COMPARISON OF ASSESSING LEVELS OF 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN IN SELECTED POPULATIONS BY BIOMONITORING AND EXPOSURE INDICES

Larry L. Needham, Donald G. Patterson, Jr., and Wayman E. Turner

National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Highway, Atlanta, GA 30341 USA

Introduction

Epidemiologists are frequently concerned with relating human exposure with health outcomes. Accurate assessment of this relationship requires accurate assessment of both components- exposure and health outcomes. In this presentation we will examine the assessment of human exposure using populations potentially exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD or dioxin) as the example chemical. Traditionally, epidemiologists have developed exposure indices for the assessment of exposure. These indices consist of at least two primary factors: the concentration of the dioxin in the media that humans contact and the time (duration or frequency) of that contact. However, these exposure indices may or may not correlate with the measured levels of dioxin in those humans; this measured level is generally considered the gold standard for assessing human exposure to chemicals such as dioxin, which has a half-life that has been calculated as 7.6 years,[1] and thus can be measured in heavily exposed people long after undue exposure has ceased. In this presentation we will relate the exposure index that was derived by epidemiologists with measured levels of dioxin.

Methods and Populations

In our laboratory we have measured the internal dose levels of dioxin in adipose tissue and serum samples from the general population and in populations potentially exposed to dioxin. These methods are based on the most accurate and precise approach for measuring these chemicals- namely, high-resolution gas chromatography/high-resolution mass spectrometry with quantification using the isotope-dilution technique.[2] The potentially exposed populations include selected residents of the State of Missouri, U.S.; industrial workers in U.S.; U.S. Army ground troops in Vietnam; U.S. Air Force veterans of Operation Ranch Hand in Vietnam; herbicide sprayers in New Zealand; and residents of Seveso, Italy.

The selected adult residents of Missouri centered around the spraying of oily material containing high levels of dioxin on roadbeds and horse arenas for dust control during the early 1970s; soil levels were measured at levels greater than 500 parts-per-billion (ppb). The exposure index defined an exposed individual as one potentially exposed to soil dioxin levels of 20-100 ppb for two or more years or to soil levels greater than 100 ppb for six or more months. Adipose tissue samples were collected in 1985.

The U.S. industrial workers were potentially exposed to dioxin as a result of working in plant sites that synthesized 2,4,5-trichlorophenol, which produces parts-per-million levels of TCDD, or used the 2,4,5-trichlorophenol, which contained dioxin, to make additional chemicals, such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and hexachlorophene. Various exposure indices were developed and compared to serum dioxin levels that were measured several years after the occupational exposure ceased.

RISK ASSESSMENT

The U.S. Vietnam veterans and New Zealand sprayers were potentially exposed to dioxin from the spraying process or from residues of the spray on environmental matrices. Seven different exposure indices, including two based on self-reports, were developed for assessing exposure to the Army ground troops, who were enlisted men serving in III Corps military region in 1967/1968. The exposure index for each member of Operation Ranch Hand was based on the following equation: concentration of dioxin in Agent Orange during one's tour multiplied by the number of gallons of Agent Orange sprayed during one's tour divided by the number of men in one's specialty during that person's tour of duty. The serum samples for the initial study of 150 Ranch Hand members and 50 controls were collected in 1987. The original exposure index and additional ones were later compared to serum dioxin levels in the entire available Ranch Hand cohort. The exposure index for the New Zealand sprayers was based on the number of years that one sprayed 2,4,5-T. This cohort consisted of nine sprayers, but they had a wide range of years spraying.

The residents of Seveso, Italy were potentially exposed to dioxin as a result of a malfunction on July 10, 1976, at a 2,4,5-trichlorophenol manufacturing plant, which resulted in several kilograms of dioxin as well as larger amounts of other chemicals being cast over several hectares. The exposure index was based zones, which, in turn were based on dioxin soil levels and vegetation and animal deaths. The serum specimens were collected in 1976.

Results

The Missouri incident:[3-5]

- Adipose tissue levels ranged from 2.8-59.1 parts-per-trillion (ppt) in residents; 5.0 to 577 ppt in horse riders in arenas; nondetectable to 20.2 ppt in controls.
- 35 % of those deemed to have been exposed had dioxin levels at or below the 95th percentile of the controls.
- There was no significant relationship of dioxin adipose tissue levels and eating homegrown vegetables, gardening, mowing lawn, playing in yard, walking or other activities related to exposure to soil.
- The only significant variable found ($p=0.029$) was whether the person resided in the sprayed area from 1971-1973, which was during or soon after the actual time of spraying.

The U.S. industrial workers:[6,7]

- Levels measured ranged from 2 to 3390 ppt; maximum extrapolated level ranged to over 30,000 ppt.
- In two plants, duration (years) of exposure in plant areas where TCDD contamination was possible was highly correlated with serum dioxin levels. Thus, duration of exposure was used as the exposure index for the entire occupational cohort.

The U.S. Army ground troops:[8]

- Distributions of measured dioxin levels in 646 Vietnam and 97 non-Vietnam veterans were similar, with a mean and median in each group of about 4 ppt.
- Two veterans had levels greater than 20 ppt. Exposure in Vietnam cannot be ruled out.
- Dioxin levels did not tend to increase with increases in any of the seven exposure indices.
- The low serum dioxin levels were consistent with previously reported serum dioxin levels for ground troops.[9]

Members of Operation Ranch Hand:[10-13]

- Dioxin levels of Ranch Hands from initial study: mean- 49 ppt; median- 26 ppt; 62% above 20 ppt; highest value- 313 ppt; in controls, mean and median- 5 ppt.
- Poor correlation of serum dioxin levels and Air Force's exposure index.

- Air Force decided to use serum dioxin levels on entire cohort for assessing exposure..
- Revisit of exposure indices on entire Ranch Hand cohort showed best exposure index (R^2=0.61) was from job classification (divided into four categories), the number of days of skin exposure, percent body fat during tour, and relative change in percent body fat. However, job classification alone had R^2=0.60. Initial exposure index was the poorest predictor of serum dioxin level. Highest 1987 serum dioxin level was 618 ppt.

Herbicide sprayers in New Zealand:[14]

- Good correlation (r=0.72, P=0.03) between duration (months) of spraying 2,4,5-T and serum dioxin levels, which ranged from 3 ppt to 131 ppt.

Residential exposure in Seveso, Italy:[15-17]

- Zone A (most contaminated zone) residents had highest serum dioxin levels- up to 56,000 ppt, median 447 ppt .
- Zone A residents with chloracne had higher levels on average than nonchloracne residents- however, there was overlap in levels between individuals in these two groups.
- Zone B residents showed no indication of continued dioxin exposure by living in this contaminated area post- July 10, 1976.
- In a large subset of women enrolled in Seveso Women's Health Study, about only 40% of women living in Zones A and B had elevated serum dioxin levels.

Discussion

Exposure indices may be of value for classifying exposure status of populations; however, the user of these indices must be aware that they may lead to a great deal of misclassification that may in turn lead to in general underestimation of any relationship determined between exposure and health outcomes. Especially when exposures are to chemicals with long biological half-lives, such as dioxin, the exposure index should be validated against the appropriate biomarker, such as serum dioxin levels. In the dioxin examples given here, the only exposure indices that highly correlated with the biomarker were those in which careful records of exposure were maintained and evaluated and when the exposure involved actual contact with the dioxin contaminated material and not with an environmental matrix containing the dioxin. We have also seen high correlations between eating dioxin-contaminated foods and serum dioxin levels.[18] However, it appears that there is a big leap in defining exposure in populations that may contact an environmental matrix that contains dioxin and the absorption and storage of dioxin in the body. This does not mean to imply that the use of biomarkers does not have some difficulties, such as individual differences in elimination rates and the occurrence of additional exposures after the last known exposure. However, we are acquiring additional information regarding understanding individual pharmacokinetic differences in eliminating dioxin, and although the elimination rate of dioxin has been shown to be slower as body mass index increases, the half-life is still lengthy, and thus the biomarker is still the best marker for classifying exposure status. It should be pointed out that the leap in defining exposure between populations eating dioxin-contaminated foods and serum dioxin levels may not be nearly as great.

In several studies of adult populations, dioxin levels that were measured many years after exposure ceased were used to estimate the cumulative levels following the last known exposure. This has generally been done in highly exposed populations using a 7-year half-life and first order kinetics. One of the particular problems in assessing exposure retrospectively is that in some populations because of relatively low initial serum levels and/or time since exposure, current serum dioxin levels may have decayed to near background levels. This does present some problems, but information on current serum

dioxin levels may still be relevant. For example, in a recent study of chemical corps veterans, those who sprayed herbicides in Vietnam had a statistically significant elevation in their mean current serum dioxin levels compared to non-Vietnam veterans without a spraying history while other 2,3,7,8-substituted dioxins levels were similar in the two groups.[19] This mean difference was possible to detect only because the background levels in the general population are decreasing. Also, because Agent Orange contained only 2,3,7,8-TCDD and not the other 2,3,7,8-substituted dioxins, we gain additional information when we ratio levels of 2,3,7,8-TCDD against other 2,3,7,8-substituted dioxins. In the case of the veterans who sprayed Agent Orange this ratio was higher than for those who did not- thus indicating that they had been exposed to a product, such as Agent Orange, that contained elevated levels of 2,3,7,8-TCDD relative to other 2,3,7,8-substituted dioxins; thus, serum dioxin levels may still be relevant for validating exposure to Agent Orange even after 35 years post-Vietnam service. Only through the use of highly precise and accurate high-resolution mass spectrometric measurements could we gather this information. Therefore, we still believe that serum dioxin measurements should still be used to attempt to validate exposures that may have occurred many years in the past.

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