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DIABETES MELLITUS AND 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN ELIMINATION IN VETERANS OF OPERATION RANCH HAND

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*Using multivariate statistical models, no significant relationship was found between the rate of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) elimination and the occurrence or time to onset of diabetes in 343 veterans of Operation Ranch Hand, the unit responsible for the aerial spraying of Agent Orange and other TCDD-contaminated herbicides during the Vietnam War. Without adjustment for age, body mass index, family history of diabetes, and smoking history, the time to onset of diabetes decreased and the risk of diabetes increased with a diminished elimination rate. However, after adjustment, diabetes time to onset and occurrence were not significantly associated with TCDD elimination. Analyses of covariance found no significant difference between the average elimination rates of diabetic and nondiabetic veterans, without or with adjustment for risk factors. To our knowledge, this is the only study to date to examine TCDD elimination and diabetes.*

An analysis of type 2 diabetes mellitus and exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in Air Force veterans of Operation Ranch Hand, the unit responsible for aerially spraying Agent Orange and other TCDD-contaminated herbicides in Vietnam, found an increased risk of diabetes in the subgroup with the highest serum TCDD levels (Henriksen et al., 1997). A recent review of the cumulative evidence in the scientific literature led the Institute of Medicine (IOM), National Academy of Sciences, to conclude that there was limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant TCDD and type 2 diabetes (Institute of Medicine, 2001). Exposure to TCDD is still ongoing from food (Guo et al., 2001; Schecter et al., 2001), and this is contributory to exposures that may have occurred during the war in Vietnam. The IOM interpretation included the limitation that chance, bias, and confounding could not be ruled out with confidence. The limited/suggestive interpretation has been applied to soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease,

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chloracne, and porphyria cutanea tarda in veterans, and spina bifida and acute myelogenous leukemia in the children of veterans (Institute of Medicine, 2001).

The interpretation of results from epidemiological studies of diabetes and TCDD exposure is complicated by interrelations between diabetes, TCDD uptake from food products, body fat, and the TCDD elimination rate (Institute of Medicine, 1996). In particular, some reviewers have hypothesized that the association between diabetes and TCDD concentration reflects an association between diabetes and the TCDD elimination rate. The idea is that individuals with slow elimination rates retain TCDD longer (have a long TCDD half-life) and are therefore at an increased risk for diabetes; those with a high elimination rate (and a short TCDD half-life) are at a decreased risk for diabetes. The results are confounded by body fat because the elimination rate is related to body fat (Michalek & Tripathi, 1999), with heavier veterans having a decreased rate and leaner veterans having an increased rate. The risk of diabetes rises with increased body fat in Ranch Hand veterans (Grubbs et al., 1995). The goal of these analyses was to study TCDD elimination and correlate findings with diabetes in Ranch Hand veterans.

METHODS

Data for these analyses were derived from a pharmacokinetic study of TCDD elimination in Ranch Hand veterans (Michalek & Tripathi, 1999). Three hundred and forty-three Ranch Hands in the pharmacokinetic study had up to four repeated TCDD measurements from blood collected during physical examinations in 1982, 1987, 1992 and 1997. Of these, 244 had four repeated measures from blood collected in all four years, 34 had three repeated measures from blood collected in 1982, 1987 and 1992, 39 had three repeated measures from blood collected in 1982, 1987, and 1997, and 26 had two repeated measures from blood collected in 1982 and 1987. Reasons for missing data include loss to follow-up, medical deferral, a broken blood bag, and death. One veteran had a TCDD result below the limit of detection (LOD) in 1992 and six had a result below the LOD in 1997.

The serum TCDD measurements were done with high-resolution gas chromatography/high resolution mass spectrometry (Patterson et al., 1987). The between assay coefficient of variation at three different concentrations of TCDD ranged from 9.4% to 15.5%. For those veterans whose serum TCDD level was below the LOD, a level equal to the detection limit divided by the square root of 2 was assigned (Hornung & Reed, 1990). TCDD results were expressed in parts per trillion (ppt) on a lipid weight basis.

The elimination rate for a subject was estimated with a linear model motivated by a first-order kinetics assumption,

$$C_i(t) = C_{0i}e^{-\lambda t} \quad (1)$$

where, for subject i, $C_i(t)$ is the TCDD concentration t years after exposure, C_{0i} is the initial concentration, and λ is a constant but unknown elimination rate. Under this first-order model (1), the half-life is given by $\ln(2)/\lambda$, where ln is the natural logarithm. Time was measured from the end of service in Vietnam to the date serum was collected for the TCDD assay.

Motivated by a logarithmic transformation of Eq. (1), the logarithm of TCDD concentration was modeled as a linear function of time. For subject i, $i=1, 2, \ldots, n$, let $j=1, 2, 3, 4$ index the years 1982, 1987, 1992, and 1997; let t_{ij} denote the time in years between the end of service in Vietnam and the measurement in year j; and $C_i(t_{ij})$ be the TCDD concentration in year j, and $y_{ij}=\ln[C_i(t_{ij})]$. The assumed model for y_{ij} was

$$y_{ij} = \mu + \tau_i + \beta t_{ij} + \varepsilon_{ij} \tag{2}$$

where μ is the intercept, τ_i is the effect of subject i, and ε_{ij} is normally distributed with mean 0 and variance σ^2. In Eq. (2), the elimination rate λ is $-\beta$.

The method of weighted least squares (WLS) was used to estimate parameters. The WLS estimates of the parameters in Eq. (2) depended on the within-subject autocorrelation structure of the joint distribution of y_{i1}, y_{i2}, y_{i3}, and y_{i4}, assumed multivariate normally distributed with covariance matrix Σ having elements σ_{jk}. We considered autoregressive of order 1 [AR(1)] and Toeplitz covariance models. Under the AR(1) model $\sigma_{jk}=\sigma^2\rho^{|j-k|}$, and under the Toeplitz model $\sigma_{jk}=\sigma^2\rho_{|j-k|}$, where $\sigma>0$, $-1\le\rho\le1$, ρ_1, ρ_2, and ρ_3 ($-1\le\rho_j\le1$, $j=1, 2, 3$) are parameters. For each of these assumptions, the WLS estimate of the elimination rate could be written as an average of subject-specific elimination rate estimates, and the estimated rate for subject i could be written as a weighted sum of slopes in log units.

For example, in the special case that there are 4 repeated measurements per subject, let $\Delta_{ijk}=t_{ik}-t_{ij}$ and, $\hat{\lambda}_{ijk}=(y_{ij}-y_{ik})/\Delta_{ijk}$, for $(j,k)=(1,2)$, $(1,3)$, $(1,4)$, $(2,3)$, $(2,4)$, and $(3,4)$. Then under the AR(1) or Toeplitz autocorrelation models, the WLS estimate of elimination rate for subject i can be written in the form

$$\hat{\lambda}_i = w_{i12}\hat{\lambda}_{i12} + w_{i13}\hat{\lambda}_{i13} + w_{i14}\hat{\lambda}_{i14} + w_{i23}\hat{\lambda}_{i23} + w_{i24}\hat{\lambda}_{i24} + w_{i34}\hat{\lambda}_{i34} \tag{3}$$

where $(j,k)=(1,2)$, $(1,3)$, $(1,4)$, $(2,3)$, $(2,4)$, and $(3,4)$, and

$$w_{ijk} = \omega_{jk}\Delta_{ijk}^2/D \tag{4}$$

$$D = \frac{1}{n}\sum_{i=1}^{n}(\omega_{12}\Delta_{i12}^2 + \omega_{13}\Delta_{i13}^2 + \omega_{14}\Delta_{i14}^2 + \omega_{23}\Delta_{i23}^2 + \omega_{24}\Delta_{i24}^2 + \omega_{34}\Delta_{i34}^2) \tag{5}$$

Under the AR(1) model,

$$\omega_{12} = 1 + 2\rho - \rho^2$$
$$\omega_{13} = (1 - \rho)^2$$
$$\omega_{14} = 1 - \rho$$
$$\omega_{23} = 1 + \rho + \rho^2 - \rho^3$$
$$\omega_{24} = (1 - \rho)^2$$
$$\omega_{34} = 1 + 2\rho - \rho^2$$

and under the Toeplitz model,

$$\omega_{12} = \rho_1 - \rho_3 + 2\rho_1\rho_3 - 2\rho_2 + \rho_2^2 - 2\rho_1^2 + \rho_1\rho_2 - \rho_2\rho_3 + 1$$
$$\omega_{13} = (1 - \rho_2)(3\rho_2 - 3\rho_1 - \rho_3 + 1)$$
$$\omega_{14} = -2\rho_1\rho_3 - 2\rho_2 - 2\rho_1 + 2\rho_1^2 + 2\rho_3 + \rho_2^2 + 1$$
$$\omega_{23} = 2\rho_2\rho_3 - 2\rho_1\rho_2 - 2\rho_2 + \rho_1^2 + \rho_2^2 - \rho_3^2 + 1$$
$$\omega_{24} = (1 - \rho_2)(3\rho_2 - 3\rho_1 - \rho_3 + 1)$$
$$\omega_{34} = \rho_1 - \rho_3 + 2\rho_1\rho_3 - 2\rho_2 + \rho_2^2 - 2\rho_1^2 + \rho_1\rho_2 - \rho_2\rho_3 + 1$$

Corresponding expressions for the case where there are two measurements and the case where there are three measurements per subject are similar.

The AR(1) and Toeplitz models were considered because they can accommodate decreasing pair-wise correlations as the time between measurements increases. Both models have the advantage that the corresponding estimates of the individual elimination rates account for all pair-wise slopes in the log scale through a weighted sum of slopes for Eq. (3).

SAS PROC MIXED (SAS Institute, Inc., Carey, NC) was applied to estimate autocorrelations, and individual elimination rates were estimated using Eqs. (3), (4), and (5) under the AR(1) and Toeplitz models among the 343 Ranch Hand veterans with repeated TCDD measurements.

Diabetes mellitus cases included for analysis were diagnosed during the post-Vietnam period from the end of the veteran's last tour of duty to 31 December 2000. Each case was verified from medical records and may represent a diagnosis at any of the five physical examinations. Medical records and laboratory results were reviewed to determine diabetic status and time to diabetes onset. Veterans who had a verified history of diabetes by medical diagnosis or exhibited a 2-h postprandial glucose laboratory value of 200 mg/dl or greater were classified as diabetic. Veterans not meeting these criteria were defined as nondiabetic.

Body mass index (BMI) was defined as weight (kg) divided by the square of height (m) and was computed from height and weight measured at the end of the tour of duty in Vietnam and at the 1982 Air Force Health Study physical examination. The change in BMI from tour to 1982 was defined as the BMI in 1982 minus the BMI at tour, the relative change as the change divided by the BMI at tour, and the percent change in BMI as the relative change multiplied by 100. Family history of diabetes in first-order relatives (father, mother, or sibling) was elicited during an in-person interview at each physical examination. A pack-year was defined as smoking one pack of cigarettes per day for 1 yr.

The relation between the occurrence of diabetes mellitus and the TCDD elimination rate (λ) was assessed with proportional hazards models, logistic regression models, and analyses of covariance. All three models were adjusted for age at the first Air Force Health Study physical examination in 1982, the logarithm of the TCDD body burden in 1982, family history of diabetes in first-order relatives (yes, no), BMI at the end of the tour of duty in Vietnam (BMI at tour), the percent change in BMI from the end of service in Vietnam to 1982 (BMI percent change), and smoking history (pack-years) (Manson et al., 2000). In the first of these analyses, the dependent variable was time to onset, or (disease-free) survival time. For diabetics, time to onset was defined as the number of years from the end of the first tour of duty in Vietnam to the first diagnosis of diabetes. For nondiabetics, time to onset was defined as the number of years from the end of the first tour of duty in Vietnam to the date of the last physical examination attended. In the second analysis, the dependent variable was binary, indicating the presence or absence of diabetes, and in the third analysis, the dependent variable was the elimination rate and the independent variables were a binary diabetes indicator and covariates. In each series, an unadjusted model was fit, followed by a sequence of adjusted main effects models corresponding to covariates being added one by one. Only the last (fully adjusted) main effects models are shown. Finally, all main effects and second-order interactions with λ were added in the proportional hazards and logistic models. In the analyses of covariance, second-order interactions with diabetes were entered. The elimination rate (λ) was multiplied by 100 in all models. One veteran with diabetes diagnosed prior to service in Vietnam was excluded from all statistical analyses. Analyses of diabetes prevalence versus extremely high (greater than the 95th percentile) and extremely low (less than the 5th percentile) elimination rates were carried out with Pearson's chi-square. The entire series of analyses was conducted twice, once using the AR(1) and again using the Teoplitz model to estimate λ. The results from the AR(1) estimation are tabulated and discussed. The Toeplitz results are briefly summarized in the text.

RESULTS

Demographics and TCDD are summarized in Table 1. Ninety-two (26.8%) of the 343 were diabetic and 125 (36.4%) had a family history of diabetes. Of those with diabetes, 48 (52.2%) had a family history of diabetes.

TABLE 1. Demographic Characteristics and TCDD Summary

	Diabetes		
Outcome	No	Yes	Total
Number	251	92	343
Mean elimination rate (SEM)	0.0866 (0.0028)	0.0763 (0.0054)	0.0838 (0.0025)
Family history (%)	77 (30.7)	48 (52.2)	125 (36.4)
Median TCDD in 1982 (range)[a]	40.3 (12.5–401.9)	41.7 (11.5–422.7)	40.8 (11.5–422.7)
Mean age in 1982 (SEM)	40.9 (0.45)	45.4 (0.77)	42.1 (0.40)
Mean BMI at tour (SEM)	24.7 (0.18)	26.9 (0.34)	25.3 (0.17)
Mean BMI in 1982 (SEM)	26.8 (0.20)	29.5 (0.44)	27.5 (0.20)
Mean BMI percent change (SEM)	9.1 (0.70)	10.3 (1.54)	9.4 (0.66)
Median pack-years (range)	9.0 (0.0–107.5)	13.0 (0.0–172.0)	10.5 (0.0–172.0)

[a] In parts per trillion.

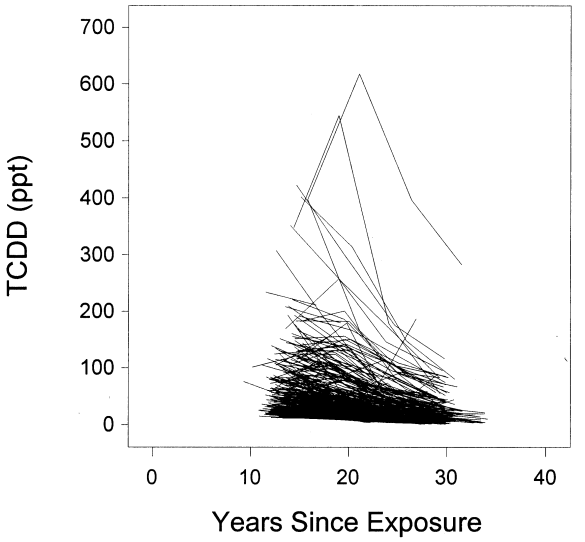

FIGURE 1. TCDD levels versus years from end of tour of service in Vietnam in 343 Ranch Hand veterans.

TCDD levels in original units versus years from the end of tour of duty in Vietnam to the date of the serum collection for the TCDD measurement are plotted in Figure 1. The minimum time from service in Vietnam to the first TCDD measurement in 1982 was 9.3 yr and the maximum time to the last measurement in 1997 was 34.1 yr.

TCDD levels in log units versus years from the end of tour of duty in Vietnam are plotted in Figure 2.

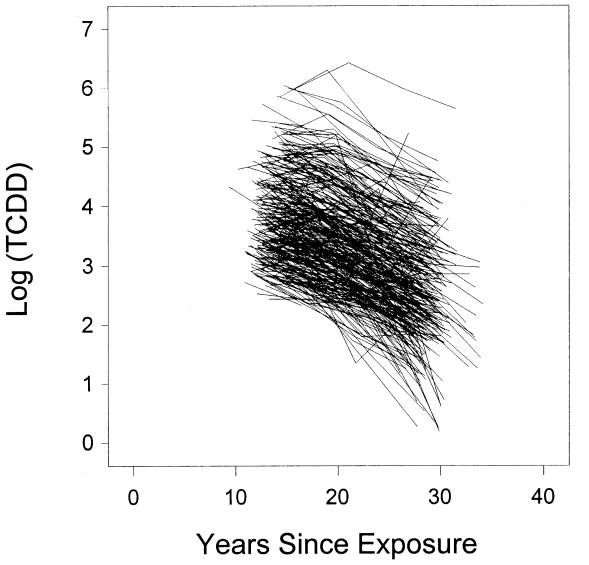

FIGURE 2. TCDD levels in log units versus years from end of tour of service in Vietnam in 343 Ranch Hand veterans.

TABLE 2. Proportional Hazards Models of the Time to Onset of Diabetes and the TCDD Elimination Rate (λ)

Source	Coefficient	SE	*p*
Unadjusted			
λ	–0.0601	0.02518	.02
Main effects			
λ	–0.01907	0.02835	.5
TCDD in 1982[a]	0.28916	0.13704	.03
Age in 1982	0.07389	0.01636	<.001
Family history of diabetes	0.38992	0.21972	.08
BMI at tour	0.21093	0.03708	<.001
BMI percent change	0.03025	0.00969	.002
Smoking history	0.00521	0.00358	.15
Interactions			
λ × TCDD[a]	2.35231	4.00153	.56
λ × Age	–0.58637	0.34813	.09
λ × Family history	0.06901	0.05244	.19
λ × BMI at tour	–0.12646	0.93082	.89
λ × BMI percent change	–0.11895	0.20776	.57
λ × Smoking history	0.01664	0.12781	.90

[a] Lipid-adjusted TCDD, in log units.

The results of analyses of time to onset of diabetes and the TCDD elimination rate are summarized in Table 2. The analyses of diabetes prevalence are summarized in Table 3, and the analyses of covariance are summarized in Table 4.

TABLE 3. Logistic Models of Diabetes Prevalence and the TCDD Elimination Rate (λ)

Source	Coefficient	SE	*p*
Unadjusted			
Intercept	–0.61879	0.25019	.01
λ	–0.04857	0.02754	.08
Main effects			
Intercept	–14.43525	2.12862	<.001
λ	0.01082	0.03222	.74
TCDD in 1982[a]	0.26778	0.19275	.16
Age in 1982	0.08880	0.02098	<.001
Family history of diabetes	0.77695	0.28285	.006
BMI at tour	0.29318	0.05456	<.001
BMI percent change	0.04810	0.0133	<.001
Smoking history	0.00578	0.00528	.27
Interactions			
λ × TCDD[a]	3.92058	4.84956	.42
λ × Age	–0.49314	0.3699	.18
λ × Family history	0.09316	0.06288	.14
λ × BMI at tour	0.44973	1.23813	.72
λ × BMI percent change	–0.21651	0.24968	.39
λ × Smoking history	0.06078	0.15066	.69

[a] Lipid-adjusted TCDD, in log units.

TABLE 4. Analysis of Covariance Models of the TCDD Elimination Rate (λ) and Diabetes Prevalence

Source	Coefficient	SE	*p*
Unadjusted			
Intercept	8.6572	0.29183	<.001
Diabetes	–1.00571	0.56574	.08
Main effects			
Intercept	21.38718	2.95509	<.001
Diabetes	0.27285	0.59639	.65
TCDD in 1982[a]	0.70790	0.33432	.03
Age in 1982	–0.07848	0.03585	.03
Family history of diabetes	0.72978	0.50337	.15
BMI at tour	–0.47876	0.08691	<.001
BMI percent change	–0.09385	0.02142	<.001
Smoking history	0.01152	0.00965	.23
Interactions			
Diabetes × TCDD[a]	0.05224	0.66694	.94
Diabetes × Age	–0.08105	0.07416	.27
Diabetes × Family history	1.06890	1.10322	.33
Diabetes × BMI at tour	0.04631	0.17214	.79
Diabetes × BMI change	–0.00298	0.03963	.94
Diabetes × Smoking history	0.00760	0.01949	.70

[a] Lipid-adjusted TCDD, in log units.

The hypothesis of interest predicts a negative coefficient of λ in the proportional hazards and logistic models, indicating a decreased time to onset and increased prevalence with a decreased elimination rate (or increased TCDD half-life). In the analyses of covariance, a negative coefficient of the diabetes indicator is predicted, with diabetics having a decreased average elimination rate relative to nondiabetics.

Without adjustment for covariates (Table 2), the time to onset of diabetes was significantly decreased with decreased values of λ ($p=.02$). After adjustment for covariates (Table 2), time to onset of diabetes and λ were not significantly related. No significant relation between diabetes prevalence and the elimination rate was found without or with adjustment for covariates (Table 3). No significant difference in the mean elimination rate between diabetic and nondiabetic Ranch Hand veterans was found without or with adjustment for covariates (Table 4).

In the analysis of diabetes time to onset (Table 2), the λ×age interaction was borderline significant ($p=0.09$). To describe the interaction, age was stratified at the median to "young" (less than 40.5 yr of age in 1982) and "old" (at least 40.5 yr of age in 1982). With this dichotomization, 172 Ranch Hands were classified as young (and 30, or 17.4%, of these were diabetic) and 170 were classified as old (and 61, or 35.9%, of these were diabetic). Separate proportional hazards models, adjusted for TCDD, family history, BMI at tour, BMI change, and smoking history, were fit within each stratum to assess the relation between the elimination rate and time to diabetes onset. Among young veterans, the coefficient of the TCDD elimination rate (λ) was 0.03846 (SE=0.06254) and among old veterans the coefficient was −0.03125 (SE= 0.03481), and neither of these coefficients was significantly different from zero ($p=.54$ and $p=.37$, respectively). Interactions with age were not evident in the logistic regression or covariance analyses (Tables 3 and 4).

The extremes of the distribution of the elimination rate were investigated with regard to diabetes prevalence by stratifying at the 5th and 95th percentiles. Veterans with TCDD elimination rates less than or equal to the 5th percentile were classified as having a low rate and those with elimination rates greater than or equal to the 95th percentile were classified as having a high rate. The 5th and 95th percentiles of the elimination rate distribution were 0.01537 per year and 0.16675 per year. Counts and percentages of diabetic veterans in each stratum are given in Table 5. There was no significant association between

TABLE 5. Number and Percentage of Veterans with Diabetes by TCDD Elimination Rate Stratum

TCDD elimination rate stratum	*n*	Diabetic (%)	*p*
λ ≤ 5th percentile	17	6 (35.3)	.41
λ > 5th percentile	325	85 (26.2)	
λ > 95th percentile	20	6 (30.0)	.72
λ ≤ 95th percentile	322	85 (26.4)	

diabetes prevalence and extremely low ($p = .41$) or high ($p = .72$) elimination rates without adjustment for covariates (Table 5).

The results were not sensitive to the autocovariance assumption, the method of accommodating TCDD results less than the LOD, background correction, or dietary patterns. Regression coefficients and their standard errors were similar under the autoregressive order one and Toeplitz models. The correlation between the AR(1) and Teoplitz estimates of λ was .998. Adding 1 before taking the logarithm, instead of replacing TCDD levels less than the LOD with $\text{LOD}/\sqrt{2}$, gave similar results. Background correction (Michalek & Tripathi, 1999) was not used because background levels have been declining (Jackson & Michalek, 2001); in comparison veterans, the mean TCDD level declined from 4.5 ppt in 1987 to 2.0 ppt in 1997. Coefficients and standard errors were similar after correcting for a background mean of 4.5 ppt or 2 ppt. The results did not change appreciably after additional adjustment for 9 food groups, in terms of fat and cholesterol intake, reported in a 126-item food frequency questionnaire administered at the 1992 physical examination (Guo et al., 2001).

DISCUSSION

Using multivariate statistical models, no significant relationship was found between the rate of TCDD elimination and the occurrence or time to onset of diabetes in 343 veterans of Operation Ranch Hand with repeated TCDD measurements. Without adjustment for age, BMI, and family history, the expected negative coefficient in the proportional hazards model relating the elimination rate and time to onset of diabetes was observed, suggesting an increased risk with a decreased elimination rate. However, after adjustment, the coefficient was not significantly different from zero. Analyses of covariance found no significant difference between the average elimination rates of diabetic and nondiabetic veterans, without or with adjustment for risk factors. To our knowledge, this is the only study of TCDD elimination and diabetes.

The study is limited by TCDD measurements made between 9 and 34 yr after exposure in Vietnam. These data cannot be extended to earlier time periods because serum was not saved prior to 1982. The possibility exists that adjustment for other factors unknown to us would alter the results. Finally, although all available data have been used, these results do not establish that the elimination rate is unrelated to diabetes, but only that it was not possible to detect a relationship.

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