Hepatic and Gastrointestinal Effects in an Occupational Cohort Exposed to 2,3,7,8-Tetrachlorodibenzo-para-dioxin

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Objective.—To examine the effect of occupational exposure to substances contaminated with 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) on the liver and gastrointestinal system.

Design.—A medical survey.

Participants.—The exposed participants were employed at two chemical plants more than 15 years earlier in the manufacture of sodium trichlorophenol and its derivatives. The reference group consisted of individuals with no occupational exposure to phenoxy herbicides and who lived within the communities of the workers. A total of 281 workers and 260 unexposed referents participated in the medical study.

Measurements and Main Results.—The workers had substantial exposure to substances contaminated with TCDD, as evidenced by a mean serum TCDD level, lipid adjusted, of 220 pg per gram of lipid compared with a mean of 7 pg per gram of lipid in the referents. Compared with the unexposed reference group, workers had a statistically significantly elevated risk for an out-of-range γ-glutamyltransferase (GGT) level (odds ratio, 2.27; 95% confidence interval, 1.17 to 4.39 [unadjusted for confounders]). In multivariate analyses run with logistic regression, a statistically significant interaction was found between TCDD exposure and lifetime alcohol consumption, indicating that the elevated risk for an out-of-range GGT was confined to those workers with a history of alcohol consumption and that the risk among the alcohol-consuming workers for an out-of-range GGT increased with increasing TCDD level. No difference was found between workers and referents for any of the other liver and gastrointestinal outcomes of interest.

Conclusions.—This study found no evidence of an elevated risk for clinical hepatic or gastrointestinal disease in a group of workers with high exposure to TCDD. However, TCDD-exposed workers with a history of sufficient alcohol consumption were found to have a statistically significantly elevated risk for an out-of-range GGT compared with referents.

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2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD) is produced as an undesirable contaminant in the manufacture of 2,4,5-trichlorophenol (TCP). Occupational exposure to TCDD has occurred during the production of TCP and its derivatives, by contact with TCDD-contaminated waste products, and during the cleanup of industrial accidents involving TCP and its derivatives. Concern about TCDD is widespread because of its high toxicity in animals.[1]

The epidemiologic studies of individuals with exposure to TCDD-contaminated substances provide conflicting evidence regarding an association between hepatic and gastrointestinal effects and TCDD exposure. Two cross-sectional medical studies found statistically significant elevations of self-reported ulcers in individuals exposed to TCDD-contaminated substances,[2,3] whereas a study of the US Air Force Ranch Hands failed to find an elevation.[4,5] Although case reports have described hepatitis,[6] liver damage,[7,8] and hepatomegaly[7,9,10] among TCDD-exposed individuals, the controlled epidemiologic studies that have examined these conditions have not found statistically significant elevations.[2,5,11,12]

Only a few studies found statistically significant differences in laboratory test results between the TCDD-exposed group and the unexposed group.[13] Furthermore, the findings for only three of the laboratory tests were found to be in a consistent direction across the published studies: γ-glutamyltransferase (GGT), D-glucaric acid, and total bilirubin. GGT and D-glucaric acid concentrations were consistently found to be elevated, and the total bilirubin concentration was consistently found to be reduced.

To evaluate the effect of occupational exposure to TCDD, the National Institute for Occupational Safety and Health (NIOSH) conducted a cross-sectional medical study. This cross-sectional 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 reference group. The workers were employed in one of two plants located in Newark, NJ, and

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Verona, Mo. This report describes the evaluation of the liver and gastrointestinal system.

METHODS

Data Collection

Four hundred ninety 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 Missouri facility, 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 comparison (referent) group, one individual with no self-reported occupational exposure to TCDD-contaminated substances was sought from within the neighborhood of each worker, matching the worker by age (within 5 years), race, and sex. A detailed description of the referent selection process is reported elsewhere.[14] 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 standardized medical examinations. The data were collected between February 1987 and March 1988. A lifetime medical history was elicited from each participant using interviewer-administered questionnaires. A lifetime occupational history was elicited from each participant apart from the medical interview. Duration of each job and duration of occupational exposure to specific substances were recorded beginning with the subject's 16th birthday. To reduce observer bias, all individuals conducting the medical interviews, examinations, and tests were blind to the exposure status (worker or referent) of the participant.

Each participant was examined by a physician. Variables from the physical examination of the abdomen and rectum that were analyzed included any visible abnormality of the abdomen, ascites, abdominal mass, any abdominal tenderness, diffuse abdominal tenderness, rebound tenderness of the abdomen, percussion tenderness of the abdomen, palpable liver, palpable spleen, percussible liver size, hemorrhoids, anal fissure, rectal mass, anal sphincter tone, and presence of occult blood in the stool.

Blood was obtained from the participants and analyzed for TCDD, alanine aminotransferase, aspartate aminotransferase, lactic dehydrogenase, GGT, total bilirubin, unconjugated bilirubin, alkaline phosphatase, total protein, albumin, triglyceride, and cholesterol concentrations. Two participants (one worker and one referent) did not have their blood drawn. Twelve-hour urine collections were obtained and analyzed for D-glucaric acid and creatinine. D-glucaric acid could not be measured in the urine of 12 participants (eight workers and four referents) due to the presence in the urine of an interfering substance (eg, ascorbic acid).

The reference values used to define the normal range for each of the laboratory tests are provided in Table 1. The referent group was used to define the reference value. A laboratory test result was considered to be out of the reference range if it fell outside the 95th percentile (or the fifth percentile for total bilirubin and unconjugated bilirubin, because it was hypothesized that TCDD exposure is associated with a reduced total bilirubin level) of the referent group.

Table 1.—Reference Values for Laboratory Tests Associated With Liver Function

Laboratory Test	Reference Value*
Alanine aminotransferase, IU/L	74
Aspartate aminotransferase, IU/L	54
Lactic dehydrogenase, IU/L	607
D-Glucaric acid, μg per gram of creatinine	28.7
γ-Glutamyltransferase, IU/L	96
Total bilirubin, μmol/L	6.16
Unconjugated bilirubin, μmol/L	3.93
Alkaline phosphatase, IU/L	131
Total protein, g/L	83
Albumin, g/L	45

*Reference values were defined as the 95th percentile for the referent cohort, except for the reference values for total bilirubin and unconjugated bilirubin concentrations, which were defined as the fifth percentile.

Analysis of Data

Although this study was designed as a matched study, the matched analyses required exclusion of 25% (70 subjects) of the examined workers and 19% (49 subjects) of the examined referents because their matched partners refused to participate in the medical examination. Therefore, to increase the power of the analyses and to avoid the possible bias associated with the exclusion of a large number of participants from the matched analyses, unmatched analyses of the gastrointestinal and hepatic effects also were performed that included all of the examined workers and referents. Because the results of the matched and unmatched analyses were similar, the results of the matched analyses have not been provided.

Unadjusted odds ratios (ORs) were calculated for the categorical outcomes of interest and tested for significance using a χ^2 test for association. For continuous variables, means for workers and referents were compared using Student's t tests.[15]

To assess the relationship between the categorical and continuous outcomes of interest and exposure to TCDD-contaminated substances while simultaneously controlling for several potential confounders and effect modifiers, logistic regression and multiple linear regression analyses, respectively, were performed.[15] The potential confounders evaluated in the regression analyses for each of the outcomes of interest are listed in Table 2. 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 in the model vs when it was excluded. Potential confounders that were retained in the final model of a particular outcome 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. Effect modification was assessed by examining interactions between the exposure variable and potential confounders. Interactions in a logistic model have a different interpretation than those in a linear model. In a logistic model, interactions indicate a departure from the underlying multiplicative relationship. In a linear model, interactions indicate departures from an additive relationship. These considerations must be taken into account when interpreting each analysis.

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 TCDD levels measured at the time of the examination and adjusted for serum lipid level, and half-life–extrapolated TCDD levels (the estimated TCDD level on the date last employed in a job with TCDD exposure).[16] The lipid-adjusted TCDD levels were found to be highly correlated with the years of exposure to TCDD-contaminated substances (Pearson product-moment correlation coefficient, .83).[16] The TCDD levels were used to assess a possible dose-response relationship. Eight workers and one referent were excluded from the dose-response analysis because serum TCDD levels were not obtained.

The a priori outcomes of interest were GGT, D-glucaric acid, and total bilirubin concentrations and the self-reported medical conditions. The selection of these

Table 2.—Potential Confounders Evaluated in the Regression Analyses by Outcome of Interest*

	Ulcer Disease	Gastritis	Total Bilirubin Concentration	γ-Glutamyl-transferase Concentration	D-Glucaric Acid Concentration
Age	X	X	X	X	X
Gender	X	X	X	X	X
Race (white vs nonwhite)	X	X	X	X	X
Current smoker†	X	X			
Former smoker‡	X	X			
Pack-years of smoking§	X	X			
Current drinker‖	X	X	X	X	X
Former drinker¶	X	X	X	X	X
Alcohol-years of drinking#	X	X	X	X	X
Aspirin use**	X	X			
Family history of ulcer disease	X				
Use of nonsteroidal anti-inflammatory drugs	X	X			
Location of TCDD exposure††	X	X	X	X	X
History of hepatitis			X	X	
History of gallbladder disease				X	
Medication use‡‡				X	X
Medication use§§			X		
Body-mass index‖‖				X	
Triglyceride level				X	
Cholesterol level				X	

*"X" indicates a potential confounder.
†Reported smoking within the past year.
‡Denied smoking within the past year.
§The average number of cigarette packs smoked per day multiplied by the number of years cigarettes were smoked.
‖Reported drinking alcohol within the past year.
¶Denied drinking alcohol within the past year.
#The average number of alcoholic drinks consumed per day multiplied by the number of years alcohol was consumed.
**Use within 2 weeks of the examination.
††New Jersey vs Missouri. TCDD indicates 2,3,7,8-tetrachlorodibenzo-para-dioxin.
‡‡Use within 2 weeks of the examination of a medication known to affect D-glucaric acid and γ-glutamyltransferase concentrations.
§§Use within 2 weeks of the examination of a medication known to affect bilirubin concentrations.
‖‖Weight in kilograms divided by height squared in meters.

Table 3.—Distribution of Self-reported Hepatic and Gastrointestinal Disease Among Workers and Referents

	No. of Workers			No. of Referents			
	Yes	No	Excluded*	Yes	No	Excluded*	Odds Ratio (95% Confidence Interval)
Ulcer disease	29	247	5	35	213	12	0.72 (0.42-1.21)
Gastritis	10	266	5	17	239	4	0.53 (0.24-1.16)
Gastrointestinal hemorrhage	3	278	0	2	255	3	1.38 (0.23-8.25)
Hepatitis (any type)	6	271	4	6	252	2	0.93 (0.30-2.92)
Hepatitis A	2	277	2	3	255	2	0.61 (0.10-3.65)
Hepatitis B	1	280	0	1	258	1	0.92 (0.06-14.83)
Hepatitis, type unknown	3	276	2	2	257	1	1.40 (0.23-8.37)
Cirrhosis	3	278	0	3	257	0	0.92 (0.19-4.63)
Fatty liver	0	280	1	0	259	1	. . .

*Participants were excluded from the analysis if they could not recall whether they had had the disease of interest or if the onset of the disease of interest preceded the date of first exposure to substances contaminated with 2,3,7,8-tetrachlorodibenzo-para-dioxin.

outcomes was based on the presence of consistent evidence in published animal and human studies for an association with TCDD. Regression analyses were performed only on the a priori outcomes. However, for self-reported medical conditions, regression analyses were performed only if at least 10 workers reported the condition. Based on these criteria, gastrointestinal ulcer disease, gastritis, GGT concentration, D-glucaric acid concentration, and total bilirubin concentration were evaluated with regression analyses.

Although multiple comparisons were performed, no adjustments to the P values were made. An adjustment of the P value to account for the number of comparisons performed was thought to increase the potential for type II error. We attempted to address the problem of multiple comparisons by carefully selecting the outcomes to be analyzed and by reporting the results of all of the analyses performed.

RESULTS

Of the 586 workers at the two plants who were eligible for participation, 400 (68.3%) were determined to be alive and could be located. A total of 142 workers (24.2%) were deceased and 44 (7.5%) could not be located. All 400 workers who were living and 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 described.[16,17] Workers were found to have a statistically significantly elevated mean serum TCDD level (workers, 220 pg per gram of lipid; referents, 7 pg per gram of lipid; $P<.001$). The mean half-life–extrapolated serum TCDD level was also statistically significantly elevated among workers (workers, 1900 pg per gram of lipid; referents, 6 pg per gram of lipid; $P<.001$). Referents were found to have a statistically significantly higher mean lifetime alcohol consumption (workers, 41.4 alcohol-years; referents, 62.1 alcohol-years; $P=.011$), which was attributed to seven referents with extremely high alcohol-year values (range, 520 to 719 alcohol-years). There were no other statistically significant differences or consistent patterns of differences between workers and referents for any other demographic characteristics (age, race, gender, education, or income).

Hepatic and Gastrointestinal Diseases

Table 3 provides the results of the unadjusted analysis of self-reported hepatic and gastrointestinal disease among workers and referents. Workers were not found to be at increased risk for any of the hepatic or gastrointestinal diseases. Similarly, logistic regression analyses of gastrointestinal ulcer disease and gastritis found neither to be statistically significantly associated with any measure of TCDD exposure.

Blood and Urine Tests Measuring Liver Function

Table 4 provides the means for blood and urine liver function test results among workers and referents. The mean GGT level for workers was significantly higher than the mean GGT level for referents ($P=.03$). In addition, workers were found to have a statistically sig-

Table 4.—Results of Laboratory Tests Associated With Liver Function for Workers and Referents

Laboratory Test	Workers N	Workers Mean (SD)	Referents N	Referents Mean (SD)	P*
Alanine aminotransferase, IU/L	280	33.8 (22.6)	259	33.0 (21.2)	.65
Aspartate aminotransferase, IU/L	280	28.3 (14.8)	259	29.9 (15.5)	.21
Lactic dehydrogenase, IU/L	280	471.8 (126.5)	259	463.8 (80.8)	.38
D-Glucaric acid, μg per gram of creatinine	273	14.1 (11.1)	256	13.2 (7.9)	.32
γ-Glutamyltransferase, IU/L	280	58.5 (73.7)	259	47.4 (41.1)	.03
Total bilirubin, μmol/L	280	12.3 (5.8)	259	11.8 (4.4)	.20
Unconjugated bilirubin, μmol/L	280	9.9 (5.3)	259	9.6 (4.1)	.58
Alkaline phosphatase, IU/L	280	89.3 (25.1)	259	86.4 (24.0)	.17
Total protein, g/L	280	72.9 (5.0)	259	73.8 (5.3)	.05
Albumin, g/L	280	40.8 (2.4)	259	40.9 (2.5)	.82

*Based on a two-tailed Student's *t* test.

Table 5.—Workers and Referents With Laboratory Test Results Outside the Reference Range

Laboratory Test	Workers N*	Workers % Abnormal	Referents N*	Referents % Abnormal	Odds Ratio (95% Confidence Interval)
Alanine aminotransferase	280	4.3	259	5.0	0.85 (0.38-1.89)
Aspartate aminotransferase	280	2.9	259	5.0	0.56 (0.23-1.35)
Lactic dehydrogenase	280	5.7	259	5.0	1.15 (0.54-2.43)
D-Glucaric acid	273	5.1	256	5.1	1.01 (0.46-2.20)
γ-Glutamyltransferase	280	10.7	259	5.0	2.27 (1.17-4.39)
Total bilirubin	280	5.7	259	5.4	1.06 (0.51-2.22)
Unconjugated bilirubin	280	3.6	259	5.0	0.70 (0.30-1.62)
Alkaline phosphatase	280	5.7	259	5.0	1.15 (0.54-2.43)
Total protein	280	2.1	259	5.0	0.41 (0.16-1.08)
Albumin	280	3.6	259	5.4	0.65 (0.28-1.48)

*Sample sizes differ due to exclusions.

nificantly elevated risk for an out-of-range GGT level compared with referents (OR, 2.27; 95% CI, 1.17 to 4.39) (Table 5). The mean total protein concentration for referents was found to be borderline significantly elevated compared with that of the workers ($P=.05$); however, the risk among referents for an out-of-range total protein concentration was not significantly elevated. There were no statistically significant differences between workers and referents for any of the other laboratory tests.

Logistic regression analyses were performed to assess the risk for out-of-range D-glucaric acid and total bilirubin concentrations. Neither of these laboratory tests was found to be statistically significantly associated with any measure of TCDD exposure. Furthermore, TCDD exposure was not associated with either D-glucaric acid or total bilirubin concentration in the linear regression analyses.

γ-Glutamyltransferase

Of the 280 workers and 259 referents who provided serum, 30 (10.7%) and 13 (5.0%), respectively, had out-of-range GGT values (OR, 2.27; 95% CI, 1.17 to 4.39). In the logistic regression analyses, a statistically significant interaction term between the dichotomous exposure variable and lifetime alcohol consumption was found (Table 6). This finding indicates that the elevated risk for an out-of-range GGT value was confined to those workers with sufficient lifetime alcohol consumption. Similarly, statistically significant interaction terms between lifetime alcohol consumption and either the serum TCDD level ($P=.03$) or the half-life–extrapolated TCDD level ($P=.05$) were also found. These findings indicate that the risk for an out-of-range GGT value at any particular TCDD level varies by the amount of alcohol consumed in one's lifetime (Figure). The findings were similar when the seven referents with excessive alcohol-year levels were removed from the analyses. Because the GGT data are highly skewed (this accounts for the large SDs reported in Table 4), a log-10 transformation was applied to the GGT data before the linear regression analyses were performed. The findings of the linear regression analyses were similar to those of the logistic regression analyses.

Abdominal and Rectal Abnormalities on Physical Examination

Among the components of the abdominal and rectal examination, only decreased anal sphincter tone was statistically significantly associated with TCDD exposure (workers, 3.9%; referents, 0.4%; OR, 10.2; 95% CI, 1.93 to 54.31). Although the anal sphincter tone examinations were conducted by one of two physicians (physician 1 conducted 204 examinations and physician 2 conducted 302 examinations), all of the participants with decreased anal sphincter tone were examined by physician 1.

COMMENT

Although previously published human studies have reported associations between TCDD exposure and adverse clinical hepatic and gastrointestinal outcomes, we found no evidence of clinical hepatic or gastrointestinal disease in a group of workers with high exposure to TCDD. However, TCDD-exposed workers with a history of sufficient alcohol consumption were found to have a statistically significantly elevated risk for an out-of-range GGT value compared with referents. The mechanism responsible for this finding is not known. Among the published studies that found an association between TCDD exposure and an elevated GGT value,[11,18-20] none reported that the association was dependent on alcohol consumption. However, the positive association between lifetime alcohol consumption and GGT level is consistent with the often-described usefulness of the GGT level as a marker for alcohol ingestion.[21]

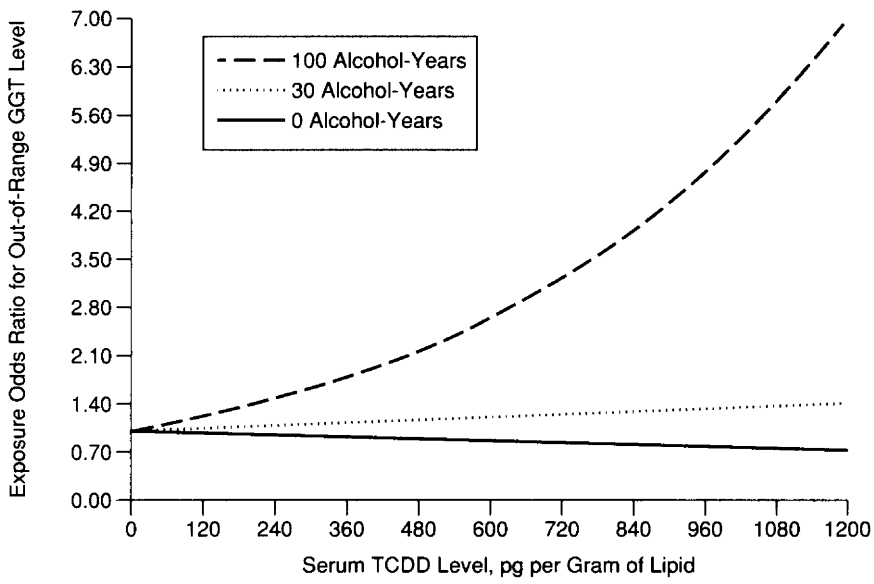
GGT is an enzyme that catalyzes the reversible transfer of a peptide-bound γ-glutamyl group to another peptide or an amino acid. It is suspected that this reaction facilitates the transfer of amino acids across cell membranes.[22] In clinical practice, the GGT level is often measured because of its usefulness as a marker for alcohol intake and because it is elevated in almost all hepatobiliary diseases.[23]

Although GGT is elevated in those with hepatobiliary disease, it is unlikely that such disease explains the GGT el-

Table 6.—Logistic Regression Model for an Out-of-Range Serum γ-Glutamyltransferase Level Using the Categorical TCDD* Exposure Measure†

Variable	β	Standard Error of the Estimate	χ^2	P
Intercept	−4.12	0.50	67.01	<.001
Exposure (worker = 1, referent = 0)	0.37	0.43	0.74	.195
Per alcohol-year	-2.4×10^{-6}	2.6×10^{-3}	0.00	.999
Current alcohol drinker (yes = 1, no = 0)‡	0.90	0.42	4.70	.030
Alcohol-years/exposure interaction§‖	7.2×10^{-3}	3.5×10^{-3}	4.24	.039
Triglyceride level	3.8×10^{-3}	1.1×10^{-3}	11.94	<.001

*TCDD indicates 2,3,7,8-tetrachlorodibenzo-para-dioxin.
†There were 536 observations.
‡The results from this logistic regression analysis change little when this term is dropped from the model.
§Interaction between alcohol-years and exposure.
‖Exposure odds ratios (ORs) for an abnormal γ-glutamyltransferase level among workers by various alcohol-year levels, adjusting for all of the variables in the model, are as follows: OR, 2.96 (95% confidence interval [CI], 1.34 to 6.54) for 100 alcohol-years; OR, 1.79 (95% CI, 0.81 to 3.97) for 30 alcohol-years; OR, 1.45 (95% CI, 0.63 to 3.36) for 1 alcohol-year; and OR, 1.44 (95% CI, 0.62 to 3.34) for 0 alcohol-years.



The risk of having an out-of-range γ-glutamyltransferase (GGT) level by the 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) level at three different alcohol-year levels, compared with participants with a TCDD level of 7 pg per gram of lipid (mean TCDD level of the controls). Estimates were obtained from a single logistic regression model.

evation that we observed. Among individuals with hepatobiliary disease, one would expect to find other hepatic enzymes (ie, transaminases, alkaline phosphatase) and metabolic products (ie, bilirubin, uroporphyrin) elevated in concert with GGT. In our study, GGT was the only enzyme that was elevated among the TCDD-exposed individuals. There is no published evidence that the subtle GGT elevations observed in this study are a marker for the subsequent development of clinically significant liver disease.[23]

Significantly higher levels of D-glucaric acid have been described in two TCDD-exposed groups: residents living in TCDD-contaminated areas of Seveso, Italy,[24,25] and workers exposed to TCDD after an explosion at a manufacturing plant that produced 2,4,5-T in Great Britain.[26] The authors of all three of these reports hypothesized that enzyme induction by TCDD may have been responsible for their findings. Indeed, there is evidence in animals that TCDD exposure induces liver microsomal enzymes,[27] and D-glucaric acid elevation may be an indirect measure of microsomal enzyme activity.[23] However, we did not find a statistically significant association between TCDD exposure and D-glucaric acid elevation. The time interval since last TCDD exposure may explain the difference in findings between our study and the earlier studies. The findings from the earlier studies indicate that D-glucaric acid may be elevated as long as 10 years after TCDD exposure is terminated, whereas our study indicates that the elevation is no longer present after 15 to 36 years.

Although not reported in previous studies of TCDD-exposed individuals, we found that workers were at increased risk for decreased anal sphincter tone compared with referents. It is curious that, although the anal sphincter tone examinations were conducted by two physicians, all of the participants with decreased anal sphincter tone were examined by the same physician. A possible explanation is observer bias. Because both physicians were blinded to the exposure status of the study participants, we postulate that the attention given to the examination of anal sphincter tone may have differed between the two physicians. The only other reasonable explanation for this finding is chance, although the magnitude of the P value ($P = .006$) makes this unlikely.

Our findings of no statistically significant increase in the self-reported cumulative incidence of liver disease are consistent with findings from several published reports.[2,4,5,11,28] Although Pazderova-Vejlupková et al[7] reported that 20% of the workers involved in the production of 2,4,5-T had elevated liver function test results consistent with "mild hepatic lesions," the elevated liver function test results in most (specific numbers of workers were not provided) were reported to resolve with time. If liver injury in TCDD-exposed individuals were reversible, as suggested by Pazderova-Vejlupková et al, this would be consistent with the negative findings in our study, which was conducted more than 15 years after TCDD exposure had ceased.

The manner of participant selection can be a source of validity problems in cross-sectional studies. To assess the potential magnitude of selection bias in our study, the workers who refused to be examined and a 10% random sample of the referents who refused to be examined were invited to be interviewed by phone. Of the 115 unexamined workers and 129 unexamined referents who were contacted, 68 (57%) and 99 (77%), respectively, agreed to be interviewed by phone. These individuals were asked questions similar to those asked in our medical study. The proportions of unexamined and examined workers who reported stomach ulcers, hepatitis, or cirrhosis were not statistically significantly different. Similar results were

found for the referents, except with regard to stomach ulcers. Compared with the unexamined referents, a statistically significantly higher proportion of examined referents reported a history of ulcers (examined referents, 16.4%; unexamined referents, 5.7%; $P = .04$). If, as this finding suggests, selection bias was present with regard to the examined referents, an association between ulcer disease and TCDD exposure may have been obscured. To explore this possibility, we used Fisher's Exact Test to perform an unadjusted analysis on ulcer disease that included examined workers and referents as well as unexamined workers and referents. The findings for the 99 unexamined referents were extrapolated to account for all 678 unexamined referents. Of the 340 workers and 884 referents included in this analysis, 32 (9.4%) and 68 (7.7%), respectively, had self-reported ulcer disease (OR, 1.25; 95% CI, 0.78 to 1.98). These comparisons between the examined and unexamined participants suggest that selection bias played little or no role in the conclusions of our study. This finding is reassuring, especially in light of the low referent participation rate (28%).

Results of a recent mortality study of US workers involved in the production of TCDD-contaminated substances, including workers from the two plants we studied, suggest that the potential for survivor bias in our study was minimal.[29] Fingerhut et al[29] found that exposed workers were not at elevated risk for death from chronic nonmalignant diseases of the digestive system (standardized mortality ratio, 70; 95% CI, 49 to 96).

It is unlikely that statistical power was a limitation with respect to the negative findings in this study. For most of the laboratory tests, the study had more than 90% power to detect a 10% difference in mean levels between workers and referents. For those outcomes present in 5% of the control group, the study had 50% power to detect a twofold rise in risk among workers compared with referents, and to detect a threefold rise in risk the power was greater than 95%.

In summary, in this population with high exposure to substances contaminated with TCDD, an association was found between prior occupational exposure to chemicals contaminated with TCDD and an elevation in GGT. However, this study did not find an association between TCDD exposure and clinical hepatic and gastrointestinal disease.

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