

LEVELS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE SERUM OF U.S. CHEMICAL
WORKERS EXPOSED TO DIOXIN CONTAMINATED PRODUCTS: INTERIM RESULTS

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ABSTRACT

NIOSH is conducting a medical study to evaluate the current health status of 400 chemical workers who made products contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) and an unexposed referent group matched for age, sex, race and neighborhood of residence. The workers are from two U. S. facilities which produced 2,4,5-trichlorophenol and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) between 1951 and 1972.

As a measure of their exposure to 2,3,7,8-TCDD, serum from each worker and from a sample of referents was analyzed for the concentration of this isomer. In this preliminary report, we present the results of the analyses for 2,3,7,8-TCDD found in the serum of 46 study participants. In general, the mean of 8.2 parts per trillion (ppt) 2,3,7,8-TCDD found in the unexposed group is comparable to levels found in unexposed persons in industrialized nations. However, the mean level of 208.2 ppt found in the workers greatly exceeds background levels ($p < .0001$). The current levels for workers are related to the duration of employment in the production of substances contaminated with 2,3,7,8-TCDD ($r = .816$, $p < .0001$). Since all workers were last exposed prior to 1973, serum levels of 2,3,7,8-TCDD at termination of employment were estimated by assuming a 7 year half-life.

KEYWORDS

2,3,7,8-TCDD; occupational exposure; serum levels.

INTRODUCTION

The National Institute for Occupational Safety and Health (NIOSH) is conducting a cross-sectional medical study to assess the current health status of workers who were employed at two U.S. chemical plants between 1951 and 1972, located in the states of New Jersey and Missouri, which manufactured chemicals contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). 2,4,5-trichlorophenol (TCP) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its esters were produced at both plants. Hexachlorophene was also produced from TCP at the Missouri facility.

As part of this study, 541 study participants (281 workers, 260 referents) underwent a comprehensive medical exam during which a sample of serum was collected for the analysis of the 2,3,7,8-TCDD isomer. In this preliminary report, the results of the analyses of 46 serum samples for 2,3,7,8-TCDD are presented. These samples from 27 workers and 19 referents in the New Jersey cohort are the only data currently available.

METHODS

The total study population is composed of 400 living workers who had been employed at the two plants. An unexposed referent group was selected from residents living in the community in which the worker resided at the time of the study. Referents, who were pair-matched to the workers on the basis of sex, age (+ or - 5 years), and race, did not work at any facility which manufactured phenoxy herbicides.

From each worker and referent, approximately 100 milliliters (ml) of blood was drawn into clean glass tubes following a 12 hour overnight fast. The unheparinized blood was centrifuged immediately after phlebotomy at 1000-1200 x gravity for ten minutes at room temperature. Approximately 50 ml of sera from each blood sample was frozen and shipped on dry ice to the Centers for Disease Control laboratory, where it was stored at -70°C until analysis. Analyses for lipid-adjusted levels of 2,3,7,8-TCDD were conducted as described previously (Patterson *et al.*, 1987, Lapeza *et al.*, 1986). Serum levels were calculated on a lipid weight basis rather than whole weight because 2,3,7,8-TCDD accumulates in the lipid stores of the body.

Using company records, length of exposure was calculated from the number of days worked in production areas with potential exposure to substances contaminated with 2,3,7,8-TCDD. Company records provided work history information, including first and last days of employment for all individuals. For ease of interpretation, it was assumed that in a year of employment, each worker spent 5/7 of the year (260 days) working at the plant. No adjustment was made for overtime work or vacation. Periods in non-production jobs, such as truck driver or secretary, and periods of disability or unemployment were excluded from the calculation of total years exposed. Two clerical workers, included in this sample, were assumed *a priori* to have no exposure to 2,3,7,8-TCDD because they had not worked in any of the production areas.

To estimate the levels of 2,3,7,8-TCDD which the workers may have had at the time they terminated employment at the company, assumptions were made that the individual had no additional occupational exposure to 2,3,7,8-TCDD, that the level of 2,3,7,8-TCDD decreased over time with a half-life of 7 years (Wolfe *et al.*, 1988) and that there is a steady state background level of 2,3,7,8-TCDD, defined as the median 2,3,7,8-TCDD level found in the referent group (7.2 ppt). A standard half-life decay equation (O'Flaherty, 1981) was used which takes into account the number of calendar years since the worker was occupationally exposed to 2,3,7,8-TCDD contaminated materials. The equation assumed a log linear one-compartment open model (Poiger and Schlatter, 1986).

To compare the current mean 2,3,7,8-TCDD levels of workers and referents, a two-sample t-test was used. The number of years exposed as well as the 2,3,7,8-TCDD levels were transformed using natural logarithms for the t-test and for the calculations of correlation coefficients (because of the skewness of the original data). After transformation, the 2,3,7,8-TCDD data were found to follow a normal distribution ($p > .05$). The relationships between number of years exposed and 2,3,7,8-TCDD levels were assessed for production workers, clerical workers and referents using the Pearson product moment correlation coefficient. The relationship between the number of years exposed and the half-life extrapolated levels was assessed for the 25 production workers. Multiple linear regression models were used to examine the relationship between the natural logarithm of current and half-life extrapolated 2,3,7,8-TCDD levels of the production workers and other variables such as age, race, number of years since last exposure, and number of years exposure.

RESULTS

Serum samples were obtained from 25 production workers and 2 clerical workers formerly employed at the New Jersey facility, and from 19 unexposed referents. The distribution of age, race, and sex is similar in the production workers and the referents (Table 1). Two referents and no workers were Vietnam veterans. The mean date of termination from the New Jersey plant was 1964. The earliest termination date was 1954 and the most recent was 1969, when the plant closed.

Table 1. Selected characteristics of study participants.

| | Production Workers | Clerical Workers | Referents |
|------------------------------|--------------------|-------------------|-----------|
| Number | 25 | 2 | 19 |
| Race (% White) | 76% | 100% | 74% |
| Sex (% male) | 100% | 0 | 95% |
| Age at Examination (Mean) | 55 | 52 | 54 |
| Year of Last Exposure (Mean) | 1964 | 1967 ^a | -- |
| Years of Exposure (Mean) | 4.2 | 0 | -- |
| Vietnam Veteran (%) | 0 | 0 | 11 |

^a mean year of termination

The mean level of 2,3,7,8-TCDD found in the serum samples from the production workers is 208.2 ppt, which differs significantly from the mean of 8.2 ppt for the 19 referents ($p < .0001$). The highest level is 717 ppt. The mean half-life extrapolated level of 2,3,7,8-TCDD present in the serum of workers at the date of termination of employment at the New Jersey facility is 2312.7 ppt. The range is from 6.4 to 14,673 ppt (Table 2).

Table 2. Lipid adjusted serum levels of 2,3,7,8-TCDD (ppt).

| | Number | Mean | Median | Range |
|-------------------------------|--------|--------|--------|--------------|
| <u>Current</u> | | | | |
| Referents | 19 | 8.2 | 7.2 | 3.7 - 17.1 |
| Clerical Workers | 2 | 18.6 | 18.6 | 11.0 - 26.1 |
| Production Workers | 25 | 208.2 | 181.0 | 4.6 - 717.0 |
| <u>Half-life Extrapolated</u> | | | | |
| Production Workers | 25 | 2312.7 | 1361.7 | 6.4-14,673.0 |

The mean number of years of exposure at the New Jersey plant was 4.2. The longest exposure was 15.5 years. Figure 1 illustrates the relationship between the number of years exposed and current 2,3,7,8-TCDD levels for the production and clerical workers, and the referents ($r = .874$, $p < .0001$). The same relationship held when the 25 production workers were considered separately ($r = .816$, $p < .0001$). Figure 2 demonstrates the relationship between the half-life extrapolated 2,3,7,8-TCDD levels and the log of total number of years exposed for 25 production workers ($r = .799$, $p < .0001$).

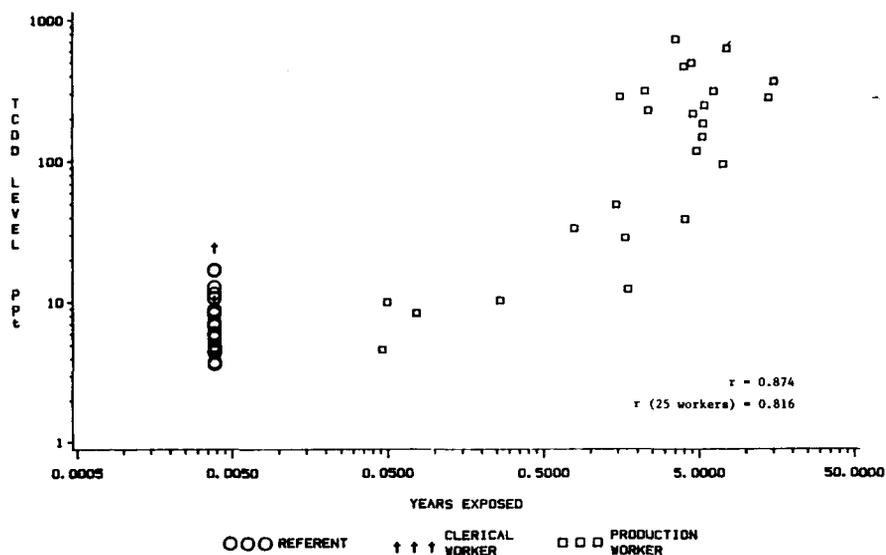


Fig. 1. Current lipid adjusted levels of 2,3,7,8-TCDD (ppt) by years exposed.

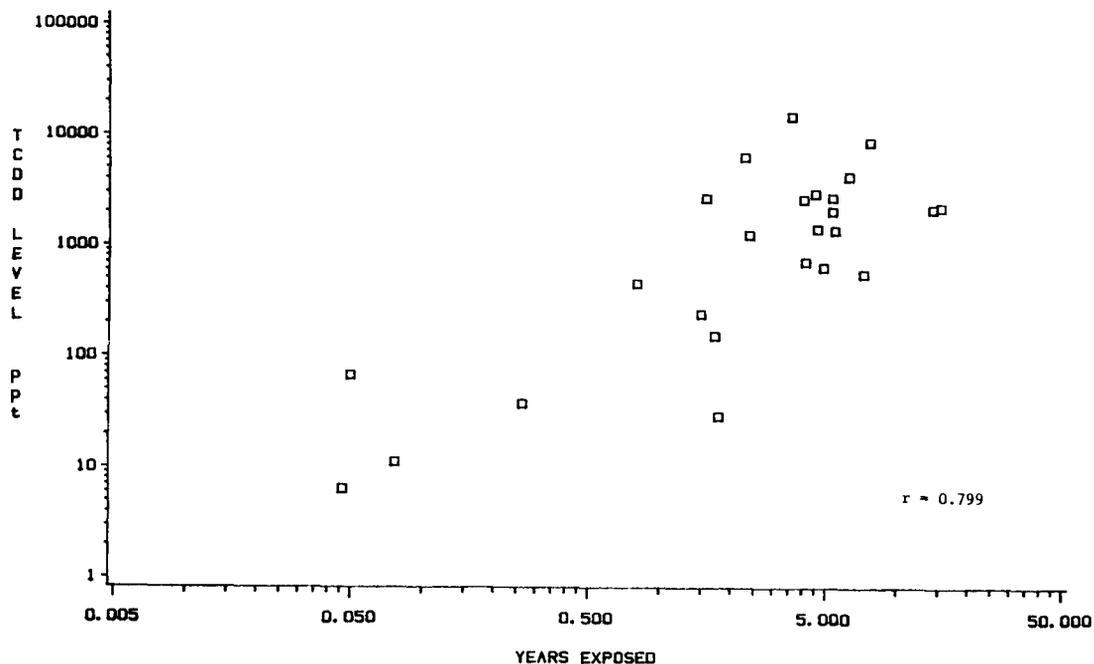


Fig. 2. Half-life (7 yr) extrapolated levels of 2,3,7,8-TCDD (ppt) in 25 workers by years exposed.

Based upon the results of these bivariate analyses a multivariate framework using multiple linear regression was used to examine whether other variables were related to 2,3,7,8-TCDD levels. The log of current 2,3,7,8-TCDD levels was used as the outcome (dependent) variable in the regression model, the log of the number of years exposed was used as an independent variable and other variables were added as independent variables to see if they improved the model significantly. Age, race, and number of years since last exposed did not contribute significantly to the model. Therefore, years of exposure in this analysis is the only variable significantly related to 2,3,7,8-TCDD levels. When the log of the half-life extrapolated levels were examined in the same multiple regression framework, years of exposure was the only significant variable.

DISCUSSION

These analyses demonstrate that the production workers in this study, who were formerly engaged in the manufacture of products contaminated with 2,3,7,8-TCDD, have statistically significantly higher serum levels of this dioxin isomer compared to an unexposed referent group. The results are consistent with levels in serum and adipose tissue reported in Table 3 for chemical workers who made products contaminated with 2,3,7,8-TCDD (Beck *et al.*, 1988, Patterson *et al.*, 1988), and in U.S. Air Force pilots and mechanics who sprayed Agent Orange, a herbicide containing 2,3,7,8-TCDD (Wolfe *et al.*, 1988). Two reports of environmental exposures also found substantial adipose tissue levels of 2,3,7,8-TCDD (Andrews *et al.*, 1988, Facchetti *et al.*, 1981). Lipid-adjusted adipose tissue and serum levels have been found to be comparable because 2,3,7,8-TCDD is stored to approximately the same extent in the lipid fraction of adipose tissue and serum (Patterson *et al.*, 1988). The 19 referents in our study had a range of levels of 2,3,7,8-TCDD from 3.7 to 17.1 ppt, an observation consistent with other studies of unexposed populations (Table 4). It has been suggested that unexposed populations generally have levels under 20 ppt (Patterson *et al.*, 1988).

Table 3. Current levels of 2,3,7,8-TCDD in exposed human populations

| POPULATION | N | Medium | Range ^a | References |
|---|-----|---------|----------------------|-----------------|
| U.S. Chemical Workers | 25 | Serum | 4.6 - 717 | See text |
| U.S. Chemical Workers | 9 | Serum | 61 - 1090 | Patterson, 1988 |
| F.R.G. Chemical Workers | 45 | Adipose | 6 - 2252 | Beck, 1988 |
| U.S. Air Force (spraying) | 147 | Serum | <5 - 313 | Wolfe, 1988 |
| Environmental-Seveso, Italy | 1 | Adipose | 1840 ^b | Facchetti, 1980 |
| Environmental (Missouri horse arena) | 16 | Adipose | 5 - 577 ^b | Andrews, 1988 |

^a Parts per trillion, lipid-adjusted

^b Parts per trillion, whole-weight

Table 4. Current Levels of 2,3,7,8-TCDD in Unexposed Human Populations

| Population | N | Medium | Range ^a | Reference |
|----------------------------|-----|---------|----------------------|-----------------|
| NIOSH Study Referents | 19 | Serum | 3.7-17.1 | See text |
| General Population | 52 | Adipose | ND - 10 | Reviewed by |
| | 309 | Adipose | ND - 33 ^b | Patterson |
| | 167 | Serum | ND - 26 | 1988 |
| Unexposed Missouri Workers | 7 | Adipose | 3.5-25.8 | Patterson, 1988 |

^a Parts per trillion, lipid-adjusted

^b Parts per trillion, whole-weight

ND Nondetectable

Although the levels of most of the workers greatly exceed population background levels, five workers have current serum levels of 2,3,7,8-TCDD under 20 ppt (Table 5). The low levels for Workers 1-4 can probably be explained by their brief periods of employment and the possibility that some of their jobs did not have a potential for exposure to 2,3,7,8-TCDD. However, there is no obvious explanation for the low 2,3,7,8-TCDD serum level in Worker 5 who was exposed for 462 days, as a trichlorophenol operator. The two clerical workers were assumed a priori to have no exposure in their work since one woman was a receptionist and the other worked as a receptionist and as a shipping-billing clerk. They had levels of 11.0 and 26.1 ppt. It is unclear whether the value of 26.1 ppt represents a high "normal" or slight exposure, since some areas of the plant beyond the production areas may have been contaminated with 2,3,7,8-TCDD, or the work as a shipping-billing clerk could have involved visits to production areas.

Table 5. Workers with low serum levels of 2,3,7,8-TCDD.

| Worker | 2,3,7,8-TCDD (ppt) ^a | Race | Sex | Total Days Exposed | Years Since Last Exposure | Job(s) |
|--------|---------------------------------|------|-----|--------------------|---------------------------|-------------------------------------|
| 1 | 4.6 | B | M | 11 | 18 | Chemical Operator Trainee |
| 2 | 8.3 | W | M | 19 | 23 | Chemical Operator Trainee |
| 3 | 9.9 | W | M | 12 | 32 | DDT Production Helper |
| 4 | 10.2 | W | M | 68 | 25 | Laboratory Technician |
| 5 | 12.2 | B | M | 462 | 18 | TCP Operator |
| 6 | 11.0 | W | F | 0 ^b | 21 | Receptionist |
| 7 | 26.1 | W | F | 0 ^c | 18 | Receptionist/Shipping-Billing Clerk |

^a Parts per trillion, lipid-adjusted

^b Employed 422 days

^c Employed 637 days

In this preliminary analysis, a positive exposure-response relationship was found between the number of years of exposure and both current serum levels and the half-life extrapolated levels of 2,3,7,8-TCDD. The increase in serum level becomes smaller with longer periods of exposure as evidenced by the logarithmic relationship between the variables.

When analysis of all of the serum samples from the NIOSH study has been completed, additional characterization of the exposure will be provided using data from an exposure matrix now being developed at NIOSH. The exposure matrix is being compiled from process and job descriptions, safety records, and analytical data reporting 2,3,7,8-TCDD levels in substances produced at the companies. The half-life extrapolated levels may be better estimated with further research to characterize the half-life of 2,3,7,8-TCDD in human populations. For the extrapolated levels, a constant (7 year) half-life was assumed for all study members, when there may actually be variation in half-lives.

This study and others, have established that high exposures to 2,3,7,8-TCDD have occurred in chemical workers who made products contaminated with 2,3,7,8-TCDD, in some USAF Ranch Hand pilots and mechanics who sprayed Agent Orange in Vietnam, and in several environmental situations. This study also shows that a good exposure-response relationship exists between cumulative exposure to 2,3,7,8-TCDD and current (as well as half-life extrapolated) serum levels of the isomer. However, to date, there is no definitive answer to the question whether such exposure causes chronic health problems. It is our hope that the NIOSH medical study of highly exposed chemical workers and an unexposed matched referent group will help to answer this question.

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