Dioxin Half-Life in Veterans of Operation Ranch Hand

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The Air Force is conducting a 20-year prospective study[1] of veterans of Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam from 1962 to 1971. A comparison group of Air Force veterans who served in Southeast Asia (SEA) during the same period who were not occupationally exposed to herbicides was selected. The study, called the Air Force Health Study (AFHS), now in its tenth year, is designed to determine whether exposure to the herbicides or their contaminant, 2,3,7,8 tetrachlorodibenzo-p-dioxin (dioxin), has adversely affected the health, survival or reproductive outcomes of Ranch Hands.

This report summarizes findings in an ongoing investigation of dioxin half-life and its possible relationship with percent body fat and disease in a subset of Ranch Hands with paired dioxin measurements.

Dioxin and other polychlorinated dibenzo-p-dioxins are lipophilic and are therefore found in body lipids. A person's percent body fat is therefore a suspected determinant of dioxin half-life in humans. We focus on the relationship between dioxin half-life and percent body fat (PBF) and changes in percent body fat in Ranch Hands. Additionally, we study the influence of major diseases in the intervening period between exposure and the serum dioxin assay.

From February through April 1987, the US Air Force collaborated with the Centers for Disease Control in a pilot study of dioxin concentrations in Air Force veterans participating in the AFHS[2]. Serum from 200 study subjects was assayed; 150 subjects were Ranch Hand veterans and 50 were Comparisons. Of the 150 Ranch Hands, 75 were selected for a half-life study[3] based on 1987 assay results and prior information about exposure. For each veteran, a 10cc serum sample had been collected in 1982 after an overnight fast and stored at -40 degrees Centigrade since 1982. Of the 75 veterans, 38 had dioxin levels in 1982 serum high enough to permit analytical quantification and had 1987 dioxin levels above 10 parts per trillion (ppt). We excluded two veterans whose 1982 dioxin levels were below 10 ppt, which left a final set of 36 paired results. Based on these data, Pirkle et al[3] estimated dioxin half-life as 7.1 years with a 95% confidence interval 5.8-9.6 years. Subsequently, an investigation of the effects of body fat on dioxin half life[4] based on these 36 paired dioxin levels and longitudinal weight and height data found a borderline significant association between half-life and percent body fat, with obese subjects having longer half-lives than lean subjects.

Subsequent to the pilot study, all 995 Ranch Hands who attended the 1987 AFHS physical examination were offered a serum dioxin assay. A total of 932 Ranch Hands were assayed during the period May 1987 through March 1988. Forty-seven of the pilot study subjects volunteered for a second assay at the physical examination. During 1990 and 1991 all remaining Ranch Hands whose 1987 dioxin level was above 10 ppt, and for whom frozen 1982 serum had been saved and had not already been assayed,

were selected for inclusion in this expanded half-life study. There were 499 Ranch Hands with 1987 dioxin levels above 10 ppt; of these, 337 also had a 1982 level above 10 ppt. These 337 are the subjects of this study. They include the 36 Ranch Hands of the first half-life study.

Weights (kg), heights (cm) and disease histories of the 337 Ranch Hands were collected and verified. Percent body fat was computed based on a linear function of the body mass index (weight divided by the square of height) using the method of Knapik et al[5]. Relative change in PBF was computed as the difference of the 1987 PBF and the 1982 PBF divided by the 1982 PBF. The effect of PBF, the relative change in PBF and disease on dioxin half-life was assessed with a repeated measures mixed-effects linear model derived from a first-order kinetics assumption[4]. Time is measured from the end of service in SEA to the date of collection of serum for the dioxin assay. With this approach, the logarithm of the dioxin concentration (in ppt) is modeled as a linear function of a subject effect, time, the covariates and the interactions of covariates with time. The significance of the effect of a covariate on half-life is revealed by the magnitude of the coefficient of the interaction term relative to its standard error. Background exposure was corrected for by subtracting 4 ppt before taking the logarithm[3].

Univariate statistics for the 1982 and 1987 concentrations and the logarithm of the corrected concentrations in the 337 Ranch Hands are shown in Table 1. Univariate statistics for PBF and the relative change in PBF are shown in Table 2.

Table 1

Univariate Summary of Dioxin Concentrations and the Logarithm of the Corrected Dioxin Concentrations in 337 Ranch Hands

	Dioxin Concentration		Logarithm of Corrected Dioxin Concentration	
Statistic	1982	1987	1982	1987
Minimum	11.5	10.2	2.0	1.8
Maximum	423.0	318.0	6.0	6.4
Median	40.8	31.9	3.6	3.3
Mean	63.7	53.1	3.7	3.4
SD	63.2	63.2	0.8	0.9

Table 2

Univariate Summary of Percent Body Fat and Relative Changes in Percent Body Fat in 337 Ranch Hands

	Percent Body Fat		
Statistic	1982	1987	Relative Change
Minimum	6.4	7.7	-0.4
Maximum	45.2	52.4	0.6
Median	21.0	21.8	0.06
Mean	21.4	22.7	0.06
SD	4.7	5.4	0.1

Because our analysis of half-life in the 36 Ranch Hands suggested that PBF influences dioxin half-life, we applied a repeated measures model with PBF entered as a linear term. This first model produced predicted half-lives much larger than would seem biologically plausible. Therefore, we considered models using other powers of PBF; a second model used PBF to the 1/2 power and a third model used PBF to the -1 power. The third model produced the most plausible range of predicted half-lives and all three models gave R^2 of 95%. The results of fitting the third model are summarized in Table 3.

Table 3

Repeated Mixed Effects Model Using the Reciprocal of PBF

Source	Coefficient	S.E.	P-value
Time	0.0358	0.0187	0.0563
PBF^{-1}	47.7989	7.1826	0.0001
$Time*PBF^{-1}$	-1.7461	0.3853	0.0001

Model-predicted half-lives were computed for each of the 337 subjects using the coefficients in Table 1 and individual dioxin levels, time and PBF. The median predicted half-life was 13.3 years and the 10th, 25th, 75th and 95th percentiles were 7.9, 9.9, 18.5 and 32.5 years.

Medical records of each of the 337 subjects were reviewed for certain diseases suspected to have some influence on half-life. A set of diseases was selected based on medical knowledge regarding associated weight loss or because the target organ of the disease was known from previous studies to be affected by dioxin exposure. The selected diseases were verified to have occurred after departure from SEA and before the second serum dioxin assay in 1987. The diseases were grouped into 8 categories named infection, cancer, goiter, diabetes, gout, copd (chronic obstructive pulmonary disease), ulcer, liver and renal. Limited space prevents a full listing of all diseases within each category. Infection includes pulmonary tuberculosis and malaria. Cancer includes all systemic cancers observed in these men. A full account of these diseases will be presented in the paper. Two hundred seventeen of the 337 subjects had diseases in at least one of these categories after service in SEA and before the 1987 dioxin assay.

Analyses of the effect of diseases on dioxin half-life are complicated by the fact that few of these disease categories occur in isolation. For example, 106 men had only diseases in the liver category, but all of the 8 men with cancer also had a disease in at least one other category. Some analyses were carried out based on prior knowledge. Diabetes, goiter and gout, because they are metabolically based, were expected to have some effect on dioxin half-life. After adjustment for PBF, the dioxin half-life among men with a history of these diseases ($n=58$) was significantly different ($p=0.04$) from the half-life in men without a history of diseases in any of the 8 categories ($n=120$). However, when copd was added to the required history ($n=78$), dioxin half-life was found to vary significantly with disease history ($p=0.0002$) and with PBF ($p=0.0001$).

References

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