Clinical Trials of TCDD

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COMMENTARY

Clinical Trials of TCDD

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A patent (No. 6,444,698) has been issued recently allowing the use of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a promoter blocker of specific, named cancers in men and women as well as multiple cancers measured as total cancers.1 Supporting the patent claim are the Kociba lifetime male and female rat feeding study (Kociba et al. 1978) and three epidemiology studies identified below heretofore regarded as environmental rather than clinical based on the presentation of study data in the literature and/or their design. In this note I would like to utilize attributes associated with TCDD’s activity to recast these epidemiology studies as clinical rather than environmental. These attributes include persistence of TCDD in humans (half-life equals 7.5 years, per Michalek et al. 1996) to a calculable and sufficiently constant TCDD body burden level, and a sufficiently long latency period to measure the effects of a chemical acting as a promoter blocker (Kayajanian 1997).

In Kociba, 50 or 49 male and female rats were fed diets of 20, 200, or 2000 ppt TCDD, which does not persist in rats (Fries and Marrow 1975). Eighty-five males and 86 females served as controls. When compared to the respective control, the measure total cancers/animal was always reduced in each exposed group, and significantly reduced \( p < 0.01 \) in each sex at low and mid exposures (Kayajanian 1997). This study establishes TCDD as a potent anticarcinogen in rats.

If TCDD behaves as an anticarcinogen in humans as it does in rats, at what stage of cancer creation does TCDD act? If TCDD were to block the final replicative step leading to a cancer diagnosis in humans, one would expect to observe a reduction in expected cancers in short order, say, within a year. If TCDD were to block the promotional step in cancer creation, the cancer reduction would take more time to register — several years, perhaps 5. If TCDD were to block an early step in cancer creation, like initiation, it might take 15, 20, or more years to register the effect as a cancer reduction. These cancer reduction effects should continue for as many

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1 The patent may be accessed at http://pair.uspto.gov. The author is the patent holder.
years as the TCDD level in man remains sufficient. Of course, many of the exposures to TCDD have occurred in settings with contemporaneous exposures to many other chemicals assumed to act as cancer initiators. Their carcinogenic effects might mask the cancer preventative effects of TCDD 15, 20, or more years after the initial exposure to them and TCDD.

TCDD AS A PROMOTER BLOCKER: USE OF THE SEVESO AND NIOSH DATA SETS FOR CLINICAL COMPARISONS

The selection of subjects for a clinical trial is purposeful, designed to maximize the ability to observe any effect(s) of the TCDD exposure at trial. These maximized health benefits can better offset any adverse effects associated with the treatment. Tamoxifen, for example, touted to reduce breast cancer incidence but a known uterine carcinogen, was clinically tested in women more likely to develop breast cancer.

In both the Seveso and NIOSH data sets, the TCDD-exposed populations were not selected for treatment and for that reason may be more representative of the general population than traditional trial groupings. Since TCDD persists in humans, the TCDD body burden level at any point in time can be backcalculated from later serum measurements. There is an assured constancy in man's daily exposure, even though it declines slowly over time.

A clinical trial sufficiently matches exposed and unexposed subjects under circumstances where the observations on the unexposed group serves as reference for the exposed cohort. Over time a trial would generate two ultimate fractions: the number of diseased individuals per cohort size for each group of subjects. In order to serve as a suitable control, the unexposed cohort is matched as closely as possible (except for exposure) to the exposed cohort. If a substantial latency period is required to observe the effect of the treatment on the disease in the exposed cohort, then each cohort would generate two fractions — one during and one after the latency period. Both exposed cohort fractions are perfectly matched to each other except for time; both unexposed cohorts also are perfectly matched to each other in the same way except for time. Consequently, any ratio of the exposed/unexposed fractions during and post latency are perfectly matched, even if the match of exposed and unexposed subjects does not meet a traditional clinical process standard. If the ratio of the fractions of the two cohorts during and post latency differ significantly in the anticipated direction, this less than clinical trial should be viewed as a clinical success.

I have made the claim that appropriate body burdens of TCDD act as a promoter blocker of cancers in man, an effect discernable about five years following exposure to TCDD. In the Seveso and NIOSH epidemiology data sets, the respective reference groups employed (matched by sex and age to within 5 years from a larger neighboring Italian town and the U.S. population) would not meet the standard for a clinical trial in a non latency comparison.

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The 1993 Bertazzi et al. paper reports time stratified cancer morbidity data in the low TCDD exposed Seveso adults (group R) and unexposed cohort (nearby town) for several cancer categories, including corpus uteri — for the first 5 years and the second 5 years following exposure. In a population of more than 16,000 low-exposure women, 9 corpus uteri were observed in the first 5 years compared with 8.6 observed in a size matched reference group. In the second 5 years, 0 corpus uteri were observed in the R group women, compared with 13.4 observed in the same sized reference group. The during and post latency ratios that simplify to 9/8.6 and 0/13.4, respectively, differ significantly from each other in the predicted direction (p < 0.0001).

Primary liver cancer in R region males also displays this second 5-year ratio reduction. From unpublished data provided by Bertazzi, three primary liver cancers were observed in the first 5 years when 4.02 were expected from men in the unexposed cohort. In the second 5 years, 0 primary liver cancers were observed in R region men, when 7.00 were expected. The reduction is significant (p < 0.05).

Total cancer incidence in these R region women is also reduced in the second five years (119 observed, when 143.2 were observed in the size matched nearby town) when compared to the first 5 years (193 observed in Seveso, when 186.5 were observed nearby), p < 0.06 (data communicated by Bertazzi).

A similar first-5/second-5-years-employment-following-TCDD-exposure argument can be generated from the NIOSH cancer mortality data for total cancers: In the first five years, 10 cancer deaths were observed when 11.76 were expected; in the second five years, 1 cancer death was observed when 5.56 were expected (p < 0.05) (Fingerhut et al. 1990).

TCDD AS A PERSISTENT PROMOTER BLOCKER: USE OF THE OPERATION RANCH HAND (ORH) DATA SET FOR CLINICAL COMPARISON

The ORH Study of Air Force veterans exposed to TCDD during their Southeast Asia duty tour was initially designed with paired TCDD-exposed and —unexposed airmen in a peer-reviewed protocol. The ORH Study Manager abandoned the pairings and divided the exposed veterans into three categories based on TCDD body burden level, then compared cancer incidence in each category with that measure in the entire group of unexposed veterans (Ketchum et al. 1999). In a 2001 analysis of that data, I defined seven TCDD body burden ranges: number 7 had the greatest TCDD body burden and the lowest cancer incidence (Kayajanian 2001).

In a revised comparison more in keeping with the original ORH Study design, total non skin cancer incidence in group 7 veterans (with TCDD body burdens in excess of 128 ppt at duty tour's end), there were 11 veterans with cancer among 227 veterans, which is lower (p < 0.06) than the incidence for the paired unexposed veterans (24/249), whom the ORH Study managers matched one- or two-to-one by sex, race, occupational classification, and same birth year. There are other TCDD-unexposed veterans matched by the ORH Study managers to the other exposed
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veterans who also could have been matched to group 7 airmen: of 475 additional TCDD-unexposed veterans, 38 developed a non-skin cancer. Matched against a larger unexposed cohort (62/724), the reduction observed in group 7 veterans (11/227) becomes significant (p < 0.05).

The matching unexposed veterans almost to a man have TCDD body burden levels between 0 to 10 ppt, when measurements were made in 1987. Roughly three out of seven TCDD-exposed veterans evince body burden measurements within the same 0 to 10 ppt range even though on paper they were classified as exposed to TCDD (Ketchum et al. 1999). Some of these veterans (164 men, 15 with non-skin cancer) would also match group 7 airmen. If this group enlarges the matching reference group (to 888 men, 77 with non-skin cancer), the reduction in cancer incidence associated with the group 7 veterans becomes more significant (p < 0.04).

To conclude, this commentary argues for the use of TCDD as a cancer prevention agent. In Kociba, TCDD reduces total cancer incidence significantly in males and females at 540 and 5100 ppt. The timing of the cancer reductions in the Seveso and NIOSH data sets (years 6 to 10) suggests TCDD acts as a promoter blocker. Beyond 10 years the cancer data are likely to be confounded by the incalculable effects of exposure to the other chemicals in the Seveso and NIOSH chemical plants; so those cancer effects expected beyond 10 years were not relied on. In the ORH data set, significant total cancer incidence reductions are observed well beyond ten years, when there was a sufficient background of cancers to reduce and no apparent excess of other, cancer initiating chemicals like those in Seveso and NIOSH to overpower that observation.

Taken together, these four data sets provide strong evidence that TCDD is a potent anticarcinogen not at every tissue site but whose activity is measurable as a significant reduction in total cancers.

REFERENCES


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