PHARMACOKINETICS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN SEVESO ADULTS AND VETERANS OF OPERATION RANCH HAND

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Introduction

On July 10, 1976, an explosion occurred during the production of 2,4,5-trichlorophenol in the ICMESA plant in Meda, about 25 km north of Milan, in the Lombardia region of Italy. A cloud of chemicals, including sodium hydroxide, ethylene glycol, the sodium salt of 2,4,5-trichlorophenol, and kilogram amounts of the synthetic by-product, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), was released into the atmosphere. Debris from this cloud fell south-southeast of the plant on an area of about 2.8 km^2, which included parts of the towns of Seveso, Meda, Cesano, Moderno, and Desio. Primarily on the basis of animal and vegetation mortality and TCDD measurements in soil and grass, the contaminated area was divided into three zones, designated A, B, and R. Zone A was closest to the plant and selected individuals from these zones, denoted the "Seveso" cohort, and from the surrounding area, zone non-ABR, have been studied for health, serum TCDD levels, TCDD pharmacokinetics, and mortality.

About a decade earlier, from 1962 to 1971, members of the US Air Force Operation Ranch Hand, were exposed to TCDD through their handling and spraying of bulk quantities of Agent Orange and other TCDD-contaminated phenoxy herbicides in Vietnam. Since 1982, these veterans and a comparison cohort have been studied for health effects, serum TCDD levels and pharmaco-kinetics, and mortality. A distinguishing feature of the Ranch Hand exposure is the lack of serum TCDD measurements prior to 1982, and hence the lack of a measured initial dose in Vietnam. The opposite is the case in the Seveso studies; TCDD levels were measured in serum collected within a few days of the explosion in some individuals. The lack of initial dose measurements in Ranch Hand veterans has motivated efforts to estimate the initial dose based on a first-order pharmacokinetic model. A second distinguishing factor is that the Seveso cohort represents a residential population exposed to a single release of TCDD, resulting in extremely high serum TCDD levels, whereas the Ranch Hand cohort experienced TCDD exposure mostly during a one-year period of service in a war zone; the maximum estimated initial dose in the Ranch Hand cohort was about 3,000 ppt, and more than 20,000 ppt has been measured in some

Seveso residents in serum collected within a few days of the accident. We describe TCDD elimination in selected Seveso adults from Zones A and B and selected Ranch Hand veterans[1].

Materials and Methods

Some individuals from zones A and B, both adults and children, donated serum after the accident up to 1993. From the Seveso cohort with repeated serum TCDD measurements, 54 individuals who were adults (at least 16 years old) at the time of the accident were selected; 29 of the 54 were males.

A study of TCDD elimination in Ranch Hand veterans has been conducted. A veteran was included in this pharmacokinetic study if a) his TCDD measurement in 1987 was greater than 10 parts per trillion (ppt), a value regarded as a threshold for background exposure, b) he had provided serum in 1982 and c) the TCDD measurement in the serum collected in 1982 was quantifiable. A total of 343 Ranch Hand veterans were selected. Because veterans were selected based on a TCDD level in 1987 being greater than 10 ppt, a statistical artifact similar to regression toward the mean would have biased the weighted least-squares estimate of the elimination rate. To correct for this, veterans were selected for the final estimate following an iterative procedure, with the result that 97 of the original 343 were actually used for the estimate. These selected 97 veterans were the subjects of the current study.

In the Seveso cohort, serum TCDD was measured periodically following the explosion until 1993. In the Ranch Hand cohort, TCDD was measured in serum collected in 1982, 1987, 1992 and 1997, or between 9 and 33 years after exposure in Vietnam. TCDD measurements from both studies were made by the Centers for Disease Control and Prevention using mass chromatography/mass spectroscopy. Weight and height were measured in both studies at the time of the serum collection for the TCDD measurement, and the body mass index (BMI), equal to weight (kg) divided by the square of height (m), was computed.

For each subject, the elimination rate (λ) of TCDD between two time points, t_1 and t_2, was estimated as $\hat{\lambda} = (y_1 - y_2)/(t_2 - t_1)$, where y_1=log(TCDD$_1$-4) and y_2=log(TCDD$_2$-4), TCDD$_1$ and TCDD$_2$ were TCDD concentrations at the first and second time points measured in parts per trillion (ppt), and log was the natural logarithm; 4 ppt was subtracted before taking the logarithm to correct for background exposure. The corresponding estimated half-life over the interval from t_1 to t_2 is $\log(2)/\hat{\lambda}$. Under a repeated measures linear model with an auto-regressive order one auto-covariance assumption, $\hat{\lambda}$ is the weighted least-squares estimate of the elimination rate for an individual, and the average of the individual estimates is the weighted least-squares estimate for the cohort. We assessed differences between the two cohorts regarding the TCDD elimination rate using contrasts of least-squares means and the mean squared error. The relative change in BMI from time t_1 to time t_2 was defined as (BMI$_2$-BMI$_1$)/BMI$_1$, where BMI$_1$ and BMI$_2$ were body mass indices at times t_1 and t_2. All models were adjusted for age in 1976, BMI at the time of exposure, and the relative change in BMI from the time of exposure.

Results and discussion

Because TCDD measurements were unequally spaced in time within and between subjects, statistical summaries in the Seveso cohort were restricted to four times: 0, 0.27, 3, and 16.35 years after exposure. TCDD measurements made 16.35 years after the accident were made in 1992 (n=43) and 1993 (n=6).

The second time point was selected because 23 of the 54 subjects (11 males and 12 females) had a TCDD measurement both at 0.27 or 0.35 years after the accident; 17 had a measurement at 0.27 years and 6 had a measurement at 0.35 years. The second time point was labeled 0.27 years to indicate the median of these times. TCDD measurements made between 2.5 years and 3.5 years after the accident were defined as having been measured 3 years after exposure. With these definitions, 32 subjects (17 males and 15 females) had a measurement at time=3 years and 24 (11 males and 13 females) had a measurement at both time=0 and at time=3 years. Forty-nine subjects (24 males and 25 females) had a TCDD measurement between 16.35 and 17.35 years after exposure, and 26 of these were at 16.35 years exactly; the fourth time point was labeled 16.35 years to indicate the median of these times.

The average ages of the Seveso males (35.4 years), females (34.4 years) or males and females (34.9 years) were not significantly different from the average age of the Ranch Hand veterans in 1976 (33.9 years); p=0.52, p=0.85, and p=0.55, respectively. The average BMI of Seveso males (26.8 kg/m^2), females (26.7 kg/m^2), and all Seveso subjects (26.8 kg/m^2) 16.35 years after exposure was significantly less than the average BMI of Ranch Hand veterans in 1992 (30.0 kg/m^2); p<0.001, p=0.004 and p<0.001, respectively. The average BMI of Seveso males (24.7 kg/m^2), females (24.5 kg/m^2), or all Seveso subjects (24.6 kg/m^2) at the time of the accident was not significantly different from the average BMI among Ranch Hand veterans during the exposure period in Vietnam (25.6 kg/m^2); p=0.33, p=0.43, and p=0.17, respectively. The median Seveso TCDD level 16.35 years after exposure (218 ppt), was 6.4 times greater than the Ranch Hand median in 1992 (34.9 ppt).

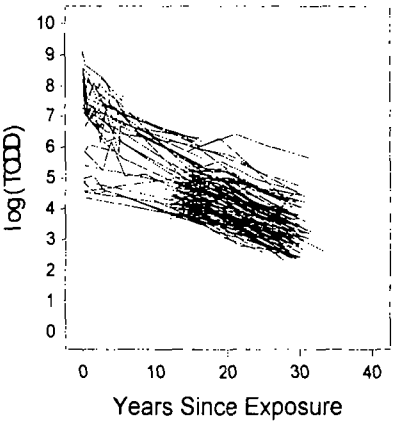
TCDD elimination rates among Seveso females were similar to those among Seveso males. The Seveso rates in the first time interval (0 to 0.27 years after exposure) were greater than Seveso rates in subsequent intervals and were greater than the Ranch Hand rate (from 9 to 33 years after exposure). The Seveso rates from 3 to 16.35 years after exposure were numerically similar to the Ranch Hand rates. The adjusted TCDD elimination rate from 0 to 0.27 years after exposure among males (2.0665 $year^{-1}$) was not significantly different from the corresponding rate among females (1.6272 $year^{-1}$); mean difference= –0.4393 $year^{-1}$, 95% CI –2.9075 to 1.0219, p=0.70. In the interval from 3 to 16.35 years after exposure, the adjusted rate among males (0.1066 $year^{-1}$) was significantly greater than the rate among females (0.0722 $year^{-1}$), mean difference= –0.0344, 95% CI –0.0695 to –0.0121, p=0.05. The TCDD half-lives among males and females on the interval from 3 to 16.35 years after exposure were 6.5 years and 9.6 years, respectively.

The Seveso TCDD elimination rate in the interval from 0 to 0.27 years after exposure among males and females was significantly greater than the Ranch Hand rate; the adjusted rate among Seveso males (2.081 $year^{-1}$) was significantly greater than the rate among Ranch Hand veterans (0.092 $year^{-1}$); mean difference= –1.989, 95% CI –2.2261 to –1.7591, p<0.001. The corresponding TCDD half-life among

Seveso males in the time interval from 0 to 0.27 years after exposure was 0.33 years. The adjusted Seveso rate in the interval 0 to 3 years after exposure among males (0.2334 $year^{-1}$) was significantly greater than the Ranch Hand rate; mean difference= –0.1409, 95% CI –0.1738 to –0.1098, p<0.001. The adjusted rate among Seveso males in the interval 3 to 16.35 years after exposure (0.1008 $year^{-1}$) was not significantly different from the Ranch Hand rate; mean difference=–0.0083, 95% CI –0.0332 to 0.0154, p=0.51. The TCDD half-life was 6.9 years among Seveso males between 3 and 16.35 years after exposure. In the interval from 3 to 16.35 years, the rate among Seveso females (0.0666 $year^{-1}$) was significantly less than the Ranch Hand rate (mean difference=0.0258, 95% CI 0.005 to 0.0453, p=0.02); the TCDD half-life among females in this interval was 10.4 years.

Figure 1 summarizes TCDD elimination in log units among Seveso males and Ranch Hand veterans. The fast elimination shortly after exposure is revealed by the steep slopes within the interval 0 to 0.27 years. Subsequent attenuation to a rate similar to that of the Ranch Hand veterans in the interval 3 to 16.35 years is revealed by lines approximately parallel to the Ranch Hand lines.

Figure 1. TCDD in Ranch Hand (n=97) and Seveso males in (n=29) log units.



LEGEND: Log denotes the natural logarithm.

A combined analysis of TCDD elimination in Seveso adults and Ranch Hand veterans found a period of fast elimination within the first 0.27 years after exposure in Seveso, followed by a period of slower elimination between 3 and 16.35 years from exposure. The TCDD elimination rate within the first 0.27 years after exposure among 6 adult males in the Seveso cohort was 2.081 $year^{-1}$, giving a half-life of 0.33 years. The rate from 3 to 16.35 years was 0.1008 $year^{-1}$, with a half-life of 6.9 years. The Ranch Hand elimination rate, 0.0925 $year^{-1}$ (equivalent to a half-life of 7.6 years between 9 and 33 years after exposure) was significantly less than the rate in Seveso males in the first 0.27 years after exposure, but not significantly different from the Seveso rate between 3 and 16.35 years after exposure. The fast elimination within the first 0.27 years followed by a slower rate after 3 years is consistent with the expected pattern in a two-compartment open model, with a distribution phase of rapid

elimination followed by a slower elimination phase. To our knowledge, this is the first time this behavior has been seen in humans with regard to TCDD elimination.

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References

1. Michalek, J., Pirkle J., Needham L., Patterson Jr. D., Caudill S., Tripathi R. and Mocarelli P. (2001) (In submission).