Dioxin and diabetes mellitus: an analysis of the combined NIOSH and Ranch Hand data

K Steenland, G Calvert, N Ketchum, J Michalek

Abstract

Objectives—To reanalyze in a similar manner the two principal studies of TCDD (tetrachlorodibenzo-p-dioxin) and diabetes in an attempt to reconcile disparate results.

Methods—Data from 990 United States Air Force veterans (Ranch Hand) and 1275 referents were reanalyzed, and a NIOSH population of 267 chemical workers and 227 referents. The Ranch Hand veterans had lower concentrations of lipid adjusted serum TCDD (median 12 parts per trillion (ppt)) than the NIOSH workers (median 75 ppt) when examined in the late 1980s. An analysis was conducted of the combined data sets, adopting a uniform approach to outcome definition, data analysis, and covariate control.

Results—The combined exposed groups did not differ markedly from the combined non-exposed groups for prevalence of diabetes (odds ratio (OR) 1.17, 95% confidence interval (95% CI) 0.92 to 1.48), with no evidence of heterogeneity of exposure effect between studies. Also virtually no difference was found between combined exposed and non-exposed groups in mean fasting serum glucose (difference in log serum glucose 0.002, 95% CI −0.006 to 0.010), and there was little evidence in either study of a dose-response trend for fasting serum glucose. An increasing trend was found (p=0.0001) in prevalence of diabetes with increased TCDD (at the time of examination or at time of last exposure) among the Ranch Hand population, with excess risk largely confined to the highest 8% of the exposed group (>78 ppt serum TCDD), which had an OR of 3.21 (95% CI 1.81 to 5.72) versus those with <10 ppt TCDD. However, no such positive dose-response was found in the NIOSH population.

Conclusions—There was little overall evidence that the exposed workers were at higher risk than the non-exposed workers of diabetes or abnormal fasting glucose. However, the Ranch Hand subjects showed a positive dose-response for diabetes, whereas the more highly exposed NIOSH subjects did not. The reason for the difference in diabetes dose-response trends between the two studies is unknown.

Keywords: dioxin; diabetes; TCDD

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is the most potent congener of a class of chemicals known as dioxins. There has been some concern about the possible relation between TCDD and diabetes, due to animal data indicating that TCDD affects glucose transport and reports about increased morbidity from diabetes or increased serum glucose in humans exposed to TCDD. The two principal reports about TCDD and diabetes in humans have been published by Henriksen et al and Calvert et al; they provide the data for the current analysis and are discussed in detail below. A third report is of limited interest because its assessment of diabetes was limited to hospital admissions. A fourth report is limited to serum glucose; these authors found a positive trend of increased fasting glucose with increasing current exposure to TCDD among 138 men occupationally exposed for at least 35 years, after controlling for age and current body mass index. Finally, a recent study reported on 69 people exposed near a plant which produced Agent Orange; their serum TCDD concentrations ranged from 2 to 94 parts per trillion (ppt). All subjects had a normal glucose tolerance test. However, the seven subjects with TCDD above 15 ppt had markedly higher concentrations of plasma insulin at fasting and after the glucose load than those below 15 ppt. High insulin with normal glucose suggests insulin resistance and may be a precursor to impaired glucose tolerance and diabetes.

There have also been reports with mixed results about mortality from diabetes among workers exposed to dioxins. However, mortality is a much less sensitive end point than morbidity and typically mortality studies are unable to control for several important risk factors for diabetes—for example, obesity and family history.

The two principal published studies on morbidity from diabetes mellitus (United States Air Force veterans and United States chemical workers) are summarised in table 1. Further details on TCDD concentrations in both populations can be found in table 2.

The first study concerned 989 United States Air Force veterans of Operation Ranch Hand, who had sprayed agent orange contaminated with TCDD in Vietnam in the 1960s and 1970s, and a non-exposed comparison group of other Air Force veterans (n=1276). A cross sectional study of prevalent diabetes relative to serum concentrations of TCDD was conducted, with prevalence of diabetes ascertained to the end of June 1995 and serum dioxin ascertained in the late 1980s or the early 1990s.

The long half life of TCDD (about 7–9 years)
## Table 1: Comparison of originally published NIOSH and Ranch Hand studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Age (y, mean)</th>
<th>Confounder adjustment</th>
<th>Median serum dioxin concentration of exposed subjects (lipid adjusted)</th>
<th>Median serum dioxin of non-exposed subjects</th>
<th>Diabetes definition</th>
<th>Diabetes prevalence</th>
<th>OR or RR of diabetes, exposed vs non-exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH</td>
<td>281 exposed, 25 non-exposed</td>
<td>65</td>
<td>Self-report of physician diagnosis or fasting glucose ≥ 126 mg/dl</td>
<td>68 ppt (range 2–3388) 1987–8 (range 0–618)</td>
<td>6.1 (range 2.0–19.7)</td>
<td></td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td>Ranch Hand</td>
<td>990 exposed, 1276 non-exposed</td>
<td>56</td>
<td>Age, race, sex, BMI, family history, medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Materials and methods

#### OUTCOME DEFINITIONS

- **Diabetes** was defined either reporting diabetes diagnosed by a physician, or having an oral glucose tolerance test (OGTT) >200 mg/dl (Ranch Hand), or having a fasting serum glucose of 126 mg/dl or more (NIOSH). The NIOSH did not conduct the OGTT test; however, a fasting glucose of 126 mg/dl is about
Table 2  Serum TCDD concentrations (ppt) of exposed subjects in the current analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
<th>&gt;10 ppt (n (%))</th>
<th>Back extrapolated median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH (n=259)*</td>
<td>229 (446)</td>
<td>75</td>
<td>2–3388</td>
<td>226 (87)</td>
<td>584 (35–19744)</td>
</tr>
<tr>
<td>Ranch Hand (n=990)†</td>
<td>27 (45)</td>
<td>12</td>
<td>0–618</td>
<td>567 (57)</td>
<td>94 (27–3290)</td>
</tr>
<tr>
<td>Total (n=1248)</td>
<td>69 (223)</td>
<td>16</td>
<td>0–3388</td>
<td>793 (63)</td>
<td>138 (27–19744)</td>
</tr>
</tbody>
</table>

*Excludes women and eight men who had missing TCDD concentrations.
†One non-exposed subject in the original analysis was found to actually have been exposed, leading to 990 exposed in the present analysis in the original publication (Hennrikus et al 1997).
‡Calculated only for those with >10 ppt.
§The limit of detection varied by sample volume of blood available; the median was 3 ppt.

This led to a combined population of 2759 exposed and non-exposed men for the analysis of prevalence of diabetes (494 from NIOSH (23%), 2265 from Ranch Hand (77%)). Of these 2759, 1257 (45%) were exposed (990 from Ranch Hand, 267 from NIOSH). Of the 2759 total population, 366 (13%) were diabetic (315 from Ranch Hand, 14% prevalence, 51 from NIOSH, 10% prevalence). All diabetic subjects had been diagnosed after exposure; 29% were diagnosed through high glucose at the time of examination.

Ranch Hand fasting serum glucose was based on a 1992 examination, which included data on 2125 subjects. For the analysis of fasting serum glucose, diabetic subjects diagnosed before the examination were eliminated from both data sets (306 from Ranch Hand and 32 from NIOSH). This left a population with fasting glucose values of 2309 subjects.

For the time to diabetes analysis, we restricted the data set to those who were exposed. Time was defined as time from last exposure to diagnosis of diabetes for diabetic subjects. For the non-diabetic group, time was defined as the time from last exposure to end of follow up. This led to a data set of 1234 people, 264 from NIOSH (21%), and 990 from Ranch Hand (79%) among whom there were 175 with diabetes (prevalence of 14%), 28 from NIOSH (11% prevalence) and 147 from Ranch Hand (15% prevalence). Thirty one per cent of the exposed diabetic subjects were diagnosed at the time of the examination.

EXPOSURE VARIABLES

Exposure variables analyzed included a dichotomous variable for exposure (exposed v non-exposed), as well as a continuous variable which was either lipid adjusted TCDD at the time of the examination, or lipid adjusted back extrapolation to time of last occupational exposure using the estimated half life of TCDD. Back extrapolation was done by assuming a first order elimination model:

$$TCDD_t = TCDD_0 \times e^{-\lambda \times \Delta t}$$

where $t$ is serum TCDD at the time of last exposure, $t_0$ is serum TCDD at the time of the examination, $\Delta t$ is the time between last exposure and the time of the examination, and $\lambda$ is 0.0797 based on assuming an 8.7 year half life.

Serum concentrations were measured by the same laboratory for both studies, with the same methods. Exposure-response analyses by back extrapolated TCDD were conducted only among exposed subjects who had TCDD > 10 ppt at the time of the examination, which excluded all referents from both studies, as well as the “background group” from Ranch Hand, and 33 (13%) of the exposed workers from the NIOSH study. The rationale for these exclusions was that a meaningful back extrapolated value cannot be calculated for subjects who have returned to background concentrations of TCDD, as it cannot be stated how long they have been at background concentration. Analyses by back extrapolated TCDD were restricted to 793 people, 226 from NIOSH (29%), 567 from Ranch Hand (71%).

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**ANALYTICAL APPROACH**

Analyses were conducted for either dichotomous exposure (exposed vs non-exposed), or by concentration of serum TCDD. Prevalence of diabetes was analyzed by logistic regression (SAS PROC LOGIST\(^3\)), fasting glucose (log serum glucose, nmol/l) was analyzed by linear regression (SAS PROC REG), and time from last exposure to diagnosis of diabetes was analyzed by Cox’s regression (SAS PROC PHREG). Supplementary logistic regression analyses also considered abnormal serum glucose (>115 mg/dl) as a dichotomous outcome. Analyses of time to diabetes were somewhat limited by the fact that 31% of the exposed diabetic subjects were ascertained by high fasting glucose at time of examination, and hence their time to diabetes was likely to be underestimated compared with those with a diagnosis by a doctor.

Both separate analyses of each study and combined analyses were conducted for all outcomes. Results of combined analyses are not presented if results differed markedly between studies, as judged by inspection of effect measures and evaluation of study-exposure interaction. TCDD (at the time of the examination) and back extrapolated TCDD were analyzed both as continuous variables (logged and unlogged) and as categorical variables. For the logged variable, 1.0 was added to the TCDD concentration if the TCDD concentration was 0, to avoid taking the log of 0. Log transformation tends to diminish the influence of those with extremely high TCDD concentrations on the regression; TCDD concentrations are log normally distributed with a few very high values. Categorical analyses were done by dividing the exposed subjects who had TCDD concentrations (at the examination) above 10 ppt into quartiles, and considering the group with TCDD ≤ 10 ppt as the referent. Those above 10 ppt represented 63% of the exposed population, and 29% of the combined exposed and non-exposed population. Those with TCDD ≤ 10 were the non-exposed population from both studies, the “background” exposed group from Ranch Hand, and the 33 NIOSH exposed subjects with TCDD < 10 ppt. Categorical analyses with back extrapolated TCDD were restricted entirely to those with TCDD above 10 ppt at the time of the examination, and were done by dividing that population into quartiles, and considering the lowest group as referent.

**Results**

**EXPOSURE CONCENTRATIONS**

Exposure concentrations in terms of serum TCDD (ppt) for the population studied here are given in table 2. The NIOSH population had considerably higher concentrations than the Ranch Hand population.

**PREVALENCE OF DIABETES**

The OR for exposed versus non-exposed subjects (not shown) was 1.17 (95% CI 0.92 to 1.48). The ORs were virtually the same for each study (1.18, 95% CI 0.91 to 1.52 for Ranch Hand, 1.22, 95% CI 0.65 to 2.29 for NIOSH).

Results for dose-response analyses by TCDD at examination are shown in table 3. The dose-response for the two study populations were markedly different. The dose-response for TCDD was considerably stronger among the Ranch Hand population, although this population overall had lower TCDD concentrations. As a consequence, results combining the two studies are not presented. The positive trend for untransformed TCDD in the NIOSH cohort was due to the fact that...
the four men with the highest TCDD values in the NIOSH data were diabetic; log transformation of TCDD lessened the influence of these very high values and eliminated most of the positive effect in the NIOSH cohort. Furthermore, categorical analyses indicated no positive trend in the NIOSH cohort.

Dose-response analyses for back extrapolated TCDD, assessed only for those with TCDD >10 ppt at the time of the examination, are shown in Table 4. These are qualitatively similar to the results for TCDD at the time of the examination; positive results are largely restricted to the Ranch Hand cohort.

To further explore the effect for TCDD in the Ranch Hand population, we considered the possibility of effect modification by age or body mass index. After dividing the Ranch Hand cohort into high and low body mass index (cut off point at the median 27.3), and high and low age (cut off point at the median 49 years), we found no marked effect modification by age or body mass index. An analogous analysis of the NIOSH data likewise found little evidence of effect modification.

We also considered a model for the Ranch Hand population in which the non-exposed subjects only were used as the comparison, and a separate category was created for the exposed subjects with TCDD <10 ppt (at the time of the examination). The ORs (95% CIs) for Ranch Hand exposed versus the non-exposed were 0.83 (0.56 to 1.21), 1.33 (0.86 to 2.06), 1.29 (0.82 to 2.04), 1.08 (0.64 to 1.83), and 3.11 (1.74 to 5.55), for exposed <10 ppt, exposed 10–17 ppt, exposed 17–30 ppt, exposed 30–78 ppt, and exposed ≥78 ppt, confirming that the increased risk was found only in the highest TCDD category. This category (>78 ppt) represents the top 8% of exposure in the Ranch Hand cohort (n=70).

**FASTING SERUM GLUCOSE**

We found little evidence of an increase in log serum glucose for the exposed versus non-exposed subjects. The difference of log serum glucose between exposed and non-exposed was 0.002 (95% CI −0.006 to 0.010). There was little evidence of effect modification by study.

Table 4 presents results for dose-response trends between TCDD and serum glucose. The combined studies showed a positive trend of increasing log serum glucose with increasing TCDD, with little heterogeneity between the two separate studies. However, quartile analyses did not suggest any consistent trend, for either study or for the combined data. Furthermore, the positive trend with TCDD in the combined data was entirely dependent on three observations (out of 2309) with the highest influence (measured by the d-beta statistic from PROC REG); these were three NIOSH subjects with very high serum glucose concentrations (above 180 mg/dl or 10 mmol/l). The positive linear trend with TCDD disappeared (in fact became slightly negative) when these three men were excluded. Calvert et al had noted the influence of these three subjects in the earlier publication of these data. A weak positive trend was noted with log TCDD in both studies separately and in the combined data; again in the combined data this trend changed from positive to negative with the exclusion of the three influential values. Analyses with back extrapolated TCDD (not shown) had a similar pattern as TCDD at the time of the examination.

We also considered a dichotomised variable, abnormal (>115 mg/dl) serum (fasting) glucose, as the outcome variable, through logistic regression. In the combined data set there were 96 subjects with abnormal serum glucose (4% of the subjects, 29 from NIOSH, and 67 from Ranch Hand). There was no effect of exposure on the risk of abnormal serum glucose (OR 0.92 for exposed subjects v non-exposed, 95% CI 0.55 to 1.92), with no evidence of heterogeneity between studies. Furthermore there were no strong trends between TCDD, log TCDD, back extrapolated TCDD, or the log of back extrapolated TCDD and abnormal serum glucose; nor was any evidence of...
Table 5  Results for linear regression

<table>
<thead>
<tr>
<th>Study</th>
<th>Coefficient for TCDD (95% CI)*</th>
<th>Coefficient for log TCDD (95% CI)*</th>
<th>Change in log serum glucose by quartile of TCDD &gt;10 ppt (95% CI), referent &lt;=10 ppt†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranch Hand</td>
<td>0.00006 (–0.00009 to 0.00221)</td>
<td>0.0016 (–0.0025 to 0.0057)</td>
<td>–0.001 (–0.016 to 0.016), –0.001 (–0.017 to 0.014), –0.011 (–0.028 to 0.004), 0.014 (–0.024 to 0.038)</td>
</tr>
<tr>
<td>NIOSH</td>
<td>0.00004 (–0.00001 to 0.00009)</td>
<td>0.0033 (–0.0047 to 0.0113)</td>
<td>–0.016 (–0.077 to 0.045), –0.017 (–0.065 to 0.031), –0.033 (0.078 to 0.012), 0.014 (–0.017 to 0.045)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.00004 (–0.00001 to 0.00008)</td>
<td>0.0025 (–0.0010 to 0.0060)</td>
<td>–0.004 (–0.019 to 0.013), –0.005 (–0.016 to 0.011), –0.017 (–0.033 to 0.007), 0.018 (0.001 to 0.035)</td>
</tr>
<tr>
<td>Combined without the three most influential observations</td>
<td>–0.00001 (–0.00005 to 0.00003)</td>
<td>–0.0004 (–0.0039 to 0.0032)</td>
<td>–0.003 (–0.018 to 0.013), –0.005 (–0.020 to 0.011), –0.017 (–0.033 to −0.001), 0.004 (–0.012 to 0.020)</td>
</tr>
</tbody>
</table>

* A test for heterogeneity of exposure effect between studies gave p=0.90 for TCDD and p=0.24 for log TCDD, when data included three most influential observations.
† Quartiles for study and for combined data are 10–17, 17–30, 30–78, >78 ppt for those >10 ppt.

**Discussion**

Overall, there was little evidence of an effect of TCDD on prevalence of diabetes in either study population or in a combined analysis when we compared the exposed to the non-exposed subjects. However, when we conducted dose-response analyses which looked for a trend of increased diabetes with increased TCDD concentrations, we found different results for each study population. There was little evidence of a trend between TCDD concentration and prevalence of diabetes in the NIOSH subjects, although these subjects had higher concentrations than the Ranch Hand subjects. On the other hand, there was evidence of increased prevalence of diabetes with increasing TCDD concentrations in the Ranch Hand subjects. This effect was concentrated in those with the highest TCDD concentrations in the Ranch Hand subjects (OR 3.21 for those with >78 ppt serum TCDD at the time of the 1992 examination (top 8% of the exposed group), compared with those with TCDD <10 ppt). It is not clear why the equivalent group (>78 ppt) in the NIOSH analysis did not show any evidence of increased risk (OR 0.84). Due to this heterogeneity of findings, it is impossible to draw any firm conclusions about the relation between concentration of exposure to TCDD and diabetes from these results.

We can only speculate why the two studies differ in dose-response for diabetes. The two studies differed somewhat for ascertainment of diabetes, other organic chemical exposures, and patterns of exposure to TCDD. We attempted to use a common definition of diabetes and a common analytical approach to both data sets. However, diabetes was self reported in the NIOSH study and confirmed by reviewing medical records after self report in the Ranch Hand study. Also, Ranch Hand and comparison (non-exposed) veterans received glucose testing in 1992 and at previous examinations in 1982, 1985, and 1987. All veterans with increased glucose concentrations were telephoned and advised to see their doctor.
which led to additional diagnosed cases (examiners and study staff conducting the telephone follow up were blinded to the exposure and dioxin concentrations of the veterans). Corresponding repeated testing and follow up did not occur in the NIOSH study. None the less, it would seem unlikely that underestimation of diabetes in the NIOSH subjects would be substantial, or that it could lead to failure to find a true positive dose-response trend.

It is possible that some Ranch Hand personnel were exposed to insecticides (Malathion and DDT) as well as herbicides, and these insecticides might have caused diabetes, preferentially among those with higher TCDD concentrations. However, we know of no publications to support an association between these insecticides and diabetes. Also, insecticide spraying accounted for only 20 of 556 (3.6%) sorties by Ranch Hand personnel during the peak spraying period in July 1967. Of the herbicides sprayed in Vietnam, agent orange (2,4-D and 2,4,5-T) represented 62.9%, agent white (2,4-D and picloram) represented 29.3%, and agent blue (caccodylic acid or dimethyl arsinic acid) represented 6.3%. There is some evidence in prevalence studies that inorganic arsenic in drinking water is associated with diabetes. A mechanism has been proposed by which inorganic arsenic may inhibit glucose uptake, based on in vitro experiments with rat cells. Caccodylic acid is the primary metabolite of inorganic arsenic, produced through methylation in the liver.

The methyl derivatives are thought in general to be less toxic than their parent inorganic compounds (Agency for Toxic Substances and Disease Registry, 1998). The proposed mechanism (through inorganic arsenic) and the lesser toxicity of methylated arsenic would make it less likely that agent blue (methylated arsenic) could cause diabetes, but this possibility cannot be excluded.

Conversely, it is theoretically possible that NIOSH chemical workers were exposed to other chemicals which were protective against the toxic effects of TCDD. Others have noted that the effects of other dioxin congeners and furans could be either additive or antagonistic. However, we know of no well established instances in the epidemiological literature where one occupational chemical exposure protected against a toxic effect of another (for any outcome).

Regarding patterns of exposure, Ranch Hand workers were exposed for a single short period (1 year on the average). The NIOSH workers were exposed from 1 day to 18 years, with a mean of 3 years (SD 4.5 years, median 1 year). It is not clear why this different pattern would affect dose-response trends. For time since exposure, Ranch Hand personnel were last exposed on the average in 1968 (SD 2.0 years), whereas NIOSH subjects were last exposed on the average in 1964 (SD 6.3 years), and some were last exposed much earlier. It is possible that there is a time window in which only recent exposure results in diabetes; however, restriction of the NIOSH subjects to those with more recent exposure (1964 or later) did not substantially change the NIOSH results.

We found little or no relation between exposure and fasting serum glucose in either data set, whether we compared the exposed to non-exposed subjects, or looked at dose-response trends. An apparent positive dose-response trend between serum glucose and TCDD in the combined group was eliminated when three outliers were deleted from the data set. The lack of a relation between serum glucose and TCDD was consistent whether the outcome we considered was either continuous serum glucose or dichotomous abnormal serum glucose (>115 mg/dl). Under the assumption that high serum glucose either defines subclinical diabetes or is a marker for increased risk of clinical diabetes, our essentially negative findings for serum glucose offer no support to the hypothesis that exposure to TCDD is related to diabetes.

Weaknesses in our data include the possibility of (a) uncontrolled confounding by unmeasured covariates, (b) selection biases, and (c) possible reverse causality inherent in our cross sectional design. For confounding, we did include data on the major known risk factors for diabetes in our models, and as already noted with other chemical exposures which might account for our findings. For possible selection biases, the Ranch Hand study has had good participation, arguing against such biases. The NIOSH study had lower participation (70% of located workers, 28% of invited neighbourhood controls), but subsequent telephone interviews of eligible non-participants did not suggest that systematic selection biases were operating. Reverse causality is certainly possible in cross sectional studies in which the outcome, diabetes, is a complex hormonal disease which could affect serum concentrations of TCDD. However, if such (hypothetical) reverse causality were operating and could explain the positive dose-response in the Ranch Hand study, it would be expected that the same mechanism would cause an analogous result in the NIOSH study, which did not occur.

In summary, the epidemiological data are consistent across two cross sectional studies in showing little difference in prevalence of diabetes or fasting serum glucose between exposed and non-exposed subjects. Dose-response trends are likewise generally absent for TCDD concentrations and serum glucose in both studies. However, the two studies are contradictory for dose-response trends for TCDD concentrations and diabetes. This analysis of the two data sets has only served to sharpen the differences in dose-response trends for diabetes which were apparent in the original publications, each of which used a somewhat different definition of outcome and a somewhat different analytical approach. When epidemiology is of necessity based on natural experiments rather than controlled clinical trials, as is the case here, it is inherently a relatively crude tool and may be subject to unknown biases or undetected effect modification. This is certainly not the first occasion when two observational studies give two
different answers. Other studies of diabetes in populations exposed to TCDD might help resolve the difference between these two studies. Heavily exposed industrial populations in Germany and the Netherlands potentially could provide more information.

Marilyn Fingerhut, Han Kang, Marie Sweeney, Michael Stoto, and Matthew Longnecker provided thoughtful comments on the manuscript. Jim Deddens provided some statistical help.


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*Occup Environ Med* 2001 58: 641-648
doi: 10.1136/oem.58.10.641

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