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Exposure opportunity models for Agent Orange, dioxin, and other military herbicides used in Vietnam, 1961–1971

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Nearly 19.5 million gallons of herbicides were sprayed on the Republic of Vietnam between 1961 and 1971 for military purposes. Amounts of spray and patterns of applications are available in an electronic file called HERBS that contains records of 9141 defoliation missions, including detailed coordinates of US Air Force Ranch Hand aircraft flight paths, along with chemical agent and gallonage sprayed. Two classes of models for use in epidemiological and environmental studies that utilize the HERBS data for estimating relative exposure opportunity indices are presented: a discrete "hits" model that counts instances of proximity in time and space to known herbicide applications, and a continuous exposure opportunity index, E4, that takes into account type and amount of herbicide sprayed, distance from spray application, and time interval when exposure may have occurred. Both direct spraying and indirect exposure to herbicide (or dioxin) that may have remained in the local environment are considered, using a conservative first-order model for environmental disappearance. A correction factor for dermal *versus* respiratory routes of entry has been incorporated. E4 has a log-normal distribution that spans six orders of magnitude, thus providing a substantial amount of discrimination between sprayed and unsprayed areas. The models improve on earlier ones by making full use of the geometry of the HERBS spray flight paths of Ranch Hand aircraft. To the extent possible so many decades after the War, the models have been qualitatively validated by comparison with recent dioxin soil and biota samples from heavily contaminated areas of Vietnam, and quantitatively validated against adipose dioxin obtained in epidemiological studies of Vietnamese. These models are incorporated within a geographic information system (GIS) that may be used, as one would expect, to identify locations such as hamlets, villages, and military installations sprayed by herbicide. In a novel application, the GIS also facilitates quantitative risk assessment in epidemiological and ecological studies by applying the models within a framework of historical reconstruction of exposure history of individuals based upon their location histories.

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Introduction

Between 1961 and 1971, nearly 19.5 million gallons of herbicides were used by the United States Armed Forces for tactical defoliation and crop destruction in Southeast Asia. The three mixtures most commonly used were Agent Orange (esters of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid), Agent White (triisopropanolamine salts of 2,4-D and picloram), and an arsenical called Agent Blue (cacodylic acid). (The colors refer to an identification stripe painted on the storage drums.) The 2,4,5-T-containing herbicides (at least 12.6 million gallons of the total) were contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, which we will refer to as dioxin, at levels estimated between 0 and 100 p.p.m., and sprayed at concentrations far higher than those used for domestic agricultural defoliation purposes. (Stellman et al., 2003a). Little is known of the long-term health or ecological consequences related to this massive, concentrated use of herbicides in the former Republic of Vietnam (RVN). (National Research Council, 1974; Institute of Medicine, 1994, 1996, 1998, 2001). Persistently high levels of dioxins in Vietnam soil and biota, as well as in samples of Vietnamese serum, adipose tissue, and breast milk have been reported and so-called "hot spots" identified (Dwernychuk et al., 2002). The military use of herbicides in Vietnam thus represents one of the most concentrated environmental exposures to dioxin-contaminated herbicides for which few systematic investigations of health and ecological effects have been carried out.

In 1994, the Institute of Medicine recommended that a methodology be developed for characterizing exposure to herbicides by historical reconstruction of military records (Institute of Medicine, 1997), recognizing that environmental sampling for estimating past exposures is of limited utility because environmental transport mechanisms will have long

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since reduced many, if not most, initially elevated levels to background. The Department of Veterans Affairs contracted with the National Academy of Sciences (NAS) to do so. The present study, carried out under a subcontract to the NAS for that effort, has led to the development of a geographical information system (GIS) for use in studies of Vietnam (Stellman et al., 2003b). More than simply a system for aggregating geocoded data, our GIS is a research tool that permits investigators to evaluate herbicide exposure for an individual, military unit, or fixed location in Vietnam (such as a village). It does so through linkage of an extensive herbicide application database to tables that contain location histories of individuals or military units, and, most importantly, to exposure estimates that are based on models developed by the authors and presented here. The GIS itself is not dependent on any particular model, and alternative models to those described below could be incorporated by a user willing to calculate the relevant exposure tables.

Exposure assessment is based on calculation of exposure scores called exposure opportunity indexes (EOIs). EOI models that represent exposure as a function of proximity in time and space to a toxic agent are becoming increasingly common in epidemiological studies (Smith, 2002). An EOI is often used, for example, in occupational or environmental studies as a surrogate estimator of historical exposure where current environmental or biomarker measurements are not good estimators of past exposures, and where measurements were never made in the past or are unavailable (Schaeffner et al., 2001). The EOI concept is complementary to traditional exposure methodologies based upon toxicological models and measures. Exposure opportunity is not a toxicological measure, but EOI scores can be incorporated into toxicological models as "presentation" dosages. They are meant to be used in large-scale studies in which a location history is the principal source of information about an individual or group such as a military unit. They are especially applicable to studies in which body burden measurements are impractical or unlikely to reflect exposures in the distant past.

The EOI presented in this paper has evolved from an earlier version introduced by us at professional meetings in 1980 (Stellman and Stellman, 1980) and 1982 (Stellman and Stellman, 1982). It has been utilized in a number of studies of health of Vietnam veterans and the civilian population of Vietnam (Stellman and Stellman, 1986; Stellman et al., 1988; Verger et al., 1994; Ha et al., 1996; Kramarova et al., 2002).

The purpose of this paper is to present details of our exposure opportunity models, including refinements of prior models; to characterize the exposure metrics; to show how EOIs are incorporated into our GIS; and to illustrate reduction of exposure misclassification compared to earlier approaches (including our own) that undercounted opportunities for exposure.

Methods

All exposure estimates produced by our EOI models are based on herbicide applications documented in the so-called HERBS file. This data file, originally created by the Department of Defense, provides the flight paths taken by Ranch Hand aircraft as they carried out their spray missions. (Data Management Agency, 1970; US Army and Joint Services, 1985). The HERBS file uses alphanumeric indicators to mark turning points and activation/deactivation of spray apparatus. The date, number of gallons, and herbicide agent used for each mission, the type of aircraft or other equipment use, as well as other details of the mission, are also included in the mission record. We have carried out extensive quality control on existing spray data and expanded the file by analysis of additional primary sources (Stellman et al., 2003a). The file now contains data on 9141 missions, primarily carried out by C-123 fixed-wing aircraft, but also by helicopter, truck, and in some cases backpacks worn by soldier-sprayers.

Since an EOI score is a measure of proximity in time and space to herbicide spraying missions, it must always be referred to a specific location and a specific time interval during which exposure may occur. The GIS provides a computational framework for the distance- and time-dependent calculations specified by our model. Two central features of the GIS are (1) geographical partitioning of Vietnam into a grid system spaced at 0.01° intervals in latitude and longitude, defining the southwest corner of cells with average area $\approx 1.2\,\mathrm{km}^2$, and (2) association of each cell defined by this grid with several measures of proximity to every herbicide mission, which occurred inside or near it. We use the centroid of each GIS cell as the reference location when calculating the EOI for all locations within it, and the residence period within the cell as the time interval during which exposure may have occurred at that location.

Our models provide two types of estimates of exposure opportunity:

- direct exposure that results from being within a defined distance from the spray path at the time in which the spray mission was executed (the "hit" score).
- indirect exposure to residual herbicide (or dioxin) from sprays that occurred prior to entry into a location (a continuous EOI).

Direct Exposure and "Hits" Counts

A "hit" is defined as an instance of a herbicide spray application falling within a prescribed distance of the centroid of a cell. By definition, a hit has an associated radius, so that we speak of "hits" within 0.5, 1, 2, or 5 km. The 5-km limit is an arbitrary figure that merely insures that computation time is not wasted on distant sprays irrelevant to exposure. Smaller and larger distances can easily be modeled. The "hits" counts concept is illustrated in Figure 1, which shows a typical Ranch Hand aerial spray path over Highway 1, approximately 80 km east of Saigon (now Ho Chi Minh City), overlaid on the GIS grid system. Each of the 210 cells that fell within 5 km of the spray path is indicated via a symbol placed at its centroid. The symbol also conveys the distance of the centroid from the flight path. For example, large black circles mark the centroids of the 15 cells that fell with 0.5 km of the spray path. "Hits" scores are based on trigonometry and do not depend upon assumptions about environmental fate or transport of herbicide or dioxin. Figure 1 also illustrates the importance of computing distances from the complete flight path rather than just the end- or mid-points as some investigators have recommended (Phan, 1998). As shown in Figure 1, restricting exposure estimates to end points would result in substantial exposure misclassification.

Indirect Exposure, Continuous EOI Models

Because herbicide and/or dioxin may persist in the environment long after the initial application, there is the possibility of exposure to residual herbicide (or dioxin) from sprays that occurred prior to entry into a location ("indirect exposure"). An individual who moved from one location to another during the years of herbicide spraying could have been subjected to both direct and indirect exposure. Our earlier EOI model defined an index called E3 as the product of three factors: (1) a quantity factor C_0; (2) the reciprocal distance ($1/D$) of the exposed location from the herbicide spray; (3) a time factor, which we chose to be a first-order environmental decay of the sprayed herbicide over time (i.e., an exponential decay curve) (Stellman and Stellman, 1986).

$$E3 = C_0 \frac{1}{D} \int_{t_1}^{t_2} \mathrm{e}^{-\lambda t} \mathrm{d}t \tag{1}$$

The concentration factor C_0, is proportional to the concentration of "toxicologically active" chemical species in the herbicide, which in turn is proportional to the volume of herbicide sprayed. In our calculations, we take as C_0 the number of gallons of herbicide sprayed, since the (unknown) proportionality constants must cancel in comparisons between groups of individuals exposed to the same substances.

Flight Path Connectivity

We have introduced an important refinement to our earlier "hit" models that "connects the dots" of the spray path, which we previously treated as series of point sources. In this refinement, we use the fact that the actual flight paths of spray aircraft may be deduced from data contained in the HERBS file (Stellman et al., 2003b) to treat every point along the flight path as an independent source of herbicide exposure. Conceptually, we first divide a given straight-line leg into k equal intervals. The gallonage for each leg j in a multi-leg spray run of j legs is taken to be $G_j/(k+1)$ (see Figure 2). We then allow the number of intervals k to increase without limit, and arrive at the following distance

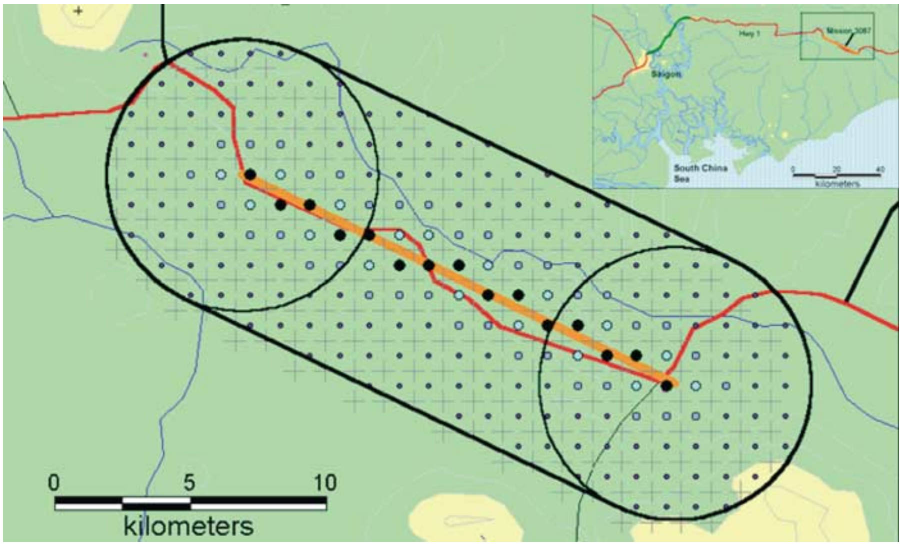

Figure 1. Region of Vietnam approximately 80 km east of Saigon (see inset), showing flight path of Ranch Hand mission no. 3087 flown on May 11, 1967 (straight orange line) along Highway 1 (jagged red line). GIS grid system is shown as horizontal and vertical lines spaced 0.01° apart. Contained within a 5 km buffer drawn around the flight path (heavy black line) are the centroids of the 210 cells that fell within 5 km of the flight path, with size and color indicating proximity to defoliation flight path: large black circles = 0.5 km or less; larger squares = 0.5–1 km; small shaded squares = 1–2 km; small black circles = 2–5 km. Each of the two large circles has a radius of 5 km about an end point of the flight path and encloses 65 of the 210 centroids. Failure to account for flight path continuity by counting "hits" only from the flight path's end points would produce an undercount of 210–130 = 80 exposed cells, or 38%.

correction factor:

$$f = \lim_{k\to\infty} G_j(1/(k+1)) \sum_{i=0}^{k} (1/d_i) \tag{2}$$

The limit in Equation (2) has a closed representation, which is given by the following integral:

$$\begin{aligned} f &= \int \frac{\lambda}{D(x_s)}\,\mathrm{d}x_s \\ &= \frac{\lambda}{\sqrt{1+m^2}} \log\left[2\left(\frac{x_s(m^2+1) - X - m(b-Y)}{\sqrt{1+m^2}}\right) + D(x_s)\right] \end{aligned} \tag{3}$$

where λ is the spray density (gallons of spray divided by length of the spray path), (X, Y) are the coordinates of the exposed unit, $D(x_s)$ is the distance along the spray path, m is the slope of the spray path in the common Cartesian coordinate system, and b is its intercept. The factor f replaces the reciprocal distance factor in Equation (1), and the resulting exposure opportunity is now called E4.

Equation (3) is symmetrical in x and y (that is, identical numerical solutions are produced if x and y are interchanged). This is important because the slope m has poor precision when the flight path orientation lies within a few degrees of the north–south axis, and becomes infinite when its direction is due north or south. To avoid this situation, the program which operationalizes Equation (3) exchanges x and y when $|m| > 1$, corresponding to a flight path ±45° from east-west.

The "Corner Effect"

Another refinement was to identify a comparatively small number of instances ($N = 3005$ cell–mission combinations) in which the cell was overflown by spray aircraft in a corner or in the narrow envelope along the perimeter of the square, just beyond the 0.5 km radius. Since cells defined by a grid spaced at 0.01° are slightly larger than 1 km on a side (and in fact vary in area with latitude), these herbicide sprays would not be counted when hits are classified as within 0.5 km from the centroid and the number of direct hits to some cells will be underestimated. We have identified them and redefined our "within 0.5 km" measure to be "within 0.5 km + within_cell_ envelope". Our final direct hit measure is the sum of the 0.5 km hits and the 3005 cell envelope hits.

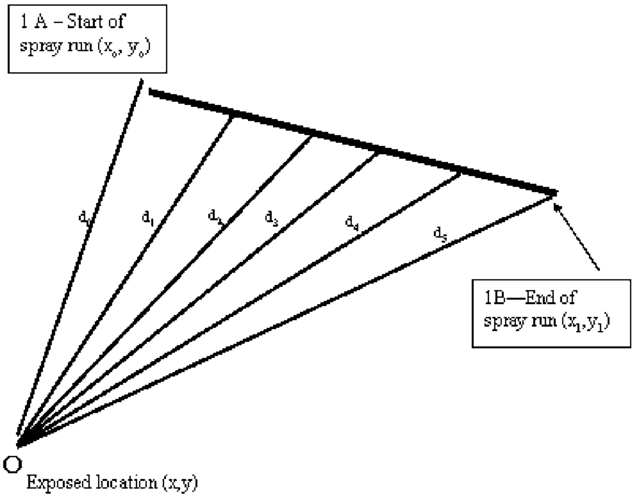

Figure 2. Treatment of exposure to herbicide spray from a continuous flight path from 1A to 1B as a limiting process. d_0, d_1, … d_k are distances between various points along the flight path and exposure point O (x, y). As k increases without limit, Equations (3) and (4) give the contribution of distance to the exposure at point O under the assumption of a reciprocal relationship.

Adjustment for residence time and herbicide half-life

In our framework, exposures to multiple sprays are additive, provided that the EOI for each individual spray is computed with the appropriate time limits for the integral. Thus, while the instantaneous exposure at a given location decreases over time as the herbicidal agent decays, the cumulative exposure score is always increasing with time (Figure 3). We chose a first-order environmental decay as the time factor in order to take the most conservative approach to the fact that the herbicide (and any toxic constituents) do not remain in the environment but decay continuously from the time of application. The integral or area under the curve (AUC) provides us with an exposure factor that is cumulative over time. We set the limits t_1 and t_2 to be the dates of spraying and the end of the residence period, respectively. The time constant λ may be specified independently.

The investigator can choose the half-life and the date-in, date-out limits in Equation (1), but if either the residence interval or the half-life for first-order decay is modified, the EOI must be adjusted to reflect the new parameters. For example, our GIS implementation of Equation (1) utilizes a

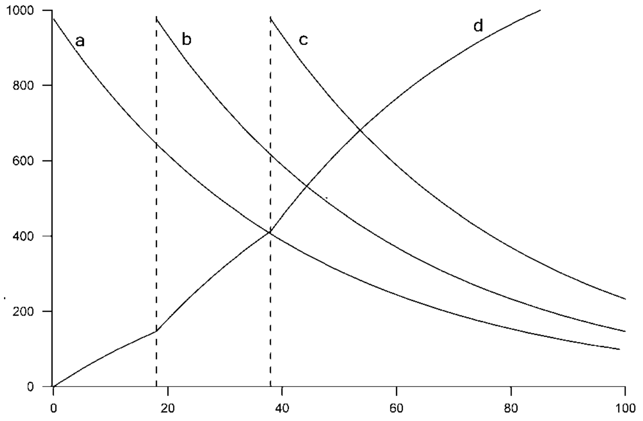

Figure 3. Accumulation of EOI scores from multiple sprays. Lines a, b, and c represent the instantaneous environmental levels of three sprays of 1000 units of herbicide applied on day 0, 18, and 38, assuming a half-life of 30 days. Line d is the total area under the curve (AUC), scaled to fit on the same graph.

conservative 30-day half-life and a time span of January 1, 1961 to December 31, 1972. Most military personnel (or the units to which they belonged) stayed in specific locations for shorter periods of time, sometimes as short as 1 day, so that they should only be "credited" with the fraction of the indirect exposure that applies to the period of time during which they resided in an exposed cell. Or consider that a researcher might wish to determine an exposure opportunity score based upon a longer or shorter half-life or to continue the decay extrapolation to incorporate dates beyond the end of the herbicide program. For example, ecological studies might leave the in- and out-dates intact but vary the half-lives to reflect different ecological conditions.

The following equations apply. We wish to transform the tabled E4 to represent a new half-life, a new residence date-in t_{in}, and a new residence date–out t_{out}. Let

$$T_0 = (1/\lambda_0)[1 - \exp(-\lambda_0 \times (4018 - \text{spray} - \text{date}))] \quad (4)$$

where the "old" time constant (i.e., the one used for the tabled values of E4) $\lambda_0 = \ln_e(2)/30$ and the "new" time constant is $\lambda_1 = \ln_e(2)/\text{new half-life}$. All time units are in days with January 1, 1961 = 1. Let t_{spray} = date of spraying (i.e., number of days since January 1, 1961), t_{in} = first day of residence at a given location, and t_{out} = last day of residence at that location +1. The constant 4018 is the number of days in the 11-year spray program interval. We calculate the new value of E4 as

$$E4' = E4\,(T_1/T_0) \quad (5)$$

where T_1 is given by one of the following two formulas:

1. If $t_{\text{out}} \geq$ spray-date $\geq t_{\text{in}}$, then this is a direct hit and
$$T_1 = (1/\lambda_1)[1 - \exp(-\lambda_1 \times (t_{\text{out}} - \text{spray-date}))] \quad (6)$$

2. If spray-date < new-date-in, then this is an indirect hit and
$$T_1 = (1/\lambda_1)[\exp(-\lambda_1 \times (t_{\text{in}} - \text{spray-date})) - \exp(-\lambda_1 \times (t_{\text{out}} - \text{spray-date}))] \quad (7)$$

Note that if spray-date > t_{out}, then the spraying is irrelevant because it occurred after the residence period. In this instance $T_1 = 0$ and therefore $E4' = 0$.

Adjustment for Route of Exposure

Although the exposure opportunity index is not formally dependent on a specific toxicological model, we recognize that studies of herbicide exposure in pesticide applicators and other occupationally exposed workers show different rates of absorption via dermal and respiratory routes of entry. Dermal exposure has been reported to be at least six times as efficient as respiratory exposure (Draper and Street, 1982; Libich et al., 1984; Abbott et al., 1987). This may seem counterintuitive, until one considers that skin is the body's largest organ, that sweating while working increases the efficacy of dermal absorption of chemicals, that clothing can facilitate their penetration into the body, and that a large fraction of inspired foreign substances are exhaled. We partition exposure opportunity into two components, one representing direct and the other indirect exposure. For every direct hit, we compute an additional E4 term in which the residence time extends from the date of spraying until 3 days later, with a half-life of 1 year, and multiply it by a correction factor to represent the approximate ratio of dermal to respiratory absorption. The result is added to that obtained using the actual residence time and postulated half-life. This correction avoids the situation whereby an individual who was not directly sprayed could accumulate a larger EOI score than someone who was, simply by staying in a once-sprayed location for a very long time.

Results

We present here characteristics of the exposure database and examples of typical use of our method for evaluating exposure. For these calculations, we excluded the 114,185 records encompassing parts of Laos and Phu Quoc Island. This left 1,340,771 records, pertaining to 9001 (98.5%) of the original 9141 HERBS missions. Table 1 shows the number of cells in RVN whose centroids fell within 0.5, 1, 2, and 5 km, respectively, of any herbicide application flight path and contrasts these numbers with counts obtained by the older method, which treated all records in the HERBS file as if they were isolated sources of herbicide. Utilizing full flight path information substantially increases the counted

Table 1. Number of instances in which the centroid of a cell fell within a specified distance of a herbicide mission.

	Hits within			
	0.5 km	1 km	2 km	5 km
Hits calculations treat all HERBS records as isolated vertices	8340	22,636	50,259	104,662
Hits calculations use continuous flight paths provided by HERBS records	32,613	47,623	70,208	112,466
Ratio	3.9	2.1	1.4	1.1

Separate runs within the same mission are counted as separate hits.

number of hits at closer ranges. At 500 m, it increases by a factor of nearly four. Even at an approach of 5 km, the undercount is approximately 10%.

The five EOI measures must obviously be correlated with one another, since they are nested (i.e., every hit within 0.5 km is also a hit within 1, 2, and 5 km). However, as Table 2 shows, the extent of correlation varies with distance and, most importantly, is considerably stronger for the E4-related measures, which use the continuous flight path data.

Since each record in the exposure database provides data on the exposure at one specific cell centroid received from a single spray mission, it is possible to tally multiple exposures at a given location by aggregating their exposure scores over all missions that affected it. Many locations in RVN sustained multiple sprayings several days apart for more effective defoliation. Subsequent spray applications may have been more likely to reach soil, and investigators may wish to give greater weight to exposures received by persons in multiply sprayed locations. Excluding spraying of perimeters of base camps and other fixed installations, there were 14,466 cells that were sprayed exactly once and 18,493 that were sprayed more than once, some as many as 43 times. In the multiply sprayed group, there were 51,987 instances of cells sprayed more than once in a 10-day period, in 4861 missions that dispersed nearly 7 million gallons of 2,4,5-T-containing herbicides. The ability to identify these areas is important, because the toxicological impact of exposure to defoliants will probably depend on the ability of the herbicide to penetrate dense jungle canopy. In addition, 1271 cells received a single perimeter spray and 755 received multiple perimeter sprays, some as many as 84 times. It should be noted that perimeter spraying generally involved amounts of herbicide 1–2 orders of magnitude smaller than those used in Ranch Hand spraying.

Table 2. Pearson's correlation coefficients between the continuous EOI and number of "hits" within 0.5, 1, 2, and 5 km.

(a) *Exposure scores treat all spray coordinates as point sources*

	E3	0.5 km	1 km	2 km	5 km
E3	1	0.20	0.31	0.42	0.50
0.5 km		1	0.67	0.48	0.30
1 km			1	0.75	0.47
2 km				1	0.69
5 km					1

(b) *Exposure scores make full use of flight path geometry*

	E4	0.5 km	1 km	2 km	5 km
E4	1	0.60	0.64	0.67	0.66
0.5 km		1	0.86	0.77	0.60
1 km			1	0.88	0.70
2 km				1	0.82
5 km					1

To be of use in epidemiological studies, an exposure score should have reasonable statistical properties, including a distribution broad enough to provide adequate contrast between persons or places with high *versus* low exposure. There were 112,466 cells that had nonzero E4 scores. These scores ranged over six orders of magnitude, from 0.24 to 4,241,013 with a mean of 161,870 and standard deviation of 322,784, and exhibited approximate log-normality (Figure 4). Table 3, which presents deciles for nonzero exposures, shows that good discrimination is attained among the highly exposed strata.

Discussion

In this paper, we have presented the computational details for exposure assessment of Vietnam veterans to military defoliants. Our work builds on previous methods for describing herbicide usage in Vietnam, such as that developed by the National Academy of Sciences in the 1970s, as well as our own published exposure opportunity models (Stellman and Stellman, 1986; Stellman et al., 1988), which it extends

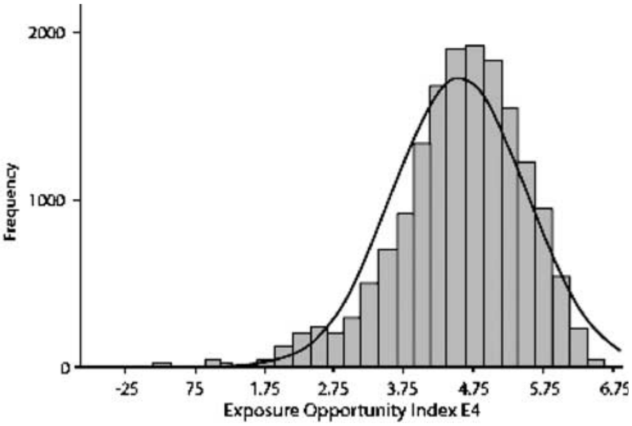

Figure 4. Distribution of log (E4) for the 112,466 cells in South Vietnam which had nonzero E4 scores (based on a 15% sample). A normal curve is superimposed.

Table 3. Cut points for deciles of the distribution of E4, based on a 15% sample ($n = 16{,}517$ observations) of nonzero EOI scores.

Percentile	Cut point
10	2272
20	7480
30	14,958
40	25,836
50	42,565
60	70,129
70	115,458
80	210,280
90	447,355

in several respects, including use of an updated and cleaned HERBS file and incorporation of a much more realistic geometric representation of the flight paths.

GIS-based historical reconstruction methods are finding increased use in assessment of exposure to environmental hazards and in epidemiological studies of large populations (Ward et al., 2000; Gunier et al., 2001; Brody et al., 2002; Reynolds et al., 2003), particularly when exposures may have occurred in wide geographical areas over a period of many years. Our model is designed to be incorporated into a GIS for RVN that permits exposure scores to be aggregated over all missions, which may have affected a specified location during a specific time period. We can thus reconstruct the spray history of that location both for direct hits and for the indirect effects of decaying residues from past missions. For military units that moved from one location to another, EOIs can be aggregated over different locations that represent the unit's movement history.

Our GIS facilitates linkage to the HERBS table via the mission ID, making it relatively simple to restrict exposure calculations to specific dates, herbicidal agents, or combinations of agents, and to take into account other mission features such as type of aircraft and number of sorties flown. Our approach is conceptually similar to that used by the National Academy of Sciences in its first appraisal of the ecological effects of herbicides used in Vietnam (National Research Council Committee on the effects of Herbicides in Vietnam, 1974). Setting up adjustments for residence time and half-life for every new set of data is straightforward but tedious and time-consuming. We have simplified and automated the process by permitting the user to specify these parameters in the GIS software.

Our calculations demonstrate the importance of deducing the full geometry of Ranch Hand flight paths from the HERBS file rather than simply calculating distances from their turning or end points as has been done in the past. If, for example, a hamlet or village was directly overflown by a herbicide mission, it could be erroneously designated as not having been directly sprayed upon if it lay near the middle of a typical 8-km spray run. Conversely, it could be misclassified if the midpoint of the run were used as the distance reference point and the hamlet lay at either end point of the spray run. As another example, individuals or military units that occupied any of the seven cells (large black dots in Figure 1) that are within 0.5 km of the Agent Orange spray, but that are outside the 5-km circles drawn around the ends of the run would be erroneously reported as completely unexposed. Use of the full flight path can thus reduce one source of nondifferential exposure misclassification that might otherwise weaken any true exposure–disease associations.

Validity

A convincing case for validity could be made by comparing our EOI estimates with environmental measurements or with a robust biomarker of exposure such as adipose or serum dioxin. Unfortunately, more than 35 years have elapsed since the number of troops was at its peak. The half-lives for both environmental persistence and body burden of dioxin appear to be in the order of 7–10 years and vary widely between individuals. Thus, present-day dioxin concentrations could be as little as 3% of their initial levels. Nevertheless, one biomarker validation has in fact been carried out. In 1989, investigators at the French research institute INSERM requested that we help evaluate exposures for a series of 27 patients admitted for abdominal surgery to the Cho Ray Hospital in Ho Chi Minh City, and for whom adipose tissue was being collected for subsequent dioxin assay. EOIs were estimated from the subjects' residential locations. Five patients' levels were at background. For the remaining 22 patients, the Pearson correlation coefficient was 0.50 for association between the log of serum dioxin and log of the EOI ($P = 0.02$) and the Spearman correlation coefficient was 0.44 ($P = 0.04$) (Verger et al., 1994). Besides this quantitative validation, a qualitative concordance has been observed between extremely high dioxin concentrations in samples of soil taken at an abandoned US air base in the Ashau valley, as reported by Dwernychuk et al. (2002) and the HERBS file locations of spraying of Agent Purple at that location. Agent Purple was an early herbicide whose dioxin contamination was estimated at 10–100 times that of Orange (Stellman et al., 2003a).

Limitations

As noted above, a limitation of our EOI methodology is the potential for misclassification due to the errors that remain in HERBS file coordinates despite our extensive efforts to identify and eliminate them, and from exposures to spray not recorded in the HERBS file or arising from other sources of contamination.

Another potential limitation is the fact that the GIS is structured so that exposure at any location within each $\approx 1.2\,\text{km}^2$ cell is assigned the exposure of the centroid. We justify this by noting that while the nominal precision of the HERBS coordinates is 100 m, their accuracy must be closer to 500 m. This exceeds the accuracy with which troop locations are known from military records, so that any attempt to use more "exact" distances could be considered an exercise in false precision.

We use a literal interpretation of the flight path coordinates in the HERBS file as straight line trajectories. However, many defoliation objectives such as railroad lines and coastal waterways follow curved routes that can easily be deduced by overlaying the HERBS file flight path on a cartographic display. A planned refinement is to imput more "realistic" flight paths that balance land topography with aircraft maneuverability constraints.

Some limitations of the EOI may be overcome with additional refinements, such as adjustment for aerial spray drift dispersion. The US Forest Service Cramer-Barry-Grim (FSCBG) model was developed to predict downwind dispersion of pesticides from aircraft, and takes into account the aircraft's wake, droplet evaporation, local meteorology, and penetration through forest canopy (Teske et al., 1993; Teske, 1996) A more recent model, AGDISP (or its commercial spin-off, AgDrift) (Teske et al., 2002), also utilizes information on weather conditions, including wind direction and speed. While such adjustments are possible, their impact on the EOI is expected to be fairly small because spraying was only carried out in clear weather, with wind speeds less than 8–10 knots, no temperature inversion present and at a calibrated spray rate (Harrigan, 1970). Nevertheless, dispersion models might be considered in future refinements of our EOI method, using meteorological data which are available from the Daily After-Action Reports (DAARS) for approximately 60% of Ranch Hand missions.

Our methods are applicable both to population and to ecological studies in Vietnam itself, as well as to studies of veterans, and are suitable for assessment of exposure at fixed locations as well as to groups of people who may have been mobile over time. Exposure assessment by location can be of great utility for ecological studies, or to evaluate exposure of residents of villages or hamlets. In a case–control study of soft-tissue sarcoma and non-Hodgkin's lymphoma among Vietnamese hospitalized in Ho Chi Minh City, Kramarova et al. (2002) have used residential locations of cases and controls as the basis for exposure calculations.

Our methods may also be of use for choosing sampling sites in future studies which gather environmental or biological samples in Vietnam. Recent surveys in Vietnam by Dwernychuk et al. (2002), Schecter et al. (2001), and others have shown persistently high levels of dioxin in soil, biota, and humans taken from areas known to have been very heavily sprayed or contaminated by spillage. In March 2002, the United States and the government of Vietnam entered into a collaborative agreement to undertake future epidemiological and ecological studies of the effects of wartime herbicide use in that country (Cyranoski, 2002). Given that decades have passed since the cessation of spraying, the extensive post-War population movement, and on-going land development, EOI methods may be the only practical exposure methodology available.

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