TCDD EXPOSURE RECONSTRUCTION FOR WORKERS AT A NEW ZEALAND 2,4,5-T MANUFACTURING FACILITY BASED ON SERUM SAMPLING DATA

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Introduction

Exposure reconstruction based on serum sampling data, work history records, and pharmacokinetic modeling has been used as a tool for assessing historical occupational exposures to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in workers involved in the manufacture of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (*1-4*). TCDD concentration measured many years after exposure is a function of intensity of occupational exposure, duration of occupational exposure, and time since last exposure. This paper describes an exposure reconstruction for a facility in New Zealand that manufactured 2,4,5-T along with other products between 1962 and 1988. Little industrial hygiene data on TCDD exposure among workers are available, but manufacture of 2,4,5-T and TCP occurred at this site when processes had already been optimized to minimize TCDD contamination in products. No case of chloracne was ever diagnosed among workers at the site. Serum TCDD concentrations measured in samples collected in 2005, 2006, and 2007 were used in conjunction with work history records and pharmacokinetic modeling to reconstruct estimated exposures at the plant. The resulting exposure reconstruction will be used in evaluations of mortality patterns among workers at the plant.

Methods

Job and department records were used to identify 1599 individuals who worked at the facility during the period of 2,4,5-T manufacture for one day or more. Serum TCDD concentrations were measured in 346 individuals (21.6% of the total group) who resided within 75 km of the plant at the time of the blood draw. Work records were examined to identify job titles, department, and start and stop date of each job for each individual. Each unique combination of study job and study department was assigned to a study "group." These groups were further categorized as to the likelihood of continuous exposure potential (for example, the trichlorophenol manufacturing jobs) or intermittent exposure potential (for example, maintenance workers) with a numeric rating of 0 to 4. The combination of study group and exposure intensity classification resulted in 28 unique job exposure groups (JEGs).

Dose rate estimation. The work history files and serum TCDD data from the serum donor group were used to estimate dose rates of TCDD exposure for each JEG. Two main assumptions were used in this exposure reconstruction modeling effort: 1) exposure to TCDD for a given job assignment within a JEG can be modeled as a constant average exposure rate in ng/yr; and 2) the toxicokinetics of TCDD can be modeled as a first-order process with distribution in the body solely to adipose or lipid tissue. Under these assumptions, for an individual with *n* job assignments, exposures due to all *n* job assignments, as well as background exposures received through diet, contribute independently to the measured serum lipid TCDD concentration at the time of measurement (C_{tm}, equation 1):

$$C_{t_m} = C_{t_{m\_background}} + \sum_{i=1}^{n} C_{t_{m\_i}} \quad (1)$$

The concentration of TCDD remaining in serum lipid at time of measurement t_m due to exposure to TCDD from a given job assignment *i*, C_{tm_i}, can be estimated using equation 2:

$$C_{t_{m\_i}} = D_i * \left[\frac{1}{Vk} \left(1 - e^{-k(t_i - t_{0i})}\right) \left(e^{-k(t_m - t_i)}\right) \right] \quad (2)$$

Where D_i is the average dose rate for job *i* in ng yr^{-1}; *V* is the volume of distribution (in this case, the mass in kilograms of adipose or lipid tissue); k is the first-order elimination rate for TCDD, yr^{-1}; and t_{0i} and t_i are the

dates of first and last exposure on that job assignment, respectively. The apparent first-order elimination rate for TCDD has been estimated in numerous studies, and demonstrates notable dependence on age, with elimination rate decreasing with increasing age (reviewed in *5*). Age- and smoking-dependent elimination rates were estimated according to the relationship proposed by Milbrath et al. (2007).

Equations 1 and 2 were entered into a multiple linear regression to estimate specific dose rates, D, associated with employment in various JEGs. Model development proceeded in several steps using the multiple linear regression function in Microsoft Excel 2003®. The model was refined through examination of the resulting dose rate estimates. The number of independent dose rate parameters in the model was iteratively reduced to identify a parsimonious model that reflected both the qualitative understanding of the exposure potential of various job assignments and an examination of information regarding non-plant exposure potential for outlying individuals.

Exposure reconstruction for the cohort. Using the estimated dose rates for each JEG resulting from the final model, the serum lipid TCDD concentration vs. time profile was estimated for each individual from the date of first employment to the date of end of follow-up using equations 1 and 2 on a month-by-month basis. A time-dependent estimate of the area under the curve (AUC) of occupationally-derived serum lipid TCDD was derived for each member of the study for use in epidemiological analyses.

Results

Based on the results of the initial multiple linear regression we identified a number of outliers, whose measured serum lipid TCDD concentrations were substantially higher than the modeled values. Inspection of questionnaire data from several outliers revealed that these individuals had been present at a trichlorophenol process release that occurred overnight on April 15, 1986, when vapor was vented from a reactor producing sodium trichlorophenate. Based on this information, a one-day work history record specific to the process release was added for each of the 18 individuals with documented direct involvement in the release (based on questionnaire responses or clinic records).

The estimated dose rates for the final dose rate regression model are presented in Table 1. The estimated dose rates associated with the various exposure categories retained in the model are coherent with one another, with the highest estimated dose rates for the exposure categories with *a priori* expectation of potential TCDD exposure (phenoxy and trichlorophenol groups) and a lower estimate for the combined General Construction and Maintenance category. The modeled serum lipid TCDD concentration at the time of measurement is plotted versus the measured concentrations in Figure 1. The model performance is relatively modest, with an adjusted R^2 of 0.30. There are a number of outliers with substantially higher measured serum TCDD concentrations than predicted by the model. In the questionnaire, several of these individuals reported potentially confounding employment spraying herbicides to control brush, in the timber industry, or at another facility handling 2,4,5-T.

The estimates of TCDD AUC attributable to occupational exposures for the full study group based on application of the estimated dose rates from the regression model to individual work histories are summarized in Figure 2. The median and mean estimated AUC values were 13 and 86 ppt•yrs, respectively; interquartile range: 2-62 ppt•yrs; maximum: 3757 ppt•yrs. These TCDD AUC estimates are substantially lower than those estimated in other studies of groups occupationally exposed to TCDD in the manufacture of 2,4,5-T. For example, the median estimated AUC attributable to occupational exposures for the NIOSH study group was approximately 500 ppt•yrs or more, depending upon the model used for exposure reconstruction and assumptions regarding background exposures (*4*), more than 40 times higher than in the current study.

Discussion

The estimated intercept of 5.1 ppt is consistent with background serum TCDD concentrations among older individuals in New Zealand (*6*). The dose rate estimate for the "other site jobs" category is roughly of the same magnitude as estimated dietary background exposures in the US during the time frame of interest (1960s, 1970s, and early 1980s) (*7*). The estimated dose rate associated with direct involvement in the 1986 release is equivalent to a single dose of approximately 0.04 µg/kg bodyweight, consistent with an increase in serum lipid TCDD concentration of approximately 100 to 150 ppt at the time of the release. The lack of diagnosed

chloracne among the individuals involved in the release and cleanup is consistent with that estimate, since chloracne has not generally been observed among individuals with serum lipid TCDD concentrations below approximately 1,000 ppt. This dose estimate is also consistent with information available from a group of 243 workers involved with a much larger process release in Germany in which more than half of the involved workers were estimated to have received doses of less than 0.1 µg/kg, while the remaining individuals received greater doses (*3*).

The overall performance of the current model was modest, explaining only 30% of the observed variance in measured serum TCDD concentrations. In addition to some limitations in the work history records, there are several possible factors that could contribute to the relatively poor performance of the model:

- The measured serum TCDD concentrations for this cohort were relatively low compared to other studied cohorts, despite similar elapsed time periods between last occupational exposure and measurement, with many of the measurements within or near the range of background (maximum in this study was 100 ppt compared to 3300 ppt in the NIOSH study of US workers). Thus, variability due to non-occupational factors such as variations in dietary background exposure rates is larger relative to the occupational exposures than in cohorts with higher occupational exposures.
- The basic model assumption of an average and consistent exposure rate across individuals in a given job ignores the possibility of isolated anomalous exposure events (small spills, failure to wear personal protective equipment, or undocumented work practices) that for individuals may have a greater impact on exposure, and measured serum TCDD concentrations than the "average" job exposure rate.
- Several individuals with outlying TCDD values reported putative exposure to 2,4,5-T from employment at other 2,4,5-T facilities, in agriculture, and in timber industries.

However, the final model was significantly better than a simplistic model that included only two exposure groups, which resulted in an R^2 of only 0.07 (details not presented). This suggests that crude assignments of individuals to "potentially exposed" and "unexposed" based on work history records could introduce substantial exposure misclassification into the study. While we found some limitations in our ability to model, our ability to estimate exposure levels based on biological monitoring allow us to more confidently use these estimates in future epidemiology studies.

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Table 1: Final model parameter estimates. The parameter estimates are dose rates associated with the composite exposure groups as discussed in the text.

Composite Exposure Groups	Parameter Estimate	Standard Error	P-value
Intercept (background concentrations, ppt)	5.1	0.7	<0.0001
Process release (ng/incident)	3840	660	<0.0001
General construction and maintenance (ng/yr)	103	53	=0.05
Phenoxyacetic acid (low exposure potential) (ng/yr)	271	156	<0.1
Phenoxyacetic acid (high exposure potential) (ng/yr)	574	150	<0.01
Trichlorphenol, pilot plant, and incinerator	1290	276	<0.001
Other site jobs (ng/yr)	74	27	<0.01

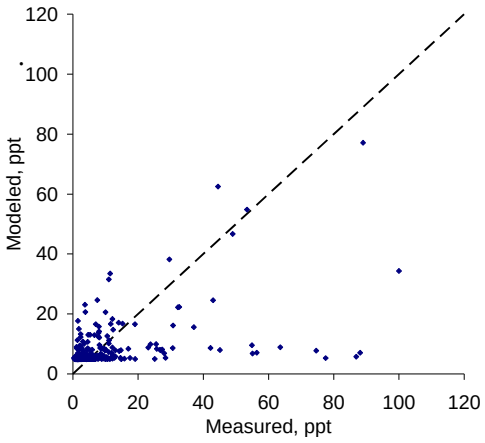

Figure 1: Modeled vs. measured serum lipid TCDD concentrations for the serum-sampled subcohort based on the final regression model (adjusted R^2=0.30). The dotted line represents the ideal one-to-one correlation between modeled and measured concentrations.

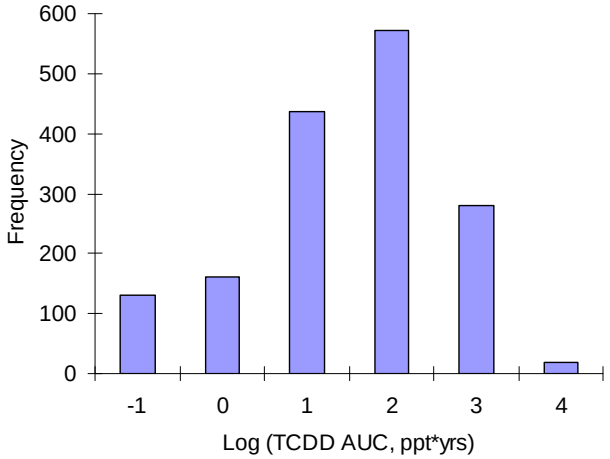

Figure 2: Distribution of cumulative TCDD AUC estimates (ppt*yrs) due to occupational exposure for the full cohort (n=1,599). The values presented here include estimated AUC attributable occupational exposures only and do not include background TCDD or TEQ AUC