Letters to the Editor

Exposure estimates in epidemiological studies of Korean veterans of the Vietnam War

From Michael E Ginevan, Deborah K Watkins and John H Ross

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In the past year, several papers on health outcomes in Korean veterans of the Vietnam War have been published. All of these papers base their exposure classifications on an ‘E4 score’ which is a proximity-based measure of ‘exposure opportunity’ calculated from a model developed at Columbia University. Calculation of an Exposure Opportunity Index (EOI) or E4 score from this model requires two inputs:

• a location input in the form of latitude and longitude;
• dates for which the location was occupied by troops.

Once this information has been provided, the model will calculate an E4 score. According to Stellman and Stellman, ‘EOI scores can be incorporated into toxicological models as “presentation dosages”’. Unfortunately, this is not the case.

In 2009, we published papers that evaluated the performance of this model in two ways. First, we compared the predictions of the Stellman EOI models to the depositions predicted on the basis of the well-validated model AgDRIFT™; and second, we evaluated the consistency of the predictions of the Stellman EOI model by calculating E4 scores for 36 defined exposure locations for each of 30 different herbicide missions for two time periods—day of herbicide application and days 2–3 post-application. We note that both our studies and the Stellman E4 model are based on data for missions using the spray system based on the Fairchild C-123 aircraft equipped with wing and tail spray booms that was used to apply approximately 95% of all herbicides during the Vietnam War. The deposition pattern produced by this system is well documented by actual measurements and has been accurately modelled using the AgDRIFT™ model and its non-commercial version, AGDISP, which are state-of-the-art dispersion models for spray drift from airborne applications. Thus the dispersion properties of the C-123 system are not a major source of uncertainty.

Our studies have demonstrated that estimates from the E4 score model have many anomalous features.

• E4 scores are assigned to an area that is more than 30 times larger than the area actually affected by a typical C-123 spray mission.
• The Stellman model estimated E4 scores for points 800 m from the flight path, that averaged slightly higher than scores for points on the flight path. The problem here is that at 800 m from the flight path, both validated model results and direct measurement show that exposure is miniscule. Even at 4 km, the Stellman model predicted E4 scores that averaged 38% of E4 scores on the flight path.
• The model’s predictions are not self-consistent. E4 scores for points on the flight path, which should be essentially identical, varied more than 500-fold (Table 2 of ref. 6). We also found that in the Stellman model, if a mission has a high E4 score for one test location, it would have relatively high scores for all test locations; and if a mission had a low score for one test location it will have relatively low scores for all test locations. This means that a given E4 score could be high or low, depending on whether one was near a ‘high’ or ‘low’ exposure mission.
• Our investigation also showed that E4 scores calculated for 2 days after application were only about 4% of E4 scores calculated for the same locations on the day of...
application (Table 3 of ref. 5). This observation means that E4 scores are almost entirely dependent on whether or not a person was present on the day of application, because if the same person were there two days later, this ‘exposure’ adds only a small increment to the E4 score.

The effect of these errors is to make E4 scores useless as even an approximate measure of relative exposure. For example, a location could have a high E4 score by being within 2 km of several ‘high exposure missions’. Here the exposure should always be essentially zero. Similarly one could postulate a ‘low exposure’ group that spent extensive periods of time in recently sprayed areas because, as noted above, E4 scores 2 days after application are only 4% of day-of-application scores for the same location.

We note that there is some misinformation in the literature concerning our studies. In a recent letter to the editor of the Journal of Exposure Science and Environmental Epidemiology commenting on our work, the Stellmans made several claims. The letter first suggested that we had devised our own approximation to the Stellman model and had not, in fact, tested the actual model. We did test the Stellman model; the version tested is the one evaluated by the Institute in fact, tested the actual model. We did test the Stellman model and had not, in fact, tested the actual model. We did test the Stellman model; the version tested is the one evaluated by the Institute

E4 scores. Here we responded that routine use of logtransformed exposure data is a dubious practice but, more importantly, a logarithmic transformation does not alter the fact the E4 scores are clearly incorrect as a measure of exposure.

One might suppose that there are other validation studies of the Stellman model that could be used to either corroborate or refute the results of our studies. Unfortunately this is not the case. Indeed, the IOM committee that produced the report The Utility of Proximity-Based Herbicide Exposure Assessment in Epidemiologic Studies of Vietnam Veterans called for additional evaluation of the Stellman model (Chapter 3), but our work remains the only attempt to assess the validity of the model.

In summary, although the studies of Korean veterans appear reasonable in most respects, they all rely on a common, deeply flawed dose metric and as such are invalid. It is simply not possible to obtain valid epidemiological results based on unreliable estimates of exposure.

Conflict of interest: All three authors are presently consultants to the Dow Chemical Company and to Monsanto. These companies also supported the work presented in references 5 and 6. However, neither company had any role in the design, data collection, analysis, writing or decision to publish those papers. Preparation of the present letter was done without support of any kind.

References

4. Stellman SD, Stellman JM. Exposure opportunity models for Agent Orange, dioxin, and other military herbicides used in
Response to: ME Ginevan et al.
Exposure estimates in epidemiological studies of Korean veterans of the Vietnam War

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The letter by Ginevan et al. regarding the studies of Yi et al. recycles a number of criticisms of our exposure opportunity modelling that they previously made and to which we responded. In addition to the old arguments, the present letter introduces additional incorrect data. Briefly, Ginevan et al. have misinterpreted the conceptual basis of our exposure opportunity methodology by attempting a ‘validation’ using AgDrift®, a system for modelling deposition of aerial spraying, against our exposure opportunity index which takes into account all past sprays at a location while accounting for environmental decay and multiple routes of exposure. This is something like attempting to validate food intake by comparing a 24-h dietary recall with a year’s accumulated grocery receipts. They also conflate two distinct models we developed—one the exposure opportunity index, E4, and the other a simple count of ‘hits’ from overflights by the spray planes.

Our exposure opportunity index E4 is designed to provide a rank-ordering of exposures, based on dates and specific residential locations in Vietnam. The resulting equation is complex and requires careful programming to avoid calculation errors. Ginevan et al. have apparently never been able to solve the equation correctly, even though they say they were using our automated software for their calculations. The equation in our model has an exact solution. The same location and the same date interval must always yield the same answer. All discussion of how ‘close’ on average their findings are to ours is thus meaningless. An exact solution is an exact solution, period.

Based on such incorrectly calculated data, Ginevan et al. have repeatedly called our model invalid. For example, one...