Chemosphere, Vol.20, Nos.7-9, pp 993-1000, 1990 0045-6535/90 $3.00 + .00
Printed in Great Britain Pergamon Press plc

COMPARISON OF SERUM LEVELS OF 2,3,7,8-TCDD IN TCP PRODUCTION WORKERS AND IN AN UNEXPOSED COMPARISON GROUP.

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ABSTRACT

Serum 2,3,7,8-TCDD levels were measured as an estimate of exposure to this isomer in 143 workers who were employed at either of two plants in New Jersey and Missouri which manufactured chemicals contaminated with 2,3,7,8-TCDD and in 54 unexposed referents. The mean serum 2,3,7,8-TCDD levels for all workers was 251.7 parts per trillion (ppt) and, for all referents combined, the mean serum level was 7.8 ppt. The mean level of 2,3,7,8-TCDD present in the serum of workers at the date of termination of exposures (half-life extrapolated) was 2600 ppt and 870 ppt for the New Jersey and Missouri workers, respectively. Overall, the levels in the workers significantly correlated with duration of exposure in 2,3,7,8-TCDD-contaminated processes ($r=0.83$, $p< .0001$).

KEYWORDS

Cross-sectional medical study, occupational exposure, serum 2,3,7,8-TCDD levels, dioxin

INTRODUCTION

In 1987-1988, the National Institute for Occupational Safety and Health (NIOSH) conducted a cross-sectional medical study to evaluate adverse health outcomes associated with exposure

to materials contaminated with 2,3,7,8-TCDD including dermatologic, hepatic, neurologic, immunologic and reproductive effects of workers and unexposed referents. In this interim report, the results of the analyses of 197 serum samples for 2,3,7,8-TCDD are presented. These samples are from 143 workers and 54 unexposed referents in the New Jersey and Missouri cohorts.

METHODS

Workers included in the study were employed at either of two plants located in Newark, New Jersey (NJ) or Verona, Missouri (MO). At the plant in New Jersey, sodium trichlorophenol (NaTCP) and 2,4,5 trichlorophenoxyacetic acid (2,4,5-T) were manufactured from 1951 - 1969. NaTCP and 2,4,5-T were produced at the Missouri facility for approximately 4 months in 1968 - 1969; NaTCP and hexachlorophene were also produced from April, 1970 through January, 1972. For comparison, unexposed referents were matched to each worker by age (± 5 years), race, sex, and current resident community of the worker. Referents were never employed where chlorophenols or phenoxyherbicides were produced (Sweeney et al., 1989). Serum samples for measurement of 2,3,7,8-TCDD levels were collected during the medical examination and were handled as reported by Fingerhut et al., (1989) and lipid-adjusted as described by Patterson et al., (1987) and Lapeza et al., (1986).

Company records were used to calculate length of exposure by determining the total number of days worked in all areas of the plant with potential exposure to 2,3,7,8-TCDD contaminated processes. To calculate the period of exposure, the total number of calendar days a worker was assigned to the production (including engineering or laboratory operations) or maintenance of processes contaminated with 2,3,7,8-TCDD was summed and divided by 365.25 to calculate years of exposure. No adjustment was made for overtime work or vacation. In addition, periods of employment in jobs as secretary, accountant or other office work, and periods of disability or unemployment were excluded from the calculation of total length of exposure. Of the 143 workers, eight New Jersey workers were employed as office workers. Because they had not worked in any production areas, these eight office workers were assumed a priori to have no occupational exposure to 2,3,7,8-TCDD contaminated processes.

Half-life extrapolated levels (serum 2,3,7,8-TCDD level at the time of termination from the last job with 2,3,7,8-TCDD exposure) were calculated for the 135 production workers. To estimate the half-life extrapolated levels, a standard half-life decay equation was used (O'Flaherty, 1981) which takes into account the number of calendar years since the worker was occupationally exposed to 2,3,7,8-TCDD contaminated processes. The equation assumes a log linear, one-compartment open model (Poiger and Schlatter, 1986). In addition, the following assumptions were made: no additional occupational exposure to 2,3,7,8-TCDD occurred after termination (based on self-reported work histories obtained in questionnaires completed by each worker and referent); a steady state background level of 2,3,7,8-TCDD was defined as the median 2,3,7,8-TCDD level found in the referent group [6.37 parts per trillion (ppt)]; and the half-life of 2,3,7,8-TCDD was 7 years (Pirkle et al, 1989). Half-life extrapolated levels were not calculated for 10 production workers whose level obtained at the time of the examination was equal to or less than the background of 6.37

ppt. Therefore, for the purposes of this interim report, the current serum levels rather than half-life extrapolated values were used in the analysis of the half-life extrapolated levels.

Both the current and half-life extrapolated 2,3,7,8-TCDD levels were found to have a log normal distribution. This is consistent with findings of Sieklen, (1987) (Figure 1). After log transformation, the 2,3,7,8-TCDD data were found to more closely approximate a normal distribution. The number of years of exposure was also log-transformed to linearize the relationship with serum 2,3,7,8-TCDD levels. The log transformed data were used for all analyses.

To compare the current mean 2,3,7,8-TCDD levels of workers and referents, a two-sample t-test was used. The relationships between length of exposure and current serum 2,3,7,8-TCDD levels and between length of exposure and half-life extrapolated levels were assessed for the 135 production workers using the Pearson product moment correlation coefficient. Multiple linear regression models were used to examine the relationship between the current and half-life extrapolated 2,3,7,8-TCDD levels of the 135 production workers and total years of exposure. In all models considered, either current or half-life extrapolated levels were included as the dependent variable and the number of years of exposure was included as an independent variable. Other potential confounders which have been explored in previous studies (Andrews et al, 1989), such as age, race, body mass index (weight/height^2), and the number of days since last exposure were added as independent variables to see if they improved the model significantly. Because of the large differences in the length of exposure between two plants, regression models were built for each plant separately.

RESULTS

Serum 2,3,7,8-TCDD levels for all samples received from the laboratory to date are presented which include analyses for 103 production workers and 8 office workers formerly employed at the New Jersey facility, and for 41 unexposed referents. Serum samples were also measured for 32 workers previously employed at the Missouri plant and for 13 unexposed referents. No worker was ever employed at both facilities.

The distribution of race, sex, and age of the 143 workers is similar to that of respective referents. The mean year of termination from the New Jersey plant was 1963 (median year=1964) and 1970 (median year=1971) for Missouri workers. Length of occupational exposure in jobs with potential exposure to 2,3,7,8-TCDD contaminated processes was examined in relation to current serum 2,3,7,8-TCDD levels. The average number of years of exposure at the New Jersey plant was 3.9 years and 10 months at the Missouri plant. The longest exposure was 18.5 years at the New Jersey plant and 2.1 years at the Missouri facility.

For all 143 workers combined, the mean serum 2,3,7,8-TCDD level was 251.7 ppt and, for all 54 referents combined, the mean serum level was 7.8 ppt. The mean level of 2,3,7,8-TCDD found in the serum samples for the New Jersey production workers was 293.4 ppt (geometric mean=76.8 ppt). In office workers the level was 12.5 ppt. Levels in production and in office workers differed significantly from the mean of 8.0 ppt (geometric mean=6.9 ppt) for

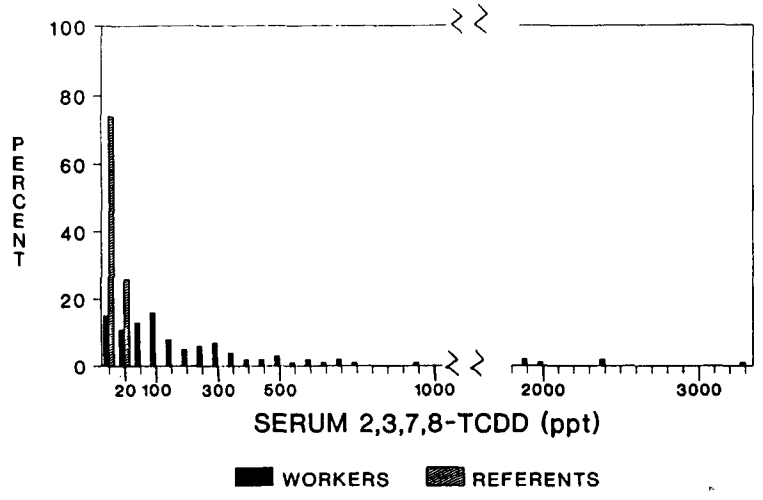
Table 1. Lipid-adjusted serum levels of 2,3,7,8-TCDD (ppt).

	New Jersey			Missouri	
	Production Workers	Office Workers	Referents	Workers	Referents
N	103	8	41	32	13
Current					
Mean[a]	293.4	12.5	8.0	177.2	7.1
Mean[b]	76.8[c]	11.0[d]	6.9	80.7[c]	6.2
Median	84.0	11.0	6.3	108.6	6.4
Range	2 - 3390	7 - 26	2 - 20	3 - 1290	2 - 17
Half-life Extrapolated					
Mean	2664.7	NA	NA	872.3	NA
Range	2 - 30,900			3 - 6100	

[a] arithmetic mean; [b] geometric mean; [c] higher than mean referent level, $p<0.0001$; [d] higher than mean referent level, $p<0.05$; NA not applicable

the 41 New Jersey referents ($p<.0001$) (Table 1). The distribution of serum levels in the production workers ranged from 2 ppt to 3390 ppt. The majority of the levels were below 100 ppt (65 of 103 measurements) as would be expected in a lognormal distribution (Figure 1). In the Missouri production workers, the mean serum 2,3,7,8-TCDD level was 177.2 ppt (geometric mean=80.7 ppt), ranging from 3.4 ppt to 1290 ppt. The mean of 7.1 ppt (geometric mean=6.2 ppt) for the 13 referents differed significantly from that of the production workers ($p<.0001$). There was no difference between the serum levels of referents selected for New Jersey or Missouri workers. The mean level of 2,3,7,8-TCDD present in the serum of production workers at the date of termination of exposure was 2240 ppt.

Figure 1. Distrubution of Serum 2,3,7,8-TCDD in Workers and Referents



There is a statistically significant correlation between the number of years of exposure and current 2,3,7,8-TCDD levels for the 135 production and 8 office workers and 54 referents ($r=0.83$, $p<0.0001$). A similar relationship was found in separate analyses of workers and referents in New Jersey ($r=.83$, $p<.0001$) and Missouri ($r=.84$, $p<.0001$). Half-life extrapolated levels for all production workers also increased significantly with increasing length of exposure ($r=.88$, $p<.0001$). This pattern was repeated for the relationship between the half-life extrapolated levels and the number of years of exposure for production workers and referents at each plant (New Jersey: $r=.88$, $p<.0001$; Missouri: $r=.88$, $p<.0001$).

Based on linear regression models, length of exposure, age and body mass index were significantly and positively related to current and half-life extrapolated serum levels ($p<.001$) in the New Jersey plant population, while the number of years since last exposure was significantly and negatively related to the current levels, as expected (Table 2). For the Missouri participants, current and half-life extrapolated serum levels were statistically significantly related to increasing length of employment ($p<.0001$) (Table 3). No other examined variable (race, smoking status) significantly contributed to the model.

Table 2. Linear regression models for current and half-life extrapolated 2,3,7,8-TCDD serum levels for New Jersey production workers

	CURRENT		HALF LIFE EXTRAPOLATED	
Variable	Parameter Estimate	Standard Error of Estimate	Parameter Estimate	Standard Error of Estimate
Intercept	1.721	0.770	1.138	1.154
Log Years of Exposure	0.566[b]	0.054	0.807[b]	0.073
# of Years Since Last Exposure	-0.085[b]	0.018	NA	NA
Age[a]	0.044[b]	0.010	0.036[c]	0.014
Body Mass Index	0.075[b]	0.021	0.107[b]	0.030
R^2 0.742			0.641	

[a]age at examination; [b]$p<.001$; [c]$p<.02$; NS, not significant in model

NA, not applicable

DISCUSSION

These analyses demonstrate that the production workers in this study who were formerly engaged in processes 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 of others who experienced occupational or environmental exposures to 2,3,7,8-TCDD contaminated materials (Table 4.). With the exception of the report by Mocarelli et al. (1988), who described levels obtained within one year of an acute exposure, the other studies report levels measured from 2-37 years after exposure ended.

Table 3. Linear regression variables for current and half-life extrapolated 2,3,7,8-TCDD serum levels for Missouri production workers

	CURRENT		HALF-LIFE EXTRAPOLATED	
Variable	Parameter Estimate	Standard Error of Estimate	Parameter Estimate	Standard Error of Estimate
Intercept	4.995	0.210	6.555	0.273
Log Years of Exposure	0.689[a]	0.120	0.858[a]	0.156
R^2	0.522		0.502	

[a] $p<.0001$

It is of interest that the highest half-life extrapolated level for the production workers is 30,900 ppt, which is in the range of the highest level found in Seveso residents shortly after the TCP reactor accident (Mocarelli et al., 1988). This worker's serum 2,3,7,8-TCDD level obtained at the time of the examination was 994 ppt. He was exposed for a total of approximately 520 days (1.4 years) during employment at the New Jersey plant; his last year of occupational exposure to 2,3,7,8-TCDD was at this plant in 1952. His elevated level may be attributed to his position as a process engineer involved in the start-up of the NaTCP and 2,4,5-T operations. The worker with the highest current level of 3390 ppt was employed for approximately 18 years from 1951-1969 as a chemical operator. His half-life extrapolated level is 19,300 ppt.

The 54 referents in our study had a range of current serum levels of 2,3,7,8-TCDD from 1.7 ppt to 19.7 ppt, an observation consistent with other studies of unexposed populations. It has been suggested that unexposed populations generally have levels under 20 ppt (Patterson et al., 1989).

In this analysis, a strong positive 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 results clearly demonstrate that the trend of increasing serum levels with increasing periods of exposures holds even when the period of exposure is two years or less as is the

case for the Missouri workers. When the serum 2,3,7,8-TCDD analyses are complete for all workers in the NIOSH Study, a comprehensive analysis is planned to evaluate biological and exposure factors which may contribute to an individual's serum level. This additional information may shed some light on the interpersonal variation observed in serum 2,3,7,8-TCDD levels.

Table 4. Levels of 2,3,7,8-TCDD in exposed human populations measured 1-37 years after exposure

POPULATION	N	Interval[a]	Range[b]	References
U.S. Chemical Workers	136	15 - 37	2 - 3389	See text
F.R.G. Chemical Workers	45	2 - 37	6 - 2252	Beck, 1989
U.S. Air Force	147	16 - 25	<5 - 313	Wolfe, 1988
Missouri horse arena	16	14	5 - 577[c]	Andrews, 1989
Seveso, Italy	10	1	1772 - 27821	Mocarelli, 1988

[a] Estimated number of years between exposure and 2,3,7,8-TCDD measurement

[b] Parts per trillion, lipid-adjusted

[c] Parts per trillion, whole-weight

ACKNOWLEDGEMENTS

I wish to thank Lance Cameron, Jolene Schottelkotte and Brent Tompkins for computer support and Julie Tolbert for manuscript preparation. This study was partially funded by the Agency for Toxic Substances and Disease Registries.

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