American Journal of Industrial Medicine 25:559–571 (1994)

Evaluation of Porphyria Cutanea Tarda in U.S. Workers Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin

Geoffrey M. Calvert, MD, MPH, Marie Haring Sweeney, PhD, Marilyn A. Fingerhut, PhD, Richard W. Hornung, Dr PH, and William E. Halperin, MD, MPH

A cross-sectional medical study was performed to evaluate whether occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-contaminated substances is associated with porphyria cutanea tarda or porphyrinuria. The exposed participants were employed more than 15 years earlier in the manufacture of sodium trichlorophenol and its derivatives. The referent group consisted of individuals with no occupational exposure to phenoxy herbicides. A total of 281 workers and 260 referents participated. The pattern of urinary porphyrin excretion for each participant was assessed to determine if symptomatic or subclinical porphyria cutanea tarda was present. None of the participants were found to have symptomatic porphyria cutanea tarda. No difference was found between workers and referents in the prevalence of subclinical porphyria cutanea tarda (odds ratio [OR] = 0.93, 95% confidence interval [CI] 0.19, 4.54). There were also no differences in the risk between workers and referents for an out-of-range urinary uroporphyrin or coproporphyrin concentration. In conclusion, this study did not find an elevated risk for porphyria cutanea tarda or porphyrinuria among workers with high serum TCDD levels. Our review of the literature indicates that there is insufficient evidence available to convincingly support or refute an association in humans between TCDD exposure and porphyria cutanea tarda or porphyrinuria. © 1994 Wiley-Liss, Inc.*

Key words: tetrachlorodibenzodioxin, dioxins, uroporphyrins, coproporphyrins, occupational exposures

INTRODUCTION

Porphyria cutanea tarda, also known as chronic hepatic porphyria, is a disorder characterized by cutaneous photosensitivity and an increase in the urinary excretion of porphyrins. Symptomatic porphyria cutanea tarda is caused by a reduction in the activity of uroporphyrinogen decarboxylase (UD). Subclinical forms of this condition in which there is uroporphyrinuria and/or coproporphyrinuria but no cutaneous symptoms can also occur (porphyria cutanea tarda Types A-C) (Table I). These subclinical

Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
Address reprint requests to Geoffrey M. Calvert, MD, MPH, NIOSH, 4676 Columbia Parkway, R-16, Cincinnati, OH 45226.
Accepted for publication April 29, 1993.

TABLE I. Urinary Porphyrin Chromatographic Patterns for PCT*

PCT	c/u (%)	c (%)	u (%)	7 (%)	u+7 (%)	Components[a]	Total porphyrins (μg/gm creatinine)	Cutaneous symptoms[a]
Normal	2–6	>70	<20	<5	<25	c>>u>>>7,6,5	0–200	—
Type A	>1	>60	<30	5–15	30–50	c>u>7>5>6	0–600	—
Type B	<1	<40	30–50	15–20	45–70	u>c>7>5>6	200–600	—
Type C	<<1	>10	>50	20–30	60–80	u>7>c>5>6	400–1,400	−/+
Type D (symptomatic)	<<<1	>10	>60	25–35	65–90	u>>7>>>c>5>6	600–1,500	+

*Adapted from Strik et al., 1980, with permission of the publisher.
[a]Cutaneous symptoms include photoenhanced mechanical fragility, vesicles/bullae, hypertrichosis, and hyperpigmentation (— = no symptoms; −/+ = symptoms may be present; + = symptoms must be present). PCT = porphyria cutanea tarda; u = uroporphyrin; c = coproporphyrin; 7 = heptacarboxyporphyrin; 6 = hexacarboxyporphyrin; 5 = pentacarboxyporphyrin.

types of porphyria cutanea tarda either are associated with a reduction in the activity of UD or can occur with some medical conditions (e.g., liver disease, medical conditions associated with increased hematopoiesis).

Porphyria cutanea tarda can be precipitated by several different environmental, occupational, and lifestyle exposures, including alcohol [Sweeney, 1986], estrogens [Sweeney, 1986], hexachlorobenzene [Cam and Nigogosyan, 1963], and polychlorinated biphenyls (PCB) [Lynch et al., 1975]. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been found to cause hepatic porphyria in rodents [Goldstein et al., 1973, 1982], and several case reports have described porphyria cutanea tarda among TCDD-exposed individuals [Bleiberg et al., 1964; Pazderova-Vejlupkova et al., 1981; Hope et al., 1984; Doss et al., 1984]. However, some investigators question the association between porphyria cutanea tarda and TCDD exposure in humans, and speculate that hexachlorobenzene may have been responsible for some of the observed cases of porphyria cutanea tarda [Jones and Chelsky, 1986]. In addition, Hoffman et al. [1986] reported elevated uroporphyrin levels among individuals who lived in a mobile home park sprayed with TCDD-contaminated waste oil, and Poland et al. [1971] reported a significant elevation in mean coproporphyrin concentration (although the mean was within the clinically normal range) in a group of workers thought to have high TCDD levels. To evaluate the effect of occupational TCDD exposure on porphyria cutanea tarda, uroporphyrinuria, and coproporphyrinuria, we compared living individuals (workers) formerly employed in the production of TCDD-contaminated substances, with an unexposed reference group.

METHODS

The National Institute for Occupational Safety and Health (NIOSH) Dioxin Morbidity Study was a cross-sectional medical study undertaken to examine the long-term health effects of occupational exposure to chemicals and materials contaminated with TCDD. The details of the study design were previously described [Sweeney et al., 1989]. In summary, this study compared living individuals (workers) employed more than 15 years earlier in the production of sodium trichlorophenol (NaTCP), 2,4,5-trichlorophenoxyacetic ester (2,4,5-T ester), or hexachlorophene, all

of which were substances contaminated with TCDD, with an unexposed comparison group. The workers were employed in one of two plants located in Newark, New Jersey and Verona, Missouri. Four hundred ninety (490) workers were employed at the New Jersey facility from 1951 through 1969 in the production of NaTCP, 2,4,5-T ester, and other chemicals. Hexachlorobenzene was also produced at the New Jersey facility from 1951 until 1960. At the facility in Verona, Missouri, 96 individuals were involved in the production of NaTCP, 2,4,5-T ester, or hexachlorophene. Production of NaTCP and 2,4,5-T ester occurred for approximately 4 months in 1968 and production of NaTCP and hexachlorophene occurred from April 1970 to January 1972. Both plants produced a variety of other chemicals. To constitute the referent (comparison) group, one individual with no self-reported occupational exposure to TCDD-contaminated substances was sought from within the neighborhood of each worker, who matched the worker by age (within 5 years), race, and gender. The study protocol was approved by the NIOSH Human Subjects Review Board and informed consent was obtained from each of the participants.

Information on worker and referent health status was collected through a comprehensive set of standardized interviews and medical examinations (including a dermatologic examination). A lifetime medical history was elicited from each participant using interviewer-administered questionnaires. In addition to questions regarding potential confounders, all participants were asked, "Did a doctor ever tell you that you had porphyria?" and "If yes, what year?" All participants were also asked, "Was there ever a time when your skin blistered after exposure to the sun, and, at the same time, you had dark reddish urine?" To reduce observer bias, all individuals conducting the medical histories, examinations, and tests were blind to the exposure status (worker or referent) of the participant. An interviewer-administered lifetime occupational history was elicited from each participant separate from the medical history. Duration of each job, and duration of occupational exposure to specific substances were recorded beginning with the participant's 16th birthday.

Twelve-hour urine collections were obtained from the participants and analyzed for creatinine, total porphyrin, uroporphyrin, coproporphyrin, heptacarboxyporphyrin, hexacarboxyporphyrin, and pentacarboxyporphyrin. The quantitative urinary porphyrin measurements were made by the Lovelace Medical Center, Albuquerque, New Mexico, using high-performance liquid chromatography [Hill et al., 1982]. Because the first morning urine specimen has been found to provide the same quantitative porphyrin findings as a 24-hour urine specimen [Hill et al., 1982; With, 1980], we have no reason to suspect that the findings from our 12-hour collection, which included the first morning urine, would differ from a 24-hour collection. Blood was also obtained from the participants and analyzed for TCDD by the National Center for Environmental Health and Injury Control, Centers for Disease Control and Prevention, using methods previously described [Patterson et al., 1989]. Two participants (one worker and one referent) did not have their blood drawn.

Currently there is no consensus on the appropriate classification scheme for porphyria cutanea tarda. Some classification schemes are based on severity [Strik et al., 1980] and others are based on the site of inhibition of uroporphyrin decarboxylase (erythrocyte and/or hepatocyte) [Anderson, 1992]. We used criteria adapted from Strik et al. [1980] (Table I), to determine if the pattern of urinary porphyrin excretion reflected the presence of porphyria cutanea tarda. Because uroporphyrin decarboxy-

lase levels were not measured, we could not use the porphyria classification scheme proposed by Anderson [1992].

The reference values used to define the normal range for uroporphyrin and coproporphyrin were calculated using the results from the control group. The reference values were defined as the 95th percentile for the control group. The uroporphyrin level or coproporphyrin level was considered to be out-of-range if it exceeded the reference value. The reference values for uroporphyrin and coproporphyrin were 23.5 μg/gm creatinine and 67.5 μg/gm creatinine, respectively.

Analysis of Data

Unadjusted odds ratios (OR) were calculated for the categorical outcomes of interest and tested for significance using a chi-square test for association. For continuous outcomes, means for workers and referents were compared using Student's t-tests.

Although we intended to perform regression analyses on all three of the a priori hypotheses (association between TCDD exposure and porphyria cutanea tarda, uroporphyrinuria, and coproporphyrinuria), there were too few cases of porphyria cutanea tarda to warrant such an analysis. To assess the uroporphyrinuria and coproporphyrinuria hypotheses, while simultaneously controlling for several potential confounders and effect modifiers, logistic regression analyses were performed. Multiple linear regression was also used to assess the association between TCDD exposure and coproporphyrin level while controlling for potential confounders. Because the uroporphyrin data departed greatly from the assumption of normal distribution (the uroporphyrin value for more than 50% of the participants was 0), multiple linear regression analyses were not performed with these data. The potential confounders evaluated in the regression analyses were: pack-years (average number of cigarettes smoked per day multiplied by the number of years cigarettes were smoked), current cigarette smoker (smoked within the past year), former cigarette smoker (denied smoking within the past year), alcohol-years (average number of alcoholic drinks consumed per day multiplied by the number of years alcohol was consumed), current drinker (drank alcohol within the past year), former drinker (denied drinking alcohol within the past year), location of TCDD exposure (New Jersey or Missouri plant), age, gender, race, use within the previous 2 weeks of medications known to affect porphyrins, self-reported history of hexachlorobenzene exposure, and self-reported history of PCB exposure. Confounding was assessed in the regression models by comparing the amount of change in the coefficient of the exposure variable when the potential confounder was included vs. when it was excluded from the model. Potential confounders that were retained in the final model were those that either were found to be statistically significant for the outcome or those that created a meaningful difference in the coefficient of the exposure variable.

The effect of exposure to TCDD-contaminated materials was assessed using each of three exposure indices in separate models: status as a worker or a referent (a dichotomous exposure variable), serum lipid-adjusted TCDD levels measured at the time of the examination, and halflife-extrapolated TCDD levels. The halflife-extrapolated TCDD level is the estimated TCDD level when occupational TCDD exposure ceased and was calculated, as was described previously [Sweeney, 1990], to reflect the 7-year estimated halflife of the serum TCDD level [Pirkle et al., 1989]. To aid in the interpretation of the dose-response data, we stratified workers into quartiles of

approximately equal size based on serum TCDD levels. Workers in the lowest quartile had serum TCDD levels less than 20 pg/gm of lipid, thereby making them roughly equivalent to the referents since all of the referents had serum TCDD levels less than 20 pg/gm of lipid. The remaining three quartiles consisted of workers with serum dioxin levels of 20–75 pg/gm of lipid, 76–237 pg/gm of lipid, and 238 pg/gm of lipid to 3,389 pg/gm of lipid. Eight workers and one referent were excluded from the dose-response analyses because serum TCDD levels were not obtained. All analyses were carried out using SAS procedures (SAS Institute, Cary, North Carolina).

RESULTS

Study Population

Descriptive information on the study cohort has been previously reported [Sweeney, 1990; Calvert et al., 1991]. A total of 281 workers and 260 referents were examined. Workers were found to have a statistically significantly elevated mean serum TCDD level (workers = 220 pg/gm of lipid, referents = 7 pg/gm of lipid, $p < 0.001$). The mean halflife-extrapolated serum TCDD level was also statistically significantly elevated among workers (workers = 1,900 pg/gm of lipid, referents = 6 pg/gm of lipid, $p < 0.001$). Referents were found to have a statistically significantly higher mean lifetime alcohol consumption (workers = 41.4 alcohol-years, referents = 62.1 alcohol-years, $p = 0.011$), which was attributed to seven referents with extremely high alcohol-year values (range: 520–719 alcohol-years). Because exclusion of these seven individuals did not change the analytic results, the analytic results that we present include these seven referents. There were no other statistically significant differences or consistent pattern of differences between workers and referents for any other demographic characteristics (age, race, gender, education, income).

Porphyria Cutanea Tarda

Based on the Strik et al. [1980] classification scheme (Table I), only three (1.1%) workers and three (1.2%) referents were found to have an abnormal urinary porphyrin pattern consistent with subclinical types of porphyria cutanea tarda (OR = 0.93, 95% confidence interval [CI] 0.19,4.54). None of the participants had clinical or laboratory findings consistent with symptomatic porphyria cutanea tarda (Type D). Four participants were determined to have porphyria cutanea tarda Type B, one had porphyria cutanea tarda Type A, and one had an unclassifiable porphyria pattern (Table II). None of these six individuals reported that a physician had ever diagnosed them with porphyria and all denied ever having sun blistered skin accompanied with red urine. All of the remaining participants in our study had a normal porphyrin pattern at the time of the examination, none reported a history of physician-diagnosed porphyria, and all denied ever having sun blistered skin accompanied with red urine.

Porphyrin Measurements in Workers and Referents

There were no statistically significant differences between workers and referents with regard to urinary uroporphyrin or urinary coproporphyrin (Tables III, IV). Only four participants had detectable levels of the other carboxyporphyrins (Table II).

In logistic regression models, the risk for an out-of-range uroporphyrin level was not significantly associated with any measure of TCDD exposure, including serum TCDD level ($p = 0.43$), halflife-extrapolated TCDD level ($p = 0.38$), or

TABLE II. Profiles From Participants With Abnormal Urinary Porphyrin Chromatographic Patterns*

Exposure status[a]	Total porphyrin[b]	URO[b]	COP[b]	HEP[b]	HEX[b]	PEN[b]	COP/URO	%URO	%COP	%HEP	%URO + HEP	Pattern classification
Worker A	208	147	61	ND	ND	ND	0.41	70.7	29.3	0	70.7	Type B
Worker B	562	422	49	40	38	13	0.12	75.1	8.7	7.1	82.2	Type B
Worker C	56	11	34	11	ND	ND	3.00	19.6	60.7	19.6	39.3	Type A
Referent A	383	99	57	ND	ND	227	0.58	25.8	14.9	0	25.8	Unclear
Referent B	326	222	62	25	5	12	0.28	68.1	19.0	7.7	75.8	Type B
Referent C	132	90	42	ND	ND	ND	0.68	68.2	31.8	0	68.2	Type B

*URO = uroporphyrin; COP = coproporphyrin; HEP = heptacarboxyporphyrin; HEX = hexacarboxyporphyrin; PEN = pentacarboxyporphyrin; ND = not detected (limit of detection = 5–10 μg/liter).
[a]The serum TCDD levels for each of these participants: Worker A = 1,947 pg/gm of lipid; Worker B = 148 pg/gm of lipid; Worker C = 10 pg/gm of lipid; Referent A = 6 pg/gm of lipid; Referent B = 6 pg/gm of lipid; Referent C = 6 pg/gm of lipid.
[b]μg/g of creatinine.

TABLE III. Mean Uroporphyrin and Coproporphyrin Levels for Workers Exposed to TCDD and Referents

	Worker		Referent		
Laboratory test	N	Mean[a] (SD)	N	Mean[a] (SD)	p value[b]
Uroporphyrin, μg/gm of creatinine[c]	281	6.9 (27.3)	260	6.4 (17.3)	0.80
Coproporphyrin, μg/gm of creatinine[d]	281	37.1 (19.1)	260	35.3 (16.7)	0.23

[a]μg/gm of creatinine.
[b]Based on Student's t-test.
[c]The high standard deviations (SDs) for uroporphyrin were due to one worker and one referent with uroporphyrin levels of 422 μg/gm of creatinine and 222 μg/gm of creatinine, respectively. After removal of the these two individuals, the SDs were lower and essentially the same (workers = 11.2, referents = 10.9), and the means between workers and referents were not significantly different (workers = 5.4 μg/gm of creatinine, referents = 5.6 μg/gm of creatinine, p = 0.88).
[d]When a natural log transformation was applied to the coproporphyrin values to approximate a normal distribution, the means between workers and referents were not significantly different (workers = 3.5 μg/gm of creatinine, referents = 3.5 μg/gm of creatinine, p = 0.35) and the SDs were lower and essentially the same (workers = 0.49, referents = 0.45).

TABLE IV. Number and Percent of Workers Exposed to TCDD and Referents With Uroporphyrin and Coproporphyrin Levels Outside the Reference Range

	Workers		Referents			
Laboratory test	N	%Abnormal	N	%Abnormal	OR[a]	95% CI[a]
Uroporphyrin	281	3.6	260	5.0	0.70	0.30, 1.62
Coproporphyrin	281	5.7	260	5.0	1.15	0.54, 2.43

[a]OR, odds ratios; CI, confidence interval.

status as a worker vs. a referent (OR = 0.69, 95% CI = 0.30, 1.61). When workers were stratified into quartiles based on serum TCDD level, we found no statistically significant difference in means or risk of an out-of-range concentration between any of the worker quartiles and the referent group (Table V).

Using logistic regression analyses, the risk for an out-of-range coproporphyrin

TABLE V. Mean Uroporphyrin Level and Adjusted OR for Out-of-Range Uroporphyrin Level by Serum 2,3,7,8-TCDD Category

Serum 2,3,7,8-TCDD Category (pg/gm lipid)	N	Mean[a] (standard error)	% Out-of-range[b]	OR (95% CI)[c]
Referents				
<20	259	6.3 (1.08)	5.0	1.0
Workers[d]	273	— ( )	—	—
<20	76	4.3 (0.63)	0	—
20–75	66	4.9 (0.97)	4.6	0.9 (0.2, 3.3)
76–237	66	10.6 (6.39)[e]	4.6	0.9 (0.2, 3.3)
≥238	65	7.9 (2.33)	4.6	0.9 (0.3, 3.3)

[a]μg/gm creatinine.
[b]>23.5 μg/gm creatinine.
[c]OR, odds ratios; CI, confidence interval.
[d]Fifteen years or more since last exposure.
[e]The high standard error for uroporphyrin was due to one worker with a uroporphyrin level of 422 μg/gm of creatinine. After removal of this individual, the mean and standard error were lower (mean = 4.3 μ/gm of creatinine, standard error = 0.92).

concentration was found not to be significantly associated with any measure of TCDD exposure, including serum TCDD level ($p = 0.31$), halflife-extrapolated TCDD level ($p = 0.48$), or status as a worker vs. a referent (OR = 1.06, 95% CI = 0.48, 2.31). Because the residuals in the coproporphyrin model approximated a normal distribution after a natural log transformation was applied, linear regression analyses were conducted using these log transformed values. The findings from the linear regression analyses were similar to those from the logistic regression analyses. When workers were stratified into quartiles based on serum TCDD level, there were no statistically significant differences in means or risk of an out-of-range concentration between referents and any of the worker quartiles (Table VI).

DISCUSSION

Most porphyrin synthesis is devoted to the production of heme, a component of hemoglobin, cytochromes, and other hemeproteins [Kappas et al., 1989]. The heme biosynthetic pathway consists of eight enzymes and is most active in the liver and bone marrow. Porphyrinogens, which spontaneously oxidize to porphyrins, are the intermediate products of the heme biosynthetic pathway. A different form of porphyria has been associated with a deficiency of each of the enzymes with the exception of the initial enzyme (δ-aminolevulinic acid synthase). Porphyria cutanea tarda (also known as chronic hepatic porphyria), which is the type of porphyria of interest in this report, is associated with a deficiency of uroporphyrinogen decarboxylase. This enzyme decarboxylates uroporphyrinogen to coproporphyrinogen.

Our study found no association between TCDD exposure and porphyria cutanea tarda or porphyrinuria among workers with high body burdens of TCDD, but whose last occupational TCDD exposure was more than 15 years earlier. Our findings are consistent with the findings from several other studies [Moses et al., 1984; Webb et al., 1987; Lathrop et al., 1987], although only the study by Moses et al. [1984] involved workers with potential for high TCDD exposure. Although all of the participants in our study denied symptoms of porphyria cutanea tarda, and denied having

TABLE VI. Adjusted Mean Coproporphyrin and Adjusted OR for Out-of-Range Coproporphyrin Level by Serum 2,3,7,8-TCDD Category*

Serum 2,3,7,8-TCDD Category (pg/gm lipid)	N	Adjusted[a] mean (standard error)[b]	% Out-of-range[c]	Adjusted[d] OR (95% CI)
Referents				
<20	259	33.2 (1.03)	5.0	1.0
Workers[e]	273	—	—	—
<20	76	31.7 (1.05)	7.9	1.6 (0.6, 4.6)
20–75	66	32.9 (1.06)	4.6	1.0 (0.3, 3.6)
76–237	66	34.5 (1.06)	4.6	0.8 (0.2, 3.1)
≥238	65	36.9 (1.06)	4.6	0.9 (0.2, 3.3)

*OR, odds ratios; CI, confidence interval.
[a]Geometric means (μg/gm creatinine) adjusted for race, alcohol status, smoking status, and race.
[b]Geometric standard error term.
[c]>67.5 μg/gm of creatinine.
[d]Adjusted for PCB exposure and pack-years.
[e]Fifteen years or more since last exposure.

ever been diagnosed with porphyria, we have no data to determine if these workers had subclinical types of porphyria cutanea tarda in the past that reversed with removal from TCDD exposure. If porphyria cutanea tarda and porphyrinuria are reversible after removal from TCDD exposure, as has been suggested by some investigators [Pazderova-Vejlupkova et al., 1981; Doss et al., 1984; Poland et al., 1971], then this reversibility may explain the negative findings in several studies [Moses et al., 1984; Lathrop et al., 1987], including ours, which were conducted more than 10 years after occupational TCDD exposure had ceased. Furthermore, small sample size is a weakness present in all of the negative studies, including ours. Assuming that 1.2% is the rate of subclinical porphyria cutanea tarda in the unexposed group, α (one-sided) = 0.05, and power = .8, then 2,090 TCDD-exposed workers and 2,090 referents would be required to observe a TCDD-associated twofold elevated risk for this condition.

An association between chronic hepatic porphyria and TCDD exposure has been clearly established in mice [Goldstein et al., 1973] and rats [Goldstein et al., 1982], although only after extremely high TCDD exposures. Our review of the literature suggests that conclusive evidence has not been provided regarding an association in humans. Although four reports have suggested that TCDD exposure in humans is associated with symptomatic porphyria cutanea tarda [Bleiberg et al., 1964; Hope et al., 1984; Doss et al., 1984; Jirasek et al., 1974], definitive evidence of the role of TCDD was not provided. A review of these four key studies is provided below.

Porphyria cutanea tarda Type D (symptomatic) was described in two individuals residing near Seveso, Italy approximately 1 year after the area was contaminated with TCDD from an accidental release at a nearby chemical plant [Doss et al., 1984]. Both of these individuals had reduced erythrocyte UD activity. A reduction in the activity of erythrocyte UD indicates the presence of an inherited form of porphyria cutanea tarda. Generally, the inherited form of porphyria cutanea tarda remains subclinical unless there is exposure to a toxic agent such as alcohol, estrogens, or as demonstrated by these Seveso residents, TCDD [Doss, 1987]. Out of 60 additional Seveso residents tested, 4 (7%) were found to have porphyria cutanea tarda Type A [Doss,

1987]. In contrast to the two individuals with porphyria cutanea tarda Type D, these four individuals with porphyria cutanea tarda Type A had normal erythrocyte UD activity. A normal erythrocyte UD activity indicates that these four individuals may have had the acquired form of porphyria cutanea tarda. These findings suggested to Doss et al. [1984] that only in the presence of a reduction of erythrocyte UD activity can TCDD exposure lead to porphyria cutanea tarda Type D. Interestingly, the time of onset of the porphyria cutanea tarda Type D in the two Seveso individuals has been challenged by another investigator [Caputo, 1989; Caputo R., personal communication]. Dr. Caputo reported that when he interviewed these two individuals he learned that their skin lesions were present before the accidental TCDD release and, therefore, he believes that their porphyria cutanea tarda is unrelated to TCDD exposure. Nonetheless, the prevalence of subclinical porphyria cutanea tarda among the other 60 Seveso residents appears high, especially when compared to the findings from our study which found a subclinical porphyria cutanea tarda prevalence of 1.2%.

In a study of TCDD-exposed workers at a Czechoslovakian chemical plant, 11 workers were reported to have symptomatic porphyria cutanea tarda [Jirasek et al., 1974; Pazderova-Vejlupkova et al., 1981]. Although these cases of porphyria cutanea tarda were attributed to TCDD exposure by the authors, others have suggested that hexachlorobenzene, which was also produced at the plant, was responsible [Jones and Chelsky, 1986].

Bleiberg et al. [1964] reported finding porphyria cutanea tarda in 11 TCDD-exposed workers who had been employed at the same New Jersey chemical plant that we studied. (We were able to ascertain the identity of only three of these workers. Two of the three were deceased and the third did not participate. We cannot determine if the other eight workers participated in our study.) Although not clearly defined in their report, the criteria used by Bleiberg et al. [1964] to diagnose porphyria cutanea tarda rested on clinical findings and/or a qualitative assessment of urinary porphyrins. The laboratory tests that were used have been criticized by others [Epstein, 1964; Pass and Larsen, 1965]. Furthermore, at the time Bleiberg et al. [1964] conducted their study, there was no satisfactory classification system for the porphyrias and the precise nature of the metabolic defects causing porphyria was unknown. An association between reduced UD activity and porphyria cutanea tarda was not discovered until the late 1970s [Kushner et al., 1976]. According to current practice, a quantitative assessment of porphyrins is required to distinguish between the different types of porphyria [Kappas et al., 1989]. Therefore, the type of porphyria experienced by the workers studied by Bleiberg et al. [1964] is unclear. The cause of the porphyria reported by Bleiberg et al. [1964] is also unclear. They suggested that exposure to either 2,4,5-T, 2,4-dichlorophenoxyacetic acid (2,4-D), or an intermediate was responsible for the porphyria. Medication use may have contributed to the development of porphyria in two cases who, prior to the onset of their symptoms, were described by Bleiberg et al. [1964] to be taking barbiturates and griseofulvin (which are more commonly associated with the development of either variegate porphyria or hereditary coproporphyria as opposed to porphyria cutanea tarda). Jones and Chelsky [1986] suggested that hexachlorobenzene exposure was responsible for some of the porphyria cases observed by Bleiberg et al. [1964]. Hexachlorobenzene was produced up until 1960 and some of the workers described in the report by Bleiberg et al. [1964] may have been exposed. Nine years after hexachlorobenzene production had been discontinued, 73 male workers at this plant were restudied [Poland et al., 1971],

including 4 of the 11 workers with porphyria cutanea tarda originally described by Bleiberg et al. [1964]. None of these workers were found to have porphyria, based on clinical findings and a quantitative assessment of urinary porphyrins. At the time of the follow-up study by Poland et al. [1971], chemicals produced at the plant continued to be contaminated with TCDD, although to a lesser extent compared with the early 1960s [Marlow and Fingerhut, 1987]. However, because the level of TCDD contamination throughout the plant may have remained unchanged throughout the 1960s (the production buildings were never scrubbed down), individual TCDD exposures also may not have changed.

Finally, a case report described symptomatic porphyria cutanea tarda in a worker employed at a TCDD-contaminated trucking terminal [Hope et al., 1984]. The symptoms of porphyria cutanea tarda arose approximately 10 years after initial occupational TCDD exposure at the trucking terminal. However, it is possible that alcohol consumption may have been responsible for, or played a substantial role in, the development of porphyria cutanea tarda. The worker had a history of heavy alcohol consumption, and his symptoms were reported to improve after abstinence from alcohol. Alcohol abuse is commonly associated with porphyria cutanea tarda [Grossman et al., 1979].

As with porphyria cutanea tarda, conclusive evidence is not available to support an association between TCDD exposure and elevated uroporphyrin. Our study did not find an association between TCDD exposure and excess uroporphyrin excretion. Although we were unable to assess the relationship between TCDD exposure and uroporphyrin level using linear regression because over half of the participants had a uroporphyrin level of 0, we did not find a statistically significant difference in mean uroporphyrin level or risk for an out-of-range level between workers and referents (Table V). U.S. Air Force servicemen (Ranch Hands) who were responsible for the aerial dissemination of herbicides in Vietnam from 1962–1971, and who had a lower serum TCDD level (median = 12.8 pg/gm of lipid, range to 620 pg/gm of lipid [Roegner et al., 1991]) than the workers we studied, were not found to have a statistically significantly elevated mean uroporphyrin level when compared to an unexposed referent group [Lathrop et al., 1987]. Lathrop et al. [1987] did not determine what proportion of participants had out-of-range uroporphyrin levels. In contrast, 153 individuals who lived in a Missouri mobile home park sprayed with TCDD-contaminated waste oil were found to have a significantly higher mean uroporphyrin level and higher prevalence of out-of-range uroporphyrin (OR not provided) as compared to 146 matched controls [Hoffman et al., 1986]. However, Hoffman's report provided neither evidence that the mobile home residents received substantial exposure to TCDD, nor a dose-response analysis between TCDD exposure and uroporphyrin level. Another study of individuals who worked, lived, or played in areas of Missouri with TCDD-contaminated soil (data on the extent of TCDD contamination was not provided) found no statistically significant association between the serum TCDD level and the uroporphyrin level [Webb et al., 1989]. However, because of small sample size (total sample size = 38), the study by Webb et al. [1989] may not have had the power to detect a difference in uroporphyrin level even if one existed.

Only a few published reports have described the association between TCDD exposure and coproporphyrin level. Our findings of no association are consistent with the Ranch Hand studies [Lathrop et al., 1984; 1987]. Poland et al. [1971] found that

15 maintenance workers employed at the same New Jersey chemical plant that we studied had a statistically significantly elevated mean coproporphyrin level when compared to 56 other workers also employed at the plant (mean coproporphyrin level: maintenance = 48.3 μg/gm creatinine, others = 36.7 μg/gm creatinine; upper limit of normal = 175 μg/gm creatinine). Ten of these 15 maintenance workers also participated in our study; however, we found no statistically significant difference in the mean coproporphyrin level for these 10 workers compared to the referents (mean coproporphyrin level: maintenance = 34.8 μg/gm creatinine, referents = 35.3 μg/gm creatinine). These findings suggest that TCDD-associated coproporphyrin elevation may be reversible. It is interesting to note that the 10 maintenance workers had a mean serum TCDD level of 559 pg/gm of lipid (range: 769–1,593 pg/gm of lipid) at the time of our study. Therefore, a high body burden of TCDD is compatible with normal levels of coproporphyrin.

It is unlikely that statistical power was a limitation with respect to the coproporphyrin and uroporphyrin analyses. The study had 95% power to detect a 5% difference in the coproporphyrin level between workers and referents and 90% power to detect a 20% difference in the uroporphyrin level. The power to detect a twofold rise in risk for elevated uroporphyrin or coproporphyrin levels among workers compared to referents was 50% and to detect a threefold rise in risk, the power was greater than 99%.

In summary, our study found that workers with high occupational TCDD exposure at least 15 years earlier, many of whom continued to have persistently elevated TCDD body burdens, had no increased risk for porphyria cutanea tarda, or porphyrinuria. No cases of symptomatic porphyria cutanea tarda were found. Although our coproporphyrin and uroporphyrin analyses had sufficient statistical power, we had weak power to detect an association between TCDD exposure and porphyria cutanea tarda. Because the workers in our study ceased occupational TCDD exposure at least 15 years earlier, we have no data to determine if porphyria cutanea tarda or porphyrinuria was present during those years before our study. A review of the literature suggests that data do not convincingly support or refute an association between TCDD exposure and porphyria cutanea tarda, uroporphyrinuria, or coproporphyinuria. The previous studies are limited by either insensitive porphyrin measurements, small sample sizes, exposure to low levels of TCDD, or possible simultaneous exposure to other porphyrinogenic chemicals.

ACKNOWLEDGMENTS

The authors are thankful for the assistance provided by Brent Tompkins, Barbara Connally, Laurie Piacitelli, Kathleen Wille, David Marlow, and many other NIOSH personnel. The extensive review and thoughtful suggestions provided by Karl Anderson, M.D. were greatly appreciated. Funding for this study was provided by the Agency for Toxic Substances and Disease Registry (ATSDR).

REFERENCES

Anderson KE (1992): The porphyrias. In Wyngaarden JB, Smith LH Jr, Bennett CJ (eds): "Cecil Textbook of Medicine. 19th ed." Philadelphia: Saunders, pp 1126–1132.

Bleiberg J, Wallen M, Brodkin R, Applebaum IL (1964): Industrially acquired porphyria. Arch Dermatol 89:793–797.

Calvert GM, Sweeney MH, Morris JA, Fingerhut MA, Hornung RW, Halperin WE (1991): Evaluation of chronic bronchitis, chronic obstructive pulmonary disease (COPD) and ventilatory function among workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Am Rev Respir Dis 144:1302–1306.

Cam C, Nigogosyan G (1963): Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. Report of 348 cases caused by this fungicide. JAMA 183:88–91.

Caputo R (1989): *Letter.* J Am Acad Dermatol 21:1321.

Doss M, Sauer H, von Tiepermann R, Colombi AM (1984): Development of chronic hepatic porphyria (porphyria cutanea tarda) with inherited uroporphyrinogen decarboxylase deficiency under exposure to dioxin. Int J Biochem 16:369–373.

Doss MO (1987): Porphyrinurias and occupational disease. Ann NY Acad Sci 514:204–218.

Epstein E (1964): On industrially acquired porphyria [Letter]. Arch Dermatol 90:630.

Goldstein JA, Hickman P, Bergman H, Vos JG (1973): Hepatic porphyria induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in the mouse. Res Commun Chem Pathol Pharmacol 6:919–928.

Goldstein JA, Linko P, Bergman H (1982): Induction of porphyria in the rat by chronic versus acute exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Biochem Pharmacol 31:1607–1613.

Grossman ME, Bickers DR, Poh-Fitzpatrick MB, DeLeo VA, Harber LC (1979): Porphyria cutanea tarda. Am J Med 67:277–286.

Hill RH, Bailey SL, Needham LL (1982): Development and utilization of a procedure for measuring urinary porphyrins by high-performance liquid chromatography. J Chromatogr 232:251–260.

Hoffman RE, Stehr-Green PA, Webb KB, Evans G, Knutsen AP, Schramm WF, Staake JL, Gibson BB, Steinberg KK (1986): Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA 255:2031–2038.

Hope W, Lischwe D, Russell W, Weiss S (1984): Porphyria cutanea tarda and sarcoma in a worker exposed to 2,3,7,8-tetrachlorodibenzo dioxin-Missouri. JAMA 251:1534–1537.

Jirasek L, Kalensky J, Kubeck K, Pazderova J, Lukas E (1974): Acne chlorine, porphyria cutanea and other manifestations of general intoxication during the manufacture of herbicides. Cesk Dermatol 49:145–157.

Jones RE, Chelsky M (1986): Further discussion concerning porphyria cutanea tarda and TCDD exposure. Arch Environ Health 41:100–103.

Kappas A, Sassa S, Galbraith RA, Nordman Y (1989): The porphyrias. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds): "The Metabolic Basis of Inherited Disease." New York: McGraw Hill, pp 1305–1365.

Kushner JP, Barbuto AJ, Lee GR (1976): An inherited enzymatic defect in porphyria cutanea tarda: Decreased uroporphyrinogen decarboxylase activity. J Clin Invest 58:1089–1097.

Lathrop GD, Machado SG, Karrison TG, Grubbs WD, Thomas WF, Wolfe WH, Michalek JE, Miner JC, Peterson MR (1987): "The Air Force Health Study: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides. First Follow-up Examination Results." Springfield, VA:National Technical Information Service, Publication AD A-188-262.

Lathrop GD, Wolfe WH, Albanese RA, Moynahan PM (1984): "The Air Force Health Study: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides: Baseline Morbidity Study Results." Springfield VA: National Technical Information Service, Publication AD A-138-340.

Lynch RE, Lee GR, Kushner JP (1975): Porphyria cutanea tarda associated with disinfectant misuse. Arch Intern Med 135:549–552.

Marlow DA, Fingerhut MA (1987): "Dioxin Registry Report of the Diamond Shamrock Corp., Diamond Alkali Company, Newark, New Jersey." Springfield, VA: National Technical Information Service, Publication PB 87222808.

Moses M, Lilis R, Crow KD, Thornton J, Fischbein A, Anderson HA, Selikoff IJ (1984): Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: Comparison of findings with and without chloracne. Am J Ind Med 5:161–182.

Pass F, Larsen WG (1965): Letter. Arch Dermatol 91:93.

Patterson DG, Fingerhut MA, Roberts DW, Needham LL, Sweeney MH, Marlow DA, Andrews JS,

Halperin WE (1989): Levels of polychlorinated dibenzo-p-dioxins and dibenzofurans in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Am J Ind Med 16:135–146.

Pazderova-Vejlupkova J, Nemcova M, Pickova J, Jirasek L, Lukas E (1981): The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Arch Environ Health 36:5–11.

Pirkle JL, Wolfe WH, Patterson DG, Needham LL, Michalek JE, Miner JC, Peterson MR, Phillips DL (1989): Estimates of the half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Vietnam veterans of Operation Ranch Hand. J Toxicol Environ Health 27:165–171.

Poland AP, Smith D, Metter G, Possick P (1971): A health survey of workers in a 2,4-D and 2,4,5-T plant. Arch Environ Health 22:316–327.

Roegner RH, Grubbs WD, Lustik MB, Brockman AS, Henderson SC, Williams DE, Wolfe WH, Michalek JE, Miner JC (1991): "The Air Force Health Study: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides. Serum Dioxin Analysis of 1987 Examination Results." Springfield, VA: National Technical Information Service, Publication AD A-237–516.

Strik JJTWA, Debets FMH, Koss G (1980): Chemical porphyria. In Kimbrough RD (ed): "Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins, and Related Products." New York: Elsevier/North Holland Biomedical Press, pp 191–239.

Sweeney GD (1986): Porphyria cutanea tarda, or the uroporphyrinogen decarboxylase deficiency diseases. Clin Biochem 19:3–15.

Sweeney MH (1990): "Evaluation of the Peripheral Nervous System Among Workers Employed in the Production of Chemicals Contaminated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin." [Dissertation]. Ann Arbor: University of Michigan.

Sweeney MH, Fingerhut MA, Connally LB, Halperin WE, Moody PL, Marlow DA (1989): Progress of the NIOSH cross-sectional medical study of workers occupationally exposed to chemicals contaminated with 2,3,7,8-TCDD. Chemosphere 19:973–977.

Webb K, Evans RG, Stehr P, Ayres SM (1987): Pilot study on health effects of environmental 2,3,7,8-TCDD in Missouri. Am J Ind Med 11:685–691.

Webb KB, Evans RG, Knutsen AP, Roodman ST, Roberts DW, Schramm WF, Gibson BB, Andrews JS, Needham LL, Patterson DG (1989): Medical evaluation of subjects with known body levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Toxicol Environ Health 28:183–193.

With TK (1980): Diagnostic tests for porphyria. Lab Med 11:446–454.