Half-Life of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Serum of Seveso Adults: Interim Report

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Introduction

Chlorinated hydrocarbon compounds, including selected pesticides, biphenyls, dioxins, and furans, have been linked to a variety of adverse health outcomes. Production in several countries of many of these compounds has ceased, and for others such as the dioxins and furans, there is evidence that the indirect production, as by-products, has declined. Yet, low-level chronic exposure via the food chain continues. This exposure remains of high concern to public health scientists, who seek to determine the relationship between exposure and adverse health effects.

The preferred biomarker for assessing exposure to these persistent compounds is the measurement of the internal dose; e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) in serum. Epidemiologic studies for assessing the effects of high-level exposures to these compounds have been retrospective in design; in most cases, the internal dose has been measured many years after the high-level exposure ceased. This internal dose of 2,3,7,8-TCDD is extrapolated back to what it may have been at the time the excessive exposure ceased. For this extrapolation, first order kinetics and a given half-life for 2,3,7,8-TCDD in humans are used.

The half-life is based on two studies. The first study involves the ingestion by an individual of a low dose (essentially the no observed adverse effect level shown in rats) of tritium-labelled 2,3,7,8-TCDD in corn oil. The half-life based on fecal excretion over

125 days of radiolabelled material was estimated to be 5.8 years[1]. Based on adipose tissue concentrations over a 6-year period, the half-life of 2,3,7,8-TCDD was determined to be 9.7 years[2].

The other half-life data for 2,3,7,8-TCDD comes primarily from the U.S. Air Force's study of veterans of Operation Ranch Hand. By using measurements of serum specimens collected in 1982 and 1987 from 36 Ranch Hand veterans, who had 2,3,7,8-TCDD serum levels greater than 10 ppt in 1982 and 1987, Pirkle et al. found a median half-life of 7.1 years (95% confidence interval about the median of 5.8-9.6 years)[3]. In a more recent report Wolfe et al. expanded this 36 person cohort to 337 Ranch Hand veterans and reported a median half-life of 11.3 years (95% confidence interval about the median of 10.0-14.1 years). They also found that the half-life of 2,3,7,8-TCDD increased with percent body fat (PBF) but decreased with an increase in PBF from 1982 to 1987 (dilution effect). They also found a decreased half-life with increasing age[4]. A third data point based on 1992/1993 blood draws has recently been added on most of these 337 veterans. This third point will be of tremendous assistance in determining the half-life of 2,3,7,8-TCDD in these veterans.

These studies are consistent in that they show that 2,3,7,8-TCDD is highly persistent in humans. However, they are limited in several ways. For example, one study consists of one person who ingested a single low dose solution. In the other study, although the TCDD levels were higher, the first serum specimens were not taken until about 12-15 years after the exposure ceased, and the second sample was taken only 5 years after the first. Therefore, in both studies, the data reported on the participants are based on a time interval of less than one half-life. In both studies, the participants are male adults.

The Seveso, Italy cohort is unique to other 2,3,7,8-TCDD related cohorts in that it represents a residential population exposed primarily to a single release of 2,3,7,8-TCDD on July 10, 1976, that resulted in extremely high serum levels as measured in specimens collected near the time of exposure[5]. Furthermore, many of these people were medically followed through 1985 and in many cases stored serum specimens from these examinations have been analyzed for 2,3,7,8-TCDD. In late 1992 and early 1993 additional serum was drawn. These participants include both sexes and adults as well as children at the time of the incident. They also represent a wide range of exposures.

For comparison purposes this abstract focuses on Seveso adults of both sexes. The objective of this portion of the study is to determine if the half-life in adult males is consistent with that found in other studies, and if it is similar in adult females. Furthermore, this portion of the study is examining the influence of age, initial body mass index, change in body mass index, and the initial 2,3,7,8-TCDD level on the half-life of 2,3,7,8-TCDD.

Methods

All serum specimens, except the 1992/1993 specimens, remained from medical examinations and were stored frozen at -30°C. Twenty-two of the initial specimens were collected during the last week of July 1976; the last initial specimen was collected on October 28, 1976. They were coded and sent to CDC for analyses for 2,3,7,8-TCDD on both a whole weight and lipid bases[6], using triglycerides and total cholesterol results obtained at the University Laboratory of the Hospital of Desio, to calculate total lipids[7]. They were analyzed from 1988 to 1994. The 1992/1993 blood draw was performed specifically for this half-life investigation.

Results

In this interim report, we examined the half-life of 2,3,7,8-TCDD in 27 adults - 15 of whom are females. From three to nine serum samples per individual were used to calculate the half-life. The time interval from the initial level to the final level is 16 years or more, except for one person who was measured over a 14 year interval. The study group characteristics are shown in Table 1.

Table 1. Study Group Characteristics

	Males	Females
N	12	15
Age range (1976) (years)	20-54	16-50
Age mean (1976) (years)	33.1	36.2
Range of initial TCDD (ppt)	130-3830	145-3730

The mean half-life for serum 2,3,7,8-TCDD in these 27 persons is 8.2 years (95% confidence interval of 7.2-9.7 years); the median half-life is 7.8 years. In addition, the

study examined the influence of age, sex, initial body mass index, change in body mass index, and initial dioxin level. Preliminary analysis suggests that the half-life is somewhat longer in women compared to men and increased slightly with increasing initial body mass index. The influence of age, change in body mass index and initial dioxin level are still being examined.

Discussion

This study is the first report that examines the half-life of 2,3,7,8-TCDD over multiple time periods from near the time of exposure out to two half-lifes. This long time interval is a major factor for the smaller 95% confidence interval in this study than in the two reported Ranch Hand studies.

This is also the first report of the half-life of 2,3,7,8-TCDD in females, which appears to be longer than in men. The actual half-life determined is consistent with other studies, and it shows the long persistence of 2,3,7,8-TCDD in humans. The findings are consistent with those in the Ranch Hand study in that the half-life increases slightly with increasing body mass index. The influence of age, change in body mass index, and initial dioxin level on the half-life are still being analyzed for males and females. A plot of log of the dioxin level versus time is approximately linear for the different persons studied. Thus, the elimination curve is consistent with first order kinetics. Both single compartment and multicompartment models are compatible with apparent first-order elimination kinetics. Additional 2,3,7,8-TCDD values are being measured on some participants, and after this is done, a more detailed analysis of half-life and the influence of these variables on half-life will be completed.

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