Response to: ME Ginevan et al.
Exposure estimates in epidemiological studies in Korean veterans of the Vietnam War

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The letter by Ginevan et al.1 regarding the studies of Yi et al.2–4 recycles a number of criticisms of our exposure opportunity modelling that they previously made and to which we responded. 5,6 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-hour 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.7 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
of their miscalculated points was a relatively high score for a point 6 km from the spray path. That point is rigorously zero, and must be zero in our model, because of the distance limits we imposed. This miscalculated point was a major crux of their claim about the invalidity of our model.1

The Ginevan et al. observation that E4 scores fall dramatically within several days of exposure is a feature of the model that we built in to reflect the importance of dermal exposure.7 Even here, however, our model and software are flexible and users can specify different half-lives of decay (and even different kinetic decay models—but this takes a little more work). A longer half-life will slow down the fall in E4; model parameters are up to the user.

Two specific points that Ginevan et al. make require further comment beyond those in our earlier detailed response.6

First, the statement that ‘use of log transformed exposure data is a dubious practice’ cites their 2010 critique of its use in pharmacokinetic models of, for example, associations of diabetes with dioxin exposure.8 That critique specifically focuses on the very low end of the dose-response curve and is not useful for the Agent Orange situation in which heavy and repeated spraying of many targets resulted in exposures varying by as much as six orders of magnitude at different locations and time periods in Vietnam, and where the high-end, rather than the low-end exposures, are of the greatest epidemiological concern. Log-transformation is purely monotonic, perfectly preserves rank ordering of exposure estimates and de-emphasizes inconsequential variability. Log-transformation creates no new information but facilitates statistical testing commonly employed in epidemiological analysis and, like the Richter scale, it is a useful way to describe and conceptualize the very wide range of exposure opportunity. Importantly, in the case of our model, log transformation is mathematically appropriate since our E4 data are log-normally distributed.9

Second, referring to the distance of an exposed individual from a spray, Ginevan et al. have twice asserted1,10 that ‘1/d is dependent on the units of d (e.g., d in metres increases much faster with distance than d in kilometres) and they apparently never specify the units of d in their model’. Although it is indisputable that kilometres are 1000 times bigger than metres, the implications of this fact for our model are incomprehensible. Had we decided to measure d in units corresponding to the length of Pinocchio’s nose when telling a lie, the model itself would function exactly the same, as long as conversion factors were consistent.

For readers’ edification, we do indeed use kilometres as our distance unit and reference to ‘km’ pervades our work: it appears 34 times in the published description of our geographical information system (GIS), for example.9

Ginevan et al. have asserted that our model was never tested by the Institute of Medicine (IOM).10 Our work was funded by the National Academy of Sciences, and the IOM established a committee to oversee our work. We made detailed lengthy presentations to the committee every 6 months for the duration of the model development and testing. That review was demanding and thorough and we modified many aspects of the work in response to committee input. Our models were evaluated a second time by a different IOM committee11 that also reviewed and tested the software. In fact, Ginevan et al. presented their critique of our work to the second committee, which considered their comments but did not alter their appraisal of our models, which they fully endorsed.

Over the years Ginevan and co-authors have been supported by Dow and Monsanto, which sponsored their 2009 paper. Dow and Monsanto were the two major chemical companies that manufactured and supplied Agent Orange. Their 2009 paper was submitted and published fully 6 years after our model paper that they criticized was published, and at the same time that the companies were defendants in two major federal class action lawsuits brought by parties who claimed injury as a result of exposure to spraying. There is currently a major lawsuit for monetary damages for Republic of Korea veterans who served in the Vietnam War under consideration in the Korean legal system.

Ginevan et al. appear closely to follow the work of all researchers who use our model, a model that has undergone intensive scrutiny and was twice evaluated by the Institute of Medicine, and we believe the presentation of fallacious arguments about its validity serves to manufacture uncertainty about epidemiological studies of military herbicides used in Vietnam (1961–71), a common approach.12,13 There is little in our model that breaks new ground: we use elementary first-order differential equations of chemical decay and a GIS system that conceptually differs little from the National Academy of Science’s 1974 report on herbicides in Vietnam.14 The model is robust, and indeed we have shown that when properly interpreted, the earlier Ginevan et al. study5 actually supports, rather than invalidates, its robustness for spray paths that deviate slightly from the straight-line projections we use.

References

We thank Dr Ginevan and his colleagues for their interest in our article.1–3 Accurately determining the level of exposure to Agent Orange is perhaps the greatest challenge in research on the association between Agent Orange exposure and health outcomes in Vietnam War veterans. Dr Ginevan and his colleagues are among those researchers who have claimed that epidemiological research on the association between Agent Orange and health outcomes cannot be done in Vietnam War veterans who were not directly involved in herbicide spraying missions, due to the difficulty of Agent Orange exposure assessment.4–6

Their previous research5,6 and their letter to the IJE editors claimed that the Exposure Opportunity Index (EOI) E4 model,7 on which our study is based, has more limited accuracy and precision than the AgDRIFT model which, they also claimed, should not be used for the purpose of epidemiological study related to herbicide exposure in Vietnam.5 Since their research methods for evaluating the EOI E4 model have already been critiqued by Stellman and Stellman,8,9 it is not necessary to discuss the detailed technical issues concerning the E4 model they raise here. Their assertion mainly focuses on differences between EOI E4 and AgDRIFT models with regard to exposure assessment at specific locations near the aerial spray path of three isolated spray missions. However, the EOI E4 model considers all past sprays at a location while accounting for multiple routes of exposure, environmental decay and weather.7,9

Furthermore, any potential inaccuracy in our Agent Orange exposure assessment should not overestimate the risk associated with Agent Orange exposure, but rather is more likely to underestimate the risk, because it could lead to a non-differential misclassification of the exposure independently of other variables.10