/m^3$ is significantly overestimated using the Van Dyke et al. LWE dose metric.

Conclusions

Although the VanDyke et al. (2011) study included unique and valuable data to better understand the risk of CBD and BeS and genetic risk factors, the use of these data for exposure-response (or risk) assessment suffers from severe limitations in

the exposure reconstruction and analysis errors which render the results unreliable for assessing risk of CBD (or BeS) with beryllium exposure.

The data from Schuler et al. (2011), which is a study of beryllium metal manufacturing facility, offer the best data currently available for risk assessment because the exposure assessment is far superior to that of any other published studies. Even using the relatively coarse dose groupings (quartiles) presented in the published Schuler et al. (2011) study, an exposure-response relationship is evident for both BeS and CBD. As such, a more realistic assessment of risk of BeS and CBD may be derived from the Schuler et al. (2011) study as compared to that published in Van Dyke e al. (2011).

Detailed Analysis of VanDyke et al. (2011)

Van Dyke et al. (2011) is the first study that attempts to quantify risk of BeS and CBD with beryllium (Be) exposure and control for genetic variability. However, there are several limitations in this study, contributing to the large uncertainty in the assessment of study findings. Study limitations are discussed below.

Matching Controls to Cases

Control subjects were frequency matched based on sex, race, and decade of hire at RFETS. Matching was not conducted for smoking. The authors did not provide explanations as to why the matching only included sex, race, and decade of hire. The matching procedure was not successful and resulted in groups that possessed a number of unintended yet important differences. Among individuals with BeS, there were more females (n=15, 21.4%) compared with controls (n=25, 9.8%, p=0.009) and CBD cases (n=5, 8.2%, p=0.036). Most of the participants were white (97.7%) and non-Hispanic (93.8%), but there were more African American CBD cases (n=4, 6.6%) compared to controls (n=3, 1.2%, p=0.028). Among individuals with BeS, Hispanics were overrepresented (n=8, 11.4%) compared to controls (n=11, 4.3%, p=0.039). In addition, those with BeS also worked fewer years at the facility (median, 12.6 years) compared with controls (median, 15.0 years, p=0.020). Increased rate of smoking among BeS subjects was observed: they were more likely to be current smokers (n=8, 11.4%) compared to controls (n=13, 5.1%, p=0.094) and CBD cases (n=2, 3.3%, p=0.104) although the difference was not statistically significant.

The matching process was not successful in that there were significant group differences in sex and race (two variables that may or may not be important in BeS and CBD but which were matched for anyway, albeit unsuccessfully), group differences in time at the facility (clearly an important variable to match on, and this variable was also unsuccessfully matched), and group differences in smoking status (potentially an important variable to match on given the respiratory nature of BeS/CBD, but for which no attempt to match was considered). Although not

explicitly stated, the decade of hire was likely matched for in an effort to control for time at the facility. However, a decade is an extremely crude time measure, and it is not surprising that unintended group differences in years at the facility arose as a result of the use of a decade as the time interval in the match process.

The authors noted that most of the differences in sex, race, and ethnicity were likely due to the underenrollment of control subjects or frequency matching on combined BeS/CBD group. It is unclear how underenrollment would account for the patterns of differences obtained, but the authors did not provide additional explanations. Further, matching on the combined group of BeS/CBD, when the intent of the analysis was to evaluate the two groups separately, demonstrates another limitation in design of the study. This particular matching process resulted in groups that possessed a number of unintended differences that could easily compromise the results of the study. Because the matching process yielded differences among controls, sensitized individuals and CBD cases for these matched variables and thus differential distribution of these potential risk factors between controls and the two groups (especially BeS), re-matching by matching the BeS and CBD groups separately should have been conducted. Further, the authors used the matching variables as covariates in the multiple logistic regressions. This is an unusual practice because once a matching variable has been selected, it is not possible to analyze it as a risk factor (Bland and Altman 1994; Rothman and Greenland, 1998; Wacholder et al. 1992). Hence, the use of matching variables as covariates in multiple logistic regression models indicated that the matching process did not achieve the desired result and had to be considered in the models.

Misclassification of Disease Status

Misclassification of disease status was likely introduced with the inclusion of 17 individuals who were confirmed to have BeS on the basis of two abnormal beryllium lymphocyte proliferation tests (BeLPTs) but did not undergo a medical evaluation to assess the occurrence of CBD. As the ratio of sensitized individuals to CBD cases in this population was approximately 1:1, and the ratio in earlier surveys was approximately 2:1, it is reasonable to surmise that some of these 17 individuals without a medical test for CBD, in fact had CBD. Hence, the inclusion of these individuals with those who were sensitized, but did not have CBD, is expected to bias the estimation of an association between beryllium exposure and BeS away from the null given that the authors noted a significant relationship between exposure and CBD. However, a significant association between BeS and beryllium exposure was not observed in this mixed group for any exposure metric. Further, all those who have CBD are also sensitized; therefore, any association between beryllium exposure and BeS might be more clearly established by evaluating all individuals with confirmed positive BeLPT results, i.e., those characterized by the authors as having CBD and those characterized as being sensitized without CBD.

Selection Criteria, Potential Selection Bias and Limitations in Statistical Power

Approximately 7,820 current and former workers at the plant were evaluated initially. Of these workers, at least 117 were diagnosed with CBD and 184 with BeS, but only a total of 399 individuals were considered in VanDyke et al. (2011) with 13 subjects excluded for not meeting the inclusion criteria. Five were excluded because they did not meet the study criteria for diagnosis of CBD or BeS (2 with only one abnormal BeLPT, 1 diagnosed with sarcoidosis without abnormal BeLPTs, and 2 had insufficient medical information), 4 had either diagnosis of BeS or CBD before their hire date at RFETS or long-term beryllium exposure at another facility, and 4 whose DNA was unavailable for genotyping. The final cohort consisted of 386 workers, i.e., 255 control subjects[1] with potential beryllium exposure, 61 CBD cases, 53 confirmed sensitized individuals, and 17 sensitized individuals with unknown CBD status. However, except for the 13 subjects that were excluded, no explanation was provided as to why the final cohort did not include all of the 117 CBD cases and 184 individuals with BeS that were identified, which would serve to increase the sample size to improve upon any associations between beryllium exposure and the health outcome of interest.

The authors did not address any selection bias that may have affected participation in the study and impacted the results. Further, due to the fairly small number of subjects enrolled in the study and even smaller number of subjects carrying any E69 allele, i.e., 97 control subjects, 65 sensitized individuals, and 51 CBD cases, wide 95% confidence intervals (CIs) were presented with the odds ratio estimates by beryllium exposure and HLA-DPB1 E69 genotype for risk of developing CBD. Wide 95% CIs indicate uncertainties about the effect measure and the need for additional data to confirm the findings of VanDyke et al. (2011). For example, there is not statistically significant difference (confidence intervals overlap) between risk for the least sensitive genotype ($E69^-$) at a LWE of 2 $\mu g/m^3$ and that for the most sensitive genotype (E69 homozygote) at a LWE of 0.02 $\mu g/m^3$ (Table 7 of Van Dyke et al. 2011), and the change in risk for each H69 variant (with the exception of $E69^-$) is not significant across that entire 100-fold exposure range (0.02 to 2 $\mu g/m^3$).

Exposure Assessment

The exposure assessment was based on administration of a questionnaire, which had been developed using information from focus groups of RFETS workers. Participants were asked to recall or verify a variety of information, including start and end dates of each job assignment (e.g., machinist, chemical operator, electrician), estimated number of hours worked per week, and specific tasked

[1] Control subjects who worked at RFETS and had at least 2 normal and no abnormal BELPTs with one performed in the last 5 years were matched approximately two to one to cases (combined group of BeS and CBD) based on sex, race, and decade of hire.

performed (e.g., lathe, grind, plating, cleaning). Participants were also asked to categorize each task into one of seven exposure categories of decreasing qualitative exposure (i.e., tasks involving direct beryllium contact, indirect beryllium exposure, or no known beryllium exposure). Participants also provided the percentage of time spent performing each task and performing each task with beryllium.

The authors used this information to create 50 unique combinations of exposure category and task (machining; cutting beryllium with a band saw), which were then separated into up to three time periods of similar exposure (e.g., exposures before and after some sort of control technology was implemented). The authors then estimated an average concentration (in $\mu g/m^3$) for each category/task/time period based on exposure data compiled from eight sources, some of which are specific to Rocky Flats, and others of which were from other facilities. These exposure concentrations were combined with information from the questionnaire to estimate cumulative exposure (in $\mu g/m^3$-years). The LWE (also in $\mu g/m^3$) was then estimated by dividing the cumulative exposure by the total number of years worked, including years recorded with zero exposure. In addition, the following exposure metrics were also identified: short-term high exposure (based on maximum task-based exposure), highest reported exposure category, year of first beryllium exposure, work with beryllium oxide or as a beryllium machinist, and percent time spent directly or indirectly exposed to beryllium.

Source and Limitations of Exposure Data: The exposure assessment relied on a disparate set of industrial hygiene measurements collected over differing time periods from eight sources. Four sources represented data collected at Rocky Flats; the remaining sources represented data collected at other facilities, which have variable and questionable relevance to RFETS exposures. These other sources include the Oak Ridge Y-12 plant, Cardiff, Wales—although it was noted that this facility had different exposure control technology—and data from a machining plant (Kelleher et la. 2001 and Madl et al. 2007). Exposure estimates for approximately one-half of the exposure category/task combinations were based on data from facilities other than Rocky Flats.

Exposure estimates for the vast majority of exposure category/task combinations were based on a single source of data, some of which are fairly limited. Thus, exposure estimates were highly generalized, increasing the likely impact of exposure misclassification. For approximately one-half of the exposure category/task combinations, a single value represented exposure for a time period spanning more than 50 years (e.g., exposure is assumed to be 0.13 $\mu g/m^3$ for all individuals and exposure periods with the job description of "General assembly work with Be parts" that occurred from 1952 to 2005), and this was the case for approximately one-half of the exposure category/task combinations. In fact, exposure estimates for the first time period for all job/task categories was in excess of 20 years (1952 to no earlier than 1974). In some cases, the available data were collected over only a fraction of the overall time period. In other cases, exposure

estimates for one time period were based on data collected during a completely different time period.
Significant limitations in the availability of personal, and relevant, industrial hygiene data hamper the exposure reconstruction and are likely to result in significant misclassification of exposure and inaccurate exposure estimates.

Use of Fixed Airhead (FAH) Measurements rather than Personal Breathing Zone (PBZ) Samples: Only a subset of the data included in the exposure assessment (percentage unknown from information presented) were personal breathing zone (PBZ) samples. The largest data sets represented summary data of fixed airhead (FAH) measurements (Barnard et al. 1996; Viet et al. 2000) and the authors noted these as providing the "best estimate of exposure" for direct exposures. Further, for indirect exposures, the authors assumed a percentage of the FAH measurements, e.g., indirect exposure within the same building was assumed to 1% of the exposure for the task. The study authors acknowledged, "… very little relevant data were available for indirect beryllium exposure tasks," yet nearly one-half of the 50 exposure category/task combinations were for indirect exposure.

Finally, regarding the use of FAH measures as the primary basis of the exposure assessment, the study authors note that relatively few PBZ samples were collected, and while there was no correlation between PBZ and corresponding FAH samples, PBZ samples were shown to be significantly higher (on average by a factor of 6.5) than FAH sample results. The authors used the PBZ data to assess indirect exposures and state that, based on this comparison, an underestimation of exposure likely occurred from multiplying FAH measures by a factor (e.g., 1%) to account for indirect exposures. However, the PBZ samples are also better measures of direct exposures than the FAH measures, and it is important to note that the PBZ sample data demonstrate that, not only are the indirect exposures likely to be substantially underestimated, so are the direct exposures. This is consistent with what is well known regarding FAH samples as compared to PBZ samples (Kolanz 2001).

It should be recognized that underestimating exposure results in an overestimation of the risk per unit of exposure. Thus, reliance on FAH measures for direct exposures, and FAH measures multiplied by some factor for estimating indirect exposure, results in significantly underestimated exposures, and significantly overestimated risk estimates.

Use of Lifetime-Weighted Average Exposure (LWE): The use of LWE—cumulative exposure divided by years of exposure, rather than use of 8-hour time weighted average is problematic for both BeS and CBD because sensitization typically occurs when an individual is exposed to a large dose. LWE is not equivalent to a peak dose and likely mischaracterizes the true beryllium exposure associated with BeS among workers. For example, an employee who works for one month with an average exposure of 1 $\mu g/m^3$ has exactly the same LWE measure (1 $\mu g/m^3$) as an employee who works 20 years with exposure that might vary from 0 to 10 $\mu g/m^3$, but with an average of 1 $\mu g/m^3$. Thus, LWE captures neither the upper-bound nor the potential

for cumulative burden of Be in the lung from long-term exposure as an indicator of increased disease, and this dose-metric does not seem reasonable for the assessment of risk for either CBD or BeS. Further, the LWE includes periods of zero exposure.

Use of Recall to Reconstruct Exposures: The exposure assessment relied on worker recall of often very detailed information (e.g., number of hours doing a specific task and subset of those hours working with beryllium) over potentially long periods of time (some workers hired as early as 1952, with a median of 15 to 16 years at the facility). Because exposure was self-reported, recall bias was likely present in the study (Rothman and Greenland, 1998). Case-control studies have greater potential for misclassification of exposure because exposure status is collected retrospectively (Aschengrau and Seage 2003; Rothman and Greenland, 1998). Interestingly in this study, the authors noted that BeS subjects were statistically significantly less likely than control subjects to report direct exposure to beryllium ($p=0.012$). In addition, a trend analysis suggested that BeS subjects were more likely to report "no known exposure to beryllium" compared to control subjects ($p=0.031$). This is highly unusual of case-control studies where cases are more likely than controls to recall exposure, and draws into question the exposure reconstruction approach and/or the validity of test results. Further, it is highly questionable whether areas and tasks characterized as having "no beryllium exposure" truly had no beryllium exposure. As the exposure reconstruction included periods of no exposure to beryllium in the calculation of cumulative and LWE estimates, these exposure estimates are expected to be biased low by assuming no exposure, when exposure actually occurred.

Multiple Regression Analyses

First, the CBD findings for reconstructed exposures are not statistically significant under proper statistical analysis. The authors separated the data into quartiles and reported significance tests focused on specific quartiles. Splitting the data into quartiles multiplies the number of tests by four, and the p-values should be interpreted with a Bonferroni correction factor of four. If this correction is included, CBD risk is not significantly correlated with either cumulative exposure or LWE. A better way to conduct the analysis would be to treat exposure as the continuous variable and use the other variable as the independent variable in an analysis that treats control, BeS, or CBD status as the outcome—either a multinomial logistic regression, if the intent is to view disease status as purely categorical, or polytomous ordinal logistic regression, if the intent is to treat disease status as a rank-ordered outcome.

Second, in the supplemental material, the authors stated that two of the levels of the genetic factor were not included in the coding of the classification variables for the multiple logistic regression models because of limited sample size (n).[2] It is not

[2] One was n=10, and one was n=3.

clear why this was deemed to be insufficient sample size, because if no other issues are present this is sufficient size to execute the coding and conduct the analysis with those classification levels included. It seems likely that the true problem was that these classification variables were collinear with another variable in the model or (more likely) with some combination of two or more other variables in the regression model. If this was the case, this should have been reported as such. If co-linearity was not the issue, some further explanation as to why these two classifications weren't included should be described. Although it seems very unlikely that this would have a substantive impact on the results, some clarification is warranted.

Third and most importantly, the results of multiple logistic regression analyses contain findings that are compromised by a fundamental misunderstanding of the proper analysis strategy. Because BeS and CBD require, by definition, exposure to beryllium, the likelihood of BeS and CBD is zero at zero average exposure. Thus, in principle, an individual who has never been exposed to beryllium should never receive a diagnosis of BeS or CBD. The study finding that individuals with BeS were significantly more likely to have no exposure than non-cases, demonstrates a fundamental error in the analysis. The general function that describes the likelihood of BeS or CBD must be a positive function with Be exposure.

If some other factor, such as genetics, influences the likelihood of BeS or CBD, the likelihood function still must start at the origin. The shape of the dose-response curve is expected to change by constraining the increased probability to positive exposures, and may vary as a function of E69 genotype, but at all levels of this genetic factor, the relationship between exposure and risk must start at zero exposure, e.g., regardless of genotype, BeS and CBD risk do not occur without exposure. The proper test of whether a genetic factor influences BeS or CBD is a test of whether there is an interaction with exposure because any level of the genetic factor cannot by itself produce BeS or CBD without exposure to beryllium.

Hence, the proper model for testing and quantifying how a genetic factor influences BeS or CBD is a model that includes both the genetic factor and exposure, includes interaction terms, and is designed so that the curves representing different levels of the genetic factor start at the same point, presumably, a zero likelihood of BeS or CBD or some practical zero value. Although it is recognized that there are diagnostic biases or other circumstances that may make it plausible for BeS or CBD to be reported at zero exposure, the authors excluded individuals with BeS or CBD before starting work at the facility (a cohort exclusion criteria), and thus likelihood of BeS or CBD at zero exposure should be approximately zero. The interaction term in such a model quantifies the magnitude and statistical significance of the genetic factor. Without the proper analysis, it is not possible to quantify the exact nature of genetic variables or the effects of beryllium exposure on CBD or BeS risk. The quantitative description of those effects under proper analysis might be quite different from those reported in this paper.

The use of Schuler et al. (2011) data for risk assessment of CBD and BeS

In Schuler et al. (2011), workers employed in 1999 with six years or less tenure in primary manufacturing facility of beryllium metal were evaluated for risk of CBD and BeS with beryllium exposure. Although this study had a relatively smaller number of cohort members and number of individuals with CBD and BeS (6 and 26, respectively) as compared to the nuclear weapon workers of VanDyke et al. (2011), the exposure characterization is far superior and the sample size is adequate for risk assessment. Only relatively coarse dose groupings (quartiles) were presented in Schuler et al. (2011), yet a dose-response relationship is evident for BeS and CBD with multiple dose metrics.

More importantly, with the original data, a confined[3] model may be fitted to generate more realistic risk estimates in the low dose range, as compared to that which has been developed with other data sets, including VanDyke et al. (2011). Because of the exposure reconstruction is far superior to that of any of the studies of the nuclear weapon workers including VanDyke et al. (2011), the original data from Schuler et al. (2011) provides the best opportunity to develop a quantitative risk assessment with scientifically valid and reasonable results across the range of current exposures and the most robust basis for a OEL.

[3] A confined model is statistically very arduous to fit; however it is feasible with sufficient expertise. A confined model is most appropriate when exposure is required for disease. For example, if we were modeling lung cancer and hexavalent chromium, an unconfined model would be appropriate because it is not necessary to have exposure to hexavalent chromium to get lung cancer. However, in the case of both BeS and CBD, it is absolutely imperative to have Be exposure to develop either disease, and thus a confined model is required.

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