# Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-p- dioxin

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# Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin

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**Abstract**

***Objective*—Some studies suggest that exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) may affect glucose metabolism and thyroid function. To further assess the relation between exposure to TCDD and endocrine function, data from the largest morbidity study of industrial workers exposed to TCDD were examined.**

***Methods*—A cross sectional study of workers employed >15 years earlier in the manufacture of 2,4,5-trichlorophenol or one of its derivatives at two United States chemical plants was conducted. The referent group consisted of people with no occupational exposure to phenoxy herbicides and were recruited from the neighbourhoods where the workers lived.**

***Results*—A total of 281 workers and 260 unexposed referents participated. The mean current serum lipid adjusted TCDD concentration among workers was 220 pg/g lipid, and among referents was 7 pg/g lipid ($p<0.05$). The half life extrapolated TCDD concentrations (the estimated TCDD concentration when occupational exposure to TCDD stopped) among workers averaged 1900 pg/g lipid (range: not detected–30 000 pg/g lipid). Overall, the prevalence of diabetes mellitus was not significantly different between the workers and referents. Also, there was not a significant positive trend between prevalence of diabetes and increasing serum TCDD concentration. However, diabetes was found in six of 10 (60%) workers with current serum TCDD concentrations >1500 pg/g lipid. After excluding subjects being treated for diabetes, workers in the group with the highest half life extrapolated TCDD concentrations had a significantly increased adjusted mean serum glucose concentration compared with referents ($p=0.03$). Workers were also found to have a significantly higher adjusted mean free thyroxine index compared with referents ($p=0.02$), especially among workers in the group with the highest half life extrapolated TCDD concentrations. However, no evidence was found that workers exposed to TCDD were at increased risk of thyroid disease.**

***Conclusions*—These findings provide modest evidence that exposure to TCDD may affect thyroid function and glucose metabolism.**

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Keywords: dioxin; diabetes mellitus; thyroid function tests; cross sectional study

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Small quantities of dioxins can be found throughout the developed world. As such, concern about the toxicity of these dioxins continues to be widespread. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is the best studied and is among the most toxic dioxin congeners. Among the concerns are effects on endocrine function.

Some human evidence indicates that TCDD may affect glucose metabolism, manifesting as hyperglycaemia. Among the previous studies that examined the association between exposure to TCDD and serum glucose concentration,[1–4] both of the studies that used serum TCDD concentration as the exposure measure found positive associations.[1 3] Among three studies of cohorts exposed to TCDD that reported mortality risk for diabetes mellitus,[5–7] only the study of Pesatori *et al* found a significant increase in risk.[5]

Although there is also human evidence for a TCDD effect on thyroid function, it is inconsistent. Among the four studies that examined the association between exposure to TCDD and effects on the thyroid gland,[2–4 8] exposure to TCDD was significantly associated with increases in serum thyroxine (total $T_4$) concentration in one study,[3] and with decreases in total $T_4$ concentration in another.[8] Only one study found an increased prevalence of thyroid disease.[2] None of the studies reported a significant association between TCDD and concentrations of thyroid stimulating hormone (TSH). To further assess the relation between exposure to TCDD and endocrine function, we examined data from the largest cross sectional morbidity study of industrial workers exposed to TCDD.

## Materials and methods

The details of the study design were previously described.[9] In summary, this study compared an unexposed comparison group with living workers employed >15 years earlier in the production of 2,4,5-trichlorophenol or one of its derivatives, which were substances contaminated with TCDD. The workers were employed in one of two plants located in Newark,

New Jersey, and Verona, Missouri. Four hundred and ninety eligible workers were employed at the New Jersey factory from 1951 to the end of 1969 in the production of 2,4,5-trichlorophenol or one of its derivatives. At the facility in Verona, Missouri, 96 eligible workers were involved in the production of 2,4,5-trichlorophenol or one of its derivatives. Production occurred for about four months in 1968 and from April 1970 to January 1972. Both plants produced various other chemicals, none of which are known or suspected to affect thyroid function or glucose metabolism. To constitute the referent group, one person with no self reported occupational exposure to substances contaminated with TCDD was sought from within the residential neighbourhood of each worker, who matched the worker by age (within 5 years), race, and sex. The study protocol was approved by the National Institute for Occupational Safety and Health (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 standardised interviews and medical examinations between 1987 and 1988. A lifetime medical history was elicited from each participant with interviewer administered questionnaires. To reduce observer bias, all people conducting the medical histories, examinations, and tests were blind to the exposure (worker or referent) of the participant.

Blood was obtained from the participants after a 12 hour fast. The serum was analysed for TCDD,[10] glucose, TSH, total $T_4$, and thyroid hormone binding resin (THBR[$T_3$]). If the initial fasting serum glucose concentration was $\geq$7.8 mmol/l, additional blood was obtained the next morning after another 12 hour fast to remeasure serum glucose. Diabetic subjects taking hypoglycaemic medications were permitted to take their prescribed dose. Glucose was measured with a standard adaptation (Ektachem, Kodak) of the glucose oxidase peroxidase chromogen coupled system for glucose determination in biological fluids.[11] Total $T_4$ was measured with an antibody radioimmunoassay system (Becton Dickinson), and TSH was measured with a standard double antibody radioimmunoassay system (the lower detection limit was 0.5 mU/l)(Becton Dickinson). Thyroid hormone binding resin was measured with the automated Aria HT $T_3$ uptake assay (Becton Dickinson). The free $T_4$ index was calculated because it is considered to be a useful screening test for thyroid dysfunction.[12] For each participant, the free $T_4$ index was calculated as the product of the THBR[$T_3$] and serum $T_4$ concentration. Two participants (one worker, one referent) did not have their blood sampled.

### CASE DEFINITIONS

A participant was defined as having diabetes mellitus if the fasting serum glucose concentration was $\geq$7.8 mmol/l on both days,[13] or if the participant reported a history of diabetes diagnosed by a physician. Medical records were not obtained to confirm self reported diabetes. Thyroid disease was defined as a self reported history of a thyroid disorder diagnosed by a physician (giotre, thyroid problems, or Graves disease). Thyroid stimulating hormone was increased if >6.5 mU/l (the TSH assay lacked sensitivity to detect clinically low TSH concentrations), $T_4$ was increased if >154.4 nmol/l, and $T_4$ was low if <57.9 nmol/l.[14] The free $T_4$ index was considered to be outside the reference range if it was above the 95th percentile (34.25 nmol/l) or below the 5th percentile (20.07 nmol/l) of the referent group.

### ANALYSIS OF DATA

Student's *t* tests were used in the analysis of continuous demographic characteristics. $\chi^2$ Statistics were used to compare categorical demographic characteristics and to evaluate for the presence of participation bias.

To evaluate the association between exposure to TCDD and categorical outcome measures, logistic regression analyses were performed. Multiple linear regression analyses were used to examine continuous outcome measures. A log transformation was applied to glucose to normalise the residuals. Confounders for each outcome were identified before the start of the analysis by a review of the literature. The regression model for diabetes mellitus included age, race, sex, body mass index (BMI, weight in kg divided by height squared in m), history of diabetes among parents or siblings, and current use of medications that can increase serum glucose. The model for glucose included age, race, sex, body mass index, and current use of medications that can increase serum glucose. The regression models for TSH, $T_4$, and free $T_4$ index included age, race, sex, and current use of medications that can alter the particular thyroid test.

For each of the analyses, some participants were excluded initially. The two participants (one worker, one referent) who did not have their blood sampled were excluded from all of the analyses. Those diagnosed with diabetes before the date of first hire into processes contaminated with TCDD were excluded from analysis of diabetes mellitus (one worker, one referent). Those under treatment for diabetes mellitus were excluded from the analyses of glucose concentration (18 workers, 15 referents). Four participants (two workers, two referents) on thyroid replacement medications were excluded from the analyses of TSH, $T_4$, and free $T_4$ index concentrations.

In each model, the linearity assumption was checked for all continuous independent variables. Variables determined to be non-linear in one or more models included BMI, current serum TCDD, and half life extrapolated lipid adjusted TCDD (the estimated TCDD concentration when occupational exposure to TCDD stopped, which was calculated to reflect the 7 year estimated half life of the serum TCDD concentration[15]). Variables found to be non-linear were stratified based on the original cut off points.

Separate regression analyses were conducted with each of three exposure indices in separate models: status as a worker or a referent (a

*Table 1 Characteristics of the study population by lipid adjusted TCDD in serum samples*

| TCDD category (pg/g lipid) | n | Mean (SD) age (y) | White (%) | Men (%) | BMI >29 (%) | Mean (SD) TCDD concentration (pg/gm lipid) |
|---|---|---|---|---|---|---|
| Referents (<20) | 260 | 56.0 (10.5) | 88.8 | 93.5 | 28.8 | 7 (2) |
| All workers† | 281 | 55.4 (10.3) | 89.0 | 95.0 | 29.2 | 220 (434)* |
| TCDD<20 | 76 | 53.0 (9.0) | 92.1 | 85.5* | 28.9 | 11 (5) |
| 20≤TCDD<75 | 66 | 53.6 (10.4) | 81.8 | 97.0 | 24.2 | 40 (16) |
| 75≤TCDD<238 | 66 | 53.1 (9.6) | 89.4 | 98.5 | 31.8 | 133 (45)* |
| 238≤TCDD<3400 | 65 | 61.4 (10.0)* | 92.3 | 100* | 30.8 | 729 (674)* |

*p<0.05 *v* the unexposed referent group.
TCDD=2,3,7,8-tetrachlorodibenzo-p-dioxin.
†The number of all workers is greater than the sum of the four subcategories of workers. This is because the group of all workers includes eight workers for whom serum TCDD was not measured.

*Table 2 Cases of diabetes (n (%)) by diagnostic criteria*

| | Physician diagnosed* | Fasting serum glucose ≥7.8 (mmol/l)† | Total |
|---|---|---|---|
| Workers (n=279) | 17 (6.1) | 9 (3.2) | 26 (9.3) |
| Referents (n=258) | 15 (5.8) | 3 (1.2) | 18 (7.0) |

One worker and one referent were excluded because the date of diagnosis preceded the date of first hire into TCDD contaminated processes (in the case of the referent the diagnosis date preceded the matched worker's date of first hire into TCDD contaminated processes). Also, two participants (one worker and one referent) did not have their blood sampled and were excluded.
*Self reported history of physician diagnosed diabetes mellitus.
†These participants did not self report a history of physician diagnosed diabetes mellitus.

*Table 3 Adjusted OR for diabetes mellitus by TCDD in serum samples*

| TCDD category (pg/g lipid) | n | Proportion with diabetes mellitus (%) | Adjusted OR* (95% CI) |
|---|---|---|---|
| Referents (<20)† | 258 | 7.0 | 1.00 |
| All workers‡ | 279 | 9.3 | 1.49 (0.77 to 2.91) |
| TCDD<20 | 76 | 9.2 | 2.11 (0.77 to 5.75) |
| 20≤TCDD<75 | 66 | 9.1 | 1.51 (0.53 to 4.27) |
| 75≤TCDD<238 | 65 | 4.6 | 0.67 (0.17 to 2.57) |
| 238≤TCDD<3400 | 65 | 15.4 | 1.97 (0.79 to 4.90) |

TCDD=2,3,7,8-tetrachlorodibenzo-p-dioxin.
*Adjusted for race, sex, age, BMI, family history of diabetes mellitus, and current use of medications that can increase serum glucose concentration.
†Two referents were excluded (one because blood was not drawn and another because the referent's date of diagnosis preceded the matched worker's date of first hire into TCDD contaminated processes).
‡The number of all workers is greater than the sum of the four subcategories of workers. This is because the group of all workers includes seven workers for whom serum TCDD was not measured. Two workers were excluded from the all worker category (one because blood was not sampled and another because the date of diagnosis preceded the worker's date of first hire into TCDD contaminated processes).

dichotomous exposure variable), current serum TCDD concentrations measured at the time of examination and adjusted for serum lipid concentration, and half life extrapolated lipid adjusted serum TCDD concentrations separately calculated for each worker. The workers were stratified before the start of the analyses into four groups of about equal size based on serum TCDD concentrations. Serum TCDD concentrations were not obtained for eight workers and these workers were excluded from analyses involving serum TCDD concentrations and half life extrapolated serum TCDD concentrations. Each group of exposed workers was compared with the unexposed referent group, and either odds ratios (ORs) (with 95% confidence intervals (95% CIs)) or p values are provided.

No important interactions between other covariates and exposure to TCDD were identified. All logistic models seemed to have adequate fit.[16] All analyses were carried out with SAS procedures (SAS Institute, Cary, North Carolina, USA).

## Results

Of the 586 workers at the two plants who were eligible for the study, 400 (68.3%) were found to be alive and could be located. A total of 142 (24.2%) workers were dead, and 44 (7.5%) could not be located. From the two plants, all 400 workers 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 is provided in table 1. Workers were found to have a significantly increased mean current serum lipid adjusted TCDD concentration (workers=220 pg/g lipid (range=not detected–3400 pg/g lipid, median=68 pg/g lipid), referents=7 pg/g lipid (range=not detected–20 pg/g lipid), p<0.001). Half life extrapolated lipid adjusted serum TCDD concentration were also increased among workers (mean=1900 pg/g lipid, median=476 pg/g lipid). Overall, there were no significant differences or consistent patterns of differences between workers and referents for any demographic characteris-

*Table 4 Adjusted geometric mean serum glucose concentration by TCDD in serum samples*

| TCDD category (pg/g lipid) | n | Adjusted geometric mean glucose concentration* (mmol/l) (GSE) | p Value* |
|---|---|---|---|
| Referents (<20)† | 244 | 5.21 (1.01) | — |
| All workers‡ | 262 | 5.30 (1.01) | 0.16 |
| TCDD<20 | 72 | 5.41 (1.02) | 0.05 |
| 20≤TCDD<75 | 61 | 5.13 (1.02) | 0.43 |
| 75≤TCDD<238 | 63 | 5.34 (1.02) | 0.21 |
| 238≤TCDD<3400 | 59 | 5.38 (1.02) | 0.12 |

TCDD=2,3,7,8-tetrachlorodibenzo-p-dioxin, GSE=geometric standard error of the adjusted geometric mean.
*Adjusted for race, sex, age, BMI, and current use of medications that can increase serum glucose concentration. The p values are for the comparison between the worker group and the referents. To calculate the 95% CI, the upper bound=geometric mean*(GSE)$^{1.96}$, and the lower bound=geometric mean* (1/GSE$^{1.96}$).
† 16 Referents were excluded (15 were receiving treatment for diabetes mellitus, and one did not have blood sampled).
‡The number of all workers is greater than the sum of the four subcategories of workers. This is because the group of all workers includes seven workers on whom serum TCDD was not measured. 19 Workers were excluded from the all worker category (18 were receiving treatment for diabetes mellitus, and one did not have blood sampled).

*Table 5 Adjusted geometric mean serum glucose concentration by half life extrapolated TCDD in serum samples*

| *Half life extrapolated TCDD category (pg/g lipid)* | *n* | *Adjusted geometric mean glucose concentration* (mmol/l) (GSE)* | *p Value** |
|---|---|---|---|
| Referents (<20)† | 244 | 5.21 (1.01) | — |
| Workers-all‡ | 262 | 5.30 (1.01) | 0.16 |
| TCDD<140 | 73 | 5.38 (1.02) | 0.10 |
| 140≤TCDD<495 | 60 | 5.27 (1.02) | 0.59 |
| 495≤TCDD<1860 | 62 | 5.16 (1.02) | 0.63 |
| 1860≤TCDD<30000 | 60 | 5.45 (1.02) | 0.03 |

TCDD=2,3,7,8-tetrachlorodibenzo-p-dioxin, GSE=geometric standard error of the adjusted geometric mean.
*, †, ‡ See footnotes for table 4.

tics (age, race, sex) identified as confounders. Workers in the group with the highest serum TCDD concentrations were older and a higher proportion were men compared with the referent group.

Among the examined participants, 26 (9.3%) workers and 18 (7.0%) referents met the case definition for diabetes (table 2). Table 3 provides the logistic regression analysis findings for diabetes mellitus. The risk for diabetes mellitus among exposed workers was not found to be significantly increased (adjusted OR 1.49, 95% CI 0.77 to 2.91). No dose response trend with serum TCDD was found. The findings were similar for the half life extrapolated serum TCDD concentrations (data not shown). However, it should be noted that among the 10 workers with serum TCDD concentrations >1500 pg/g lipid (and among the 10 workers with half life extrapolated serum TCDD concentrations over 11 600 pg/g lipid), six (60%) had diabetes mellitus.

Recently, the Expert Committee of the American Diabetes Association lowered the diagnostic criterion for diabetes from 7.8 to 7.0 mmol/l.[17] We reanalysed our data with these new criteria. When we classified as diabetic all participants with initial serum glucose concentrations of ⩾7.0 mmol/l, the findings were essentially unchanged from those using the initial definition for diabetes.

Tables 4 and 5 provide the results of the linear regression analyses for serum glucose concentration. Serum glucose concentrations were not significantly different between exposed workers and referents (p=0.16). Also, no dose-response trend with serum TCDD was found. However, workers in the group with the highest half life extrapolated serum TCDD concentrations had a significantly increased adjusted mean serum glucose concentration compared with referents (p=0.03, table 5). When the three participants (two workers and one referent) with glucose concentrations >10 mmol/l were removed, this increase was no longer significant (p=0.29).

Only three participants (two workers and one referent) self reported a history of thyroid disorder that was diagnosed after the start of employment in a process contaminated with TCDD. The specific type of thyroid disorder experienced by these participants is unknown; however, two were currently receiving thyroid replacement medication, and the third reported admission to hospital for the thyroid condition that required "nuclear medicine".

Tables 6 and 7 provide the linear regression findings for the thyroid function measures. Workers were found to have a significantly higher adjusted mean free $T_4$ index than referents (p=0.02). Although there was not a clear dose-response trend with either serum measure of exposure to TCDD, workers in the group with the highest half life extrapolated serum TCDD concentrations had the highest adjusted mean free $T_4$ index, which was significant when compared with the referent mean (p=0.004, table 7). With current serum TCDD concentrations, workers in the group with the third highest TCDD concentrations (74–237 pg/g lipid) had the highest adjusted mean free $T_4$ index (table 6). However, a higher proportion of referents than workers had an free $T_4$ index concentration above the reference range (workers 3.0%, referents 5.1%, adjusted OR 0.58, 95% CI 0.24 to 1.43), and below the reference range (workers 2.2%, referents 5.1%, adjusted OR 0.41, 95% CI 0.15 to 1.11). Also, each of the worker groups had a lower proportion with out of range free $T_4$ index concentrations than the referent group (data not shown); however, none of the differences were significant.

Workers also had a higher adjusted mean total $T_4$ concentration than referents (p=0.07, tables 6 and 7). Although each of the worker

*Table 6 Adjusted mean TSH, $T_4$, and free $T_4$ index (FTI) by TCDD category in serum samples*

| | | *TSH (mU/l)* | | *$T_4$ (nmol/l)* | | *FTI (nmol/l)* | |
|---|---|---|---|---|---|---|---|
| *TCDD category (pg/gm lipid)* | *n* | *Adjusted mean* (SE)* | *p Value* | *Adjusted mean† (SE)* | *p Value* | *Adjusted mean† (SE)* | *p Value* |
| Referents (<20)‡ | 257 | 1.91 (0.13) | — | 98.8 (1.05) | — | 26.8 (0.28) | — |
| All workers¶ | 278 | 1.99 (0.13) | 0.66 | 101.4 (1.01) | 0.07 | 27.8 (0.27) | 0.02 |
| TCDD<20 | 75 | 2.21 (0.25) | 0.28 | 102.7 (1.99) | 0.08 | 27.7 (0.54) | 0.15 |
| 20≤TCDD<75 | 66 | 1.95 (0.26) | 0.88 | 99.4 (2.09) | 0.79 | 27.4 (0.56) | 0.36 |
| 75≤TCDD<238 | 66 | 1.89 (0.26) | 0.94 | 102.7 (2.09) | 0.09 | 28.2 (0.56) | 0.03 |
| 238≤TCDD<3400 | 64 | 1.77 (0.27) | 0.65 | 100.1 (2.16) | 0.58 | 27.7 (0.58) | 0.19 |

TCDD=2,3,7,8-tetrachlorodibenzo-p-dioxin, SE=standard error of the adjusted mean.
*Adjusted for race, sex, age, and current use of medications that can alter TSH. The p values are for the comparison between the worker group and the referents.
†Adjusted for race, sex, age, and current use of medications that can alter $T_4$. The p values are for the comparison between the worker group and the referents.
‡Three referents were excluded (one because blood was not sampled and two because they were taking thyroid replacement medication).
¶The number of all workers is greater than the sum of the four subcategories of workers. This is because the group of all workers includes seven workers on whom serum TCDD was not measured. Three workers were excluded from the all worker category (one because blood was not sampled and two because they were taking thyroid replacement medication).

*Table 7 Adjusted mean TSH, $T_4$, and free $T_4$ index (FTI) by half life extrapolated TCDD category in serum samples*

| Halflife extrapolated TCDD category (pg/g lipid) | n | TSH (mU/l) | | $T_4$ (nmol/l) | | FTI (nmol/l) | |
|---|---|---|---|---|---|---|---|
| | | Adjusted mean* (SE) | p Value | Adjusted mean† (SE) | p Value | Adjusted mean† (SE) | p Value |
| Referents (<20)‡ | 257 | 1.91 (0.13) | — | 98.8 (1.05) | — | 26.8 (0.28) | — |
| Workers-all¶ | 278 | 1.99 (0.13) | 0.66 | 101.4 (1.01) | 0.07 | 27.8 (0.27) | 0.02 |
| TCDD<140 | 74 | 2.11 (0.26) | 0.48 | 102.7 (2.03) | 0.08 | 27.8 (0.55) | 0.11 |
| 140≤TCDD<495 | 65 | 1.82 (0.27) | 0.76 | 100.4 (2.11) | 0.48 | 27.6 (0.57) | 0.25 |
| 495≤TCDD<1860 | 66 | 2.15 (0.26) | 0.42 | 99.3 (2.09) | 0.81 | 26.9 (0.56) | 0.95 |
| 1860≤TCDD<30000 | 66 | 1.77 (0.27) | 0.64 | 102.3 (2.16) | 0.14 | 28.7 (0.58) | 0.004 |

TCDD=2,3,7,8-tetrachlorodibenzo-p-dioxin, SE=standard error of the adjusted mean.
*, †, ‡, ¶ See footnotes to table 6.

*Table 8 Comparison of self reported history of physician diagnosed diabetes mellitus between examined and refusing subjects and between examined and refusing referents*

| Outcome | Examined workers | | | Refusant workers | | | Unadjusted OR (95% CI) |
|---|---|---|---|---|---|---|---|
| | Yes | No | Excluded | Yes | No | Excluded | |
| Comparison between examined and refusing workers: | | | | | | | |
| Total number | 281 | | | 68 | | | |
| Diabetes mellitus: self reported | 17 (6.1%) | 263 | 1* | 8 (11.8%) | 60 | 0 | 0.49 (0.20 to 1.16) |
| Comparison between examined and refusing referents: | | | | | | | |
| Total number | 260 | | | 100 | | | |
| Diabetes mellitus: self reported | 15 (5.8%) | 244 | 1† | 9 (9.3%) | 88 | 3 | 0.60 (0.26 to 1.41) |

*The participant was excluded because the date of diagnosis preceded the date of first hire into TCDD contaminated processes.
†Participants were excluded from the analysis if they could not recall whether they had the disease of interest, or because the date of diagnosis preceded the matched worker's date of first hire into TCDD contaminated processes.

groups had a higher adjusted mean total $T_4$ than the referent group, none of the differences was significant, and a dose-response trend was not found with either measure of exposure to TCDD. Only two participants (both referents) had low $T_4$ concentrations, and only two participants (both workers) had increased $T_4$ concentrations. For TSH concentration, little difference was found between workers and referents (tables 6 and 7). Only seven participants had increased TSH concentrations (three workers and four referents).

## Discussion

Our study does not provide strong evidence that exposure to TCDD is associated with an increased risk of diabetes mellitus. However, diabetes was found in a high proportion (60%) of workers with current serum TCDD concentrations >1500 pg/g lipid. This finding suggests that workers with very high TCDD body burdens may have an increased risk of diabetes mellitus. It should be noted that data collected from 211 workers while still working at the two study plants showed that the mean BMI was significantly higher among the six diabetic workers with TCDD concentration >1500 pg/g lipid compared with all other workers (p=0.002) and the other diabetic workers (p=0.03). However, with data from our study, no differences were found in BMI between these three groups of workers. Although antecedent obesity is a known risk factor for diabetes,[18] it is unlikely that the higher BMIs completely explain the high proportion of heavily exposed workers with diabetes.

The initial criteria used in this study to identify undiagnosed diabetic patients (fasting glucose ⩾7.8 mmol/l) have been shown to produce an underestimate of the numbers.[19] New diagnostic criteria for diabetes, based on a fasting plasma glucose of 7.0 mmol/l, improves the ability to identify undiagnosed diabetic subjects.[17] When we re-examined our data with this new cut off point, the findings were essentially unchanged from those with the initial definition for diabetes. Therefore, the findings from this study do not seem to be limited by the diabetes case definition. However, a possible limitation in this study is the low statistical power for examining diabetes mellitus. Our study had about 50% power to detect a twofold increase in risk of this condition.

Other studies have examined the association between exposure to TCDD and the risk of diabetes mellitus.[1 2 5–8] However, the findings from these studies are mixed. A study of United States Air Force personnel (Ranch Hands) responsible for spraying agent orange, a herbicide mixture contaminated with TCDD, in Vietnam from 1962–71 found that the proportion of ranch hands and unexposed people with diabetes were similar.[8] However, Ranch Hands with half life extrapolated TCDD concentrations of ⩾94 pg/g lipid had an increased relative risk (RR) of diabetes (RR 1.5, 95% CI 1.2 to 2.0).[1] Another morbidity study of workers occupationally exposed to TCDD found that the unexposed referent group had a higher lifetime prevalence of diabetes than the group exposed to TCDD.[2] This study did not use serum TCDD concentration as the exposure measure in the diabetes analyses.

Three mortality studies of populations exposed to TCDD reported risk of mortality from diabetes mellitus.[5–7] Pesatori *et al*[5] studied those in the Seveso region of Italy who were exposed to TCDD after an explosion at a trichlorophenol plant. The Seveso region was divided into zones A, B, and R (zone A had the highest TCDD contamination, and zone R the lowest). The reference group consisted of residents in the surrounding non-contaminated territory. Fifteen years after the Seveso explosion, risk of mortality from diabetes mellitus

was increased among female residents of zone B (RR 1.9, 95% CI 1.1 to 3.2) and zone R (RR 1.2, 95% CI 1.0 to 1.6). Male residents in these zones had non-significantly increased risks. Risk of diabetes mellitus was not significantly increased among residents in Zone A.

The two other mortality studies of populations exposed to TCDD involved workers employed at pesticide producing chemical plants.[6 7 20] Neither found a significantly increased risk of mortality from diabetes mellitus. The two plants that we studied were included in a large cohort mortality study that found a standardised mortality ratio (SMR) of 1.08 (95% CI 0.61 to 1.74) for mortality from diabetes mellitus.[6 20]

Our finding that workers with the highest half life extrapolated serum TCDD concentrations had significantly increased mean serum glucose concentrations suggests that high exposure to TCDD may have an effect on glucose metabolism. Among the three previous studies that examined the association between exposure to TCDD and serum glucose concentration,[1 3 4] both of the studies that used serum TCDD concentration as the exposure measure found positive associations.[1 3]

As for effects on thyroid hormone homeostasis, our study found that workers exposed to TCDD had a modestly higher mean free $T_4$ index than the referents. However, the proportion of workers with free $T_4$ index concentrations above the reference range was non-significantly lower than referents. It should also be noted that this study had limited statistical power to detect a difference in out of range free $T_4$ index concentrations (50% power to detect a twofold rise in risk). These findings suggest that exposure to TCDD may have a modest, subclinical effect on thyroid function. Although the free $T_4$ concentration is a useful screening test for thyroid dysfunction, only one other study has evaluated this outcome.[21] The 1982 Ranch Hand baseline study found no significant differences in free $T_4$ index between Ranch Hands and the unexposed comparison group; however, analyses with serum TCDD concentrations were not performed.[21]

We also examined the total $T_4$ (protein bound $T_4$ plus free $T_4$) concentration which is less specific for thyroid dysfunction and more difficult to interpret than the free $T_4$ index. Our study found that exposed workers had modest subclinical increases in serum total $T_4$ concentration, which is consistent with the findings among another group of chemical workers.[3] That study found positive associations between current serum TCDD concentration and both total $T_4$ ($p=0.02$) and thyroid binding globulin ($p=0.001$), but not TSH.[3] Those workers also had an increased prevalence of pooled thyroid disorders (giotre, thyrotoxicosis, hypothyroidism, and thyroid adenoma) than an unexposed referent group ($p<0.05$).[2] Two other cross sectional studies examined the association between exposure to TCDD and effects on the thyroid gland.[4 8] In one study,[8] an association was found between current lipid adjusted TCDD concentration and an abnormally low total $T_4$ ($p=0.03$). Several other thyroid outcomes examined in that study were found not to be associated with serum lipid adjusted TCDD concentration (history of thyroid disease, and serum concentrations of TSH, antithyroid antibodies, and total $T_4$ (when examined continuously)).[8] Finally, another cross sectional study found no significant differences in either serum total $T_4$ or thyroid binding globulin between the workers exposed to TCDD and the unexposed control group.[4] Serum TCDD concentrations were not measured in that study.

To assess the potential magnitude of participation bias in our study, a telephone interview was attempted with all of the workers who refused to be examined, a 10% random sample of the referents who refused all participation, and all of the referents who provided lifetime occupational histories but refused to be examined. Of the 115 refusing workers and 129 refusing referents who were contacted, 68 (57%) and 100 (78%), respectively, agreed to be interviewed by phone. These people were asked questions about diabetes similar to those asked in our medical study. A lower proportion of workers examined reported a history of diabetes than did the refusing workers; however, the difference was not significant (table 8). Also, no significant differences in age or sex were found between the two groups of workers. Similar results were found for the referents (table 8). These results suggest that participation bias is unlikely to be responsible for our study findings.

In conclusion, this study of workers with high occupational exposure to TCDD $\geqslant$15 years earlier, many of whom continued to have persistently increased TCDD body burdens, found evidence for modest effects on glucose metabolism and thyroid function. Our findings are consistent with some but not all other cross sectional medical studies of people exposed to TCDD.

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