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Review and Update of the Results of the NIOSH Medical Study of Workers Exposed to Chemicals Contaminated With 2,3,7,8-Tetrachlorodibenzodioxin

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In 1987, the National Institute for Occupational Safety and Health conducted a cross-sectional medical study to examine the long-term health effects of occupational exposure to chemicals and materials contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This study compared living workers employed more than 15 years earlier in the production of sodium trichlorophenol (NaTCP), and 2,4,5-trichlorophenoxyacetic ester (2,4,5-T ester) with an unexposed comparison group. Health status of the worker and comparison populations was collected through a comprehensive set of standardized interviews and medical examinations. Lipid adjusted serum TCDD levels were also measured.

Workers had a statistically significantly elevated mean serum lipid-adjusted TCDD level (workers = 220 pg per g of lipid [range = not detected–3,400 pg per g of lipid], and referents 7 pg per g of lipid [range not detected–20 pg per g of lipid], $P < 0.001$). Compared to a community-based referent population, the prevalence of chronic bronchitis, chronic obstructive pulmonary disease, peripheral neuropathy, depression, cardiovascular outcomes (myocardial infarction, angina, cardiac arrhythmias, hypertension, and abnormal peripheral arterial flow), abnormal porphyrin levels, and abnormal ventilatory function parameters $FEV_{1.0}$, FVC, or $FEV_{1.0}$/FVC% in workers, was not statistically significantly different. In contrast, relationships were observed between serum 2,3,7,8-TCDD levels and the enzyme γ-glutamyltransferase (GGT), the reproductive hormones serum testosterone, luteinizing, and follicle-stimulating hormones, and abnormal high-density lipoprotein concentration, counts of CD3/Ta1 cells (helper lymphocytes), and fasting serum glucose levels. Current diagnosis of chloracne was associated with the highest levels of serum 2,3,7,8-TCDD. Analysis of other endpoints continues. *Teratogenesis Carcinog. Mutagen. 17:241–247, 1997/98.* © 1998 Wiley-Liss, Inc.

Key words: dioxin; lipids; serum glucose; male reproductive hormones; NIOSH study

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INTRODUCTION

In 1987, the National Institute for Occupational Safety and Health (NIOSH) conducted a cross-sectional medical study to examine the long-term noncancer health effects of occupational exposure to chemicals and materials contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The details of the study design were previously described [11].

METHODS

This study compared living individuals (workers) employed more than 15 years earlier in the production of sodium trichlorophenol (NaTCP) or one of its derivatives, 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. 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 2,4,5-trichlorophenol and hexachlorophene occurred from April 1970 to January 1972. Both plants produced a variety of other chemicals. The referent (comparison) group was composed of individuals with no self-reported occupational exposure to TCDD-contaminated substances. Referents selected to participate in the study lived within the neighborhood of a worker and matched the worker by age (within 5 years), race, and gender.

Information on worker and referent health status was collected through a comprehensive set of standardized interviews and medical examinations. A lifetime medical history was elicited from each participant using interviewer-administered questionnaires. 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. Duration of exposure to TCDD-contaminated products was also calculated from personnel records.

In this paper, we review and update the findings of the analyses of noncancer health effects in this highly exposed population of chemical workers. System-specific analyses were conducted and reported for chronic bronchitis, chronic obstructive pulmonary disease, and ventilatory function [2], hepatic and gastrointestinal intestinal effects [3], diabetes and serum glucose concentration [4], depression [5], peripheral neuropathy [6], porphyria cutanea tarda [7], serum testosterone and gonadotropin [8], P-450 induction [9], lipid concentrations [10], immunologic function [11], chloracne status [12], and cardiovascular morbidity [13]. Serum concentrations of polychlorinated dibenzodioxins and dibenzofurans were also measured on all workers and a weighted sample of referents [14]. Detailed descriptions of the system-specific analytic strategies can be found in the publications cited above.

RESULTS

Of the 586 workers at the two plants who were eligible for the study, 400 (68.3%) were alive and could be located at the time of the study. A total of 142 (24.2%)

workers were deceased, and 44 (7.5%) could not be located. All 400 workers from the two plants who were living and could be located were invited to participate in the study; 281 (70%) were examined. A total of 938 referents were invited to participate in the study, of whom 260 (28%) were examined. Descriptive information on the study cohort has been previously reported [2,15].

Serum TCDD Concentration

Workers had a statistically significantly elevated mean serum lipid-adjusted TCDD concentration (workers = 220 pg per g of lipid (range = not detected–3,400 pg per g of lipid], and referents = 7 pg per g of lipid [range not detected–20 pg per g of lipid], $P < 0.001$) [14]. The mean halflife-extrapolated lipid-adjusted serum TCDD concentration was also statistically significantly elevated among workers (workers = 1,900 pg per g of lipid, referents = 6 pg per g of lipid, $P < 0.001$). There were no statistically significant differences or consistent patterns of differences between workers and referents for demographic characteristics (age, race, gender, education, income) [15] except alcohol-years, which was attributed to seven individuals with extremely high alcohol-year values [3] and for most PCDDs or PCDFs other than 2,3,7,8-TCDD, 2,3,4,7,8-pentachlorodibenzofuran, and 1,2,3,4,7,8-hexachlorodibenzofuran (Table I) [14]. The significant difference in TCDD concentration between workers and referents validated worker exposure. Differences in the concentrations of the two furans were due to high values in a few workers in the New Jersey plant, the source of which has not been established.

Health Outcomes

Compared to the community-based referent population, the prevalence of the following conditions was not statistically significantly different in the TCDD-exposed workers: chronic bronchitis, chronic obstructive pulmonary disease [2], peripheral neuropathy [6], depression [5], cardiovascular outcomes (myocardial infarction, angina, cardiac arrhythmias, hypertension, and abnormal peripheral arterial flow) [13], abnormal porphyrin concentrations [7], and abnormal ventilatory function parameters forced expiratory volume at one second ($FEV_{1.0}$), forced vital capacity (FVC) or the ratio of $FEV_{1.0}$ to FVC ($FEV_{1.0}$/FVC%) [2]. On the other hand, statistically significant positive relationships were observed between serum 2,3,7,8-TCDD concentrations and the enzyme γ-glutamyltransferase (GGT) [3], serum testosterone, luteinizing hormone and follicle-stimulating hormone [8], concentrations of triglycerides and abnormal high density lipoprotein [10], counts of CD3/Ta1 cells (helper lymphocytes) [11], diagnosis of chloracne [12], and fasting serum glucose concentrations [4].

Out-of-Range γ-Glutamyltransferase

In the analysis of liver function and gastrointestinal disorders, 10.7% of workers and 5.0% of the referents had an out-of-range concentration of the enzyme γ-glutamyltransferase (GGT) (OR = 2.27; 95% CI, 1.17, 4.39) [3]. In the logistic regression analyses, the elevation in risk for an out-of-range GGT was confined only to workers with a history of alcohol consumption. Workers did not have increased liver disease nor elevations in other liver enzymes compared to unexposed comparisons.

Serum Glucose Concentrations and Diabetes

Fasting serum glucose concentrations were measured in each study participant on the first day of the examination and repeated if the concentration was 140 mg/dl or

TABLE I. Lipid-Adjusted Serum Concentrations in Picograms Per Gram of Lipid for Selected PCDDs and PCDFs[†]

	Workers				Referents			
Analyte	Number	Mean	Median	Range	Number	Mean	Median	Range
2387D	273	220*	69	2–3,400	79	7§	6	2–20
12378D	161	13	11	4.5–50	54	12	10	3.5–51
123478D	153	12	11	1.9–41	49	13	11	3.2–58
123678D	150	90	84	38–290	53	84	73	17–183
1234678D	111	160	150	41–520	40	160	130	39–460
OCDD	102	1,090	990	270–3,800	42	1,010	920	480–2,300
2387F[a]	118	2.4	—	160[b]	41[a]	1.2	—	3.5[b]
23478F	131	15*	12	3.8–170	44	11*	9.4	3.3–28
123478F	94	15*	13	4.2–120	44	11*	9.6	4.2–28
123678F	102	10	8.7	3.3–49	37	8.5	7.5	3.7–18
1234678F	82	23	22	8–49	30	20	19	8.7–46
OCDF[a]	73	0.95	—	21[b]	26[a]	1.1	—	16[b]

[†]PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans. Reproduced from Piacitelli et al. [14] with permission of the publisher.
[a]Less than 50% of samples for this analyte were detectable values.
[b]Maximum concentration detected in samples analyzed.
*$P < 0.05$.

greater [4]. We noted a slight but statistically significant and positive increase in the risk of diabetes (OR = 1.12, $P < 0.003$) and fasting serum glucose ($P < 0.001$) with increasing serum concentrations of 2,3,7,8-TCDD. However, in this population, traditional risk factors for diabetes, age, weight, and family history or diabetes appear to be more influential than TCDD in the development of diabetes.

Serum Testosterone, Follicle-Stimulating Hormone, and Luteinizing Hormone

In linear regression analysis of total serum testosterone and gonadotrophin concentrations, current serum dioxin concentration was positively and significantly related to luteinizing hormone and follicle-stimulating hormone and inversely related to total testosterone concentrations after adjustment for potential confounders [8]. These trends were also apparent in logistic regression analysis of high luteinizing hormone (>28 IU/liter), high follicle-stimulating hormone (>31 IU/liter), and low testosterone (<10.4 IU/liter) by serum dioxin quartiles (Table II). The trends observed in these data suggest some evidence of alterations in male reproductive hormone concentrations associated with TCDD exposure. Further studies are needed to clarify these results.

Serum Lipid Concentrations

Total cholesterol, high-density lipoprotein (HDL), and triglyceride concentrations were measured for each study participant [10]. The total cholesterol/HDL cholesterol ratio was calculated for each participant. A statistically significant association was noted between serum TCDD concentration and triglyceride concentration (test for trend, $P < 0.05$), while there was a positive but moderate relationship for an abnormal HDL (≤0.91 mmol/L) (test for trend, $P < 0.09$) (Table III). Although overall triglyceride concentration increased by 0.4 mmol/L over the range of serum TCDD values, there was no association demonstrated between an abnormally elevated tri-

TABLE II. Adjusted Odd Ratios and 95% Confidence Intervals for High Serum Luteinizing Hormone, High Serum Follicle-Stimulating Hormone, and Low Serum Testosterone by Serum 2,3,7,8-TCDD Category (479 Observations)*

	High luteinizing hormone[a]		High follicle-stimulating hormone[b]		Low testosterone[c]	
Serum 2,3,7,8-TCDD category (pg/g)	Adjusted odds ratio[d]	95% confidence limit	Adjusted odds ratio[e]	95% confidence limit	Adjusted odds ratio[f]	95% confidence limit
Referents < 20	1.0	—	1.0	—	1.0	—
Workers	1.6	0.8, 3.3	1.5	0.7, 3.3	2.1	1.0, 4.6
<20	0.8	0.2, 3.0	1.1	0.3, 3.9	0.9	0.2, 4.5
20–75	1.9	0.7, 5.5	1.7	0.5, 5.4	3.9	1.3, 11.3
76–240	2.5	0.9, 7.3	1.7	0.5, 5.6	2.7	0.9, 8.2
241–3,400	1.9	0.7, 5.0	2.0	0.7, 5.6	2.1	0.8, 5.8

*Reproduced from Egeland et al., [8] with permission of the publisher.
[a]>28 IU/liter.
[b]>31 IU/liter.
[c]<10.4 IU/lliter.
[d]Adjusted for age, body mass index, alcohol, smoking, and diabetes mellitus.
[e]Adjusted for age, alcohol, smoking, and diabetes mellitus.
[f]Adjusted for age, body mass index, alcohol, smoking, and diabetes melllitus.

TABLE III. Mean HDL Cholesterol and Triglyceride Concentrations and Adjusted Odds Ratios (OR) for an Abnormal HDL Cholesterol by Serum TCDD Category[†]

Serum 2,3,7,8-TCDD category	HDL cholesterol						Triglyceride	
(fg/g serum)	No.	Mean[a]	SE[b]	%Abnormal[c]	OR[d]	95% CI	Mean[e]	SE[†]
Referents <158	259	1.2	1.01	12.7	1.0		1.15	1.03
Workers	273	1.2	1.01	16.8	1.2	0.7, 2.1	1.20	1.03
<158	87	1.3	1.03	9.2	0.6	0.3, 1.4	1.04	1.06
158–520	62	1.2	1.03	21.0	1.6	0.8, 3.5	1.26	1.07
521–1515	62	1.1	1.03	12.9	1.0	0.4, 2.4	1.23	1.07
1,516–19,717	62	1.1	1.03	25.8	2.2	1.1, 4.7	1.35*	1.07
Test for trend		$P = 0.15$		$P = 0.09$			$P = 0.05$	

[†]fg/g = femtograms/gram; OR = odds ratio; CI = confidence interval. Reproduced from Calvert et al. [13] with permission of the publisher.
[a]Geometric means (mmol/L) adjusted for gender, body weight index, pack years, use for beta-blocker medication, and current diabetes.
[b]Geometic standard error term.
[c]Abnormal defined as an HDL cholesterol concentration ≤ 0.91 mmol/L.
[d]Adjusted for body weight index, use of beta-blocker medication, age, and current diabetes.
[e]Geometric means (mmol/L) adjusted for body weight index, pack years, use of beta-blocker medication, race, gender, and current diabetes.
*$P < 0.05$ when compared to the referent group.

glyceride (>2.82 mmol/L) concentration and category of serum TCDD concentration. These data suggest that there is evidence to suspect a slight effect on lipid metabolism in this group of highly exposed workers. However, the magnitude of the effect of TCDD on lipid concentration is small when compared to that of other factors such as gender, body weight index, use of beta-blocker medication, and smoking.

Chloracne

Diagnosis of chloracne at the time of the study was associated with the highest stratum of serum TCDD (Odds Ratio 2.3, 95% CI 1.1, 4.3) [12].

DISCUSSION

In this population, we evaluated a series of health outcomes hypothesized to be related to exposure to TCDD. These endpoints were selected for study because previous studies or case reports had observed these outcomes in exposed populations. Although our population was clearly highly exposed to TCDD-contaminated chemicals, we found relatively few outcomes to be associated with TCDD exposure. The prevalence of the following was not related to serum TCDD concentrations: chronic bronchitis, chronic obstructive pulmonary disease, peripheral neuropathy, depression, cardiovascular outcomes (myocardial infarction, angina, cardiac arrhythmias, hypertension, and abnormal peripheral arterial flow), abnormal porphyrin concentrations, and abnormal ventilatory function parameters forced expiratory volume at one second ($FEV_{1.0}$), forced vital capacity (FVC), or the ratio of $FEV_{1.0}$ to FVC ($FEV_{1.0}$/FVC%). On the other hand, modest, but statistically significant positive relationships were observed between serum TCDD concentrations and the enzyme γ-glutamyltransferase (GGT), serum testosterone, luteinizing hormone and follicle-stimulating hormone, concentrations of triglyceride and abnormal

high density lipoprotein, counts of CD3/Ta1 cells (helper lymphocytes), diagnosis of chloracne, and fasting serum glucose.

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