

## Commentaries

## Serum TCDD Levels and Health Effects from Elevated Exposure: Medical and Scientific Evidence

Alvin L. Young<sup>1\*</sup> and James L. Regens<sup>2</sup><sup>1</sup>Institute for Science and Public Policy, Sarkeys Energy Center, University of Oklahoma, Norman, Oklahoma, USA<sup>2</sup>Department of Occupational and Environmental Health, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

\* Corresponding author (YoungRisk@aol.com)

DOI: <http://dx.doi.org/10.1065/espr2004.12.131>

## Recent Headlines and Quotes

"... Doctors at Vienna's elite Rudolfiner clinic said tests run over the weekend proved beyond a doubt that it was dioxin poisoning that caused a mystery illness in September that left Yushchenko disfigured and in pain." *Ukraine Reopens Poisoning Probe* 22/12/2004 <[www.cbsnews.com](http://www.cbsnews.com)>

"... UKRAINIAN opposition leader Viktor Yushchenko was poisoned with a chemical used to make Agent Orange during the Vietnam War, the scientist who carried out blood tests on him said yesterday." *Yushchenko given Vietnam War poison* 18/12/2004 (The Scotsman)

"...There is 'no doubt' that Mr. Yushchenko's disease 'has been caused by a case of poisoning by dioxin,' Dr. Michael Zimpfer, the head of the Rudolfinerhaus hospital, said at a news conference on Saturday. He said that Mr. Yushchenko's blood dioxin level was 'more than 1,000 times' the upper limits of normal and that his initial severe abdominal pain suggested that he had eaten the poison." *Liberal Leader From Ukraine Was Poisoned* 12/12/2004 (International Herald Tribune)

## Introduction

In conjunction with its coverage of the disputed presidential election in the Ukraine, the print and television media in the United States and the European Union have extensively reported the dioxin poisoning of the Ukrainian opposition leader, Viktor Yushchenko, with TCDD (presumably 2,3,7,8-tetrachlorodibenzo-*p*-dioxin). Initial reports noted that Mr. Yushchenko experienced severe headache and stomach pains within hours after a dinner on 5 September 2004 [1]. Chloracne, the disfiguring skin condition characteristic of dioxin poisoning reportedly appeared three weeks later [1]. In describing the poisoning incident, the media's reporting on medical issues (i.e., chloracne, cancer, diabetes, and nerve damage) and scientific issues (i.e., analytical tests, routes of exposure, and the second-highest concentration on record) often was linked to more wide ranging political issues, especially the 25-year controversy surrounding Agent Orange and the Vietnam War.

The media's meshing of medical and scientific evidence with political issues is not surprising given the public history of dioxin. Substantial reliance on anecdotal stories, often disconnected from the results of studies published in the medical and scientific literature, has generally informed the media and, consequently, the public's understanding of the relative risk to human health posed by exposure to dioxin. However, dioxin's effects on human health can only be determined by careful consideration of pertinent medical and scientific evidence of the relationship between various serum TCDD levels and human health effects. Testing of serum dioxin levels has been widely regarded as the gold stand-

ard of exposure assessment of dioxin for epidemiological studies since its development in the late 1980s [2]. Although such testing is expensive, the major industrial studies have employed it to validate various methodologies for estimation of exposure. Where testing for serum TCDD levels is delayed until long after exposure has ended, use of the results can be complicated although such testing still provides the best evidence of dose absorbed as a result of exposure [2]. Its superior predictive power has been confirmed repeatedly; for example, in the observation of chloracne.

## 1 Serum TCDD Levels

TCDD is bound very tightly to the lipid portion of serum, and serum measurements are reported on the basis of the concentration of dioxin in lipid, such as pg/g or parts per trillion (ppt). Mr. Yushchenko reportedly has a blood serum level of 100,000 ppt, or 100 parts per billion, ppb, TCDD [1]. In view of the Yushchenko poisoning, it is appropriate to ask: "What is the highest human serum concentration recorded?" Episodes of chloracne have been recorded and serum analyses conducted in an industrial setting, an environmental setting, and, in a poisoning episode reported in 2001 by the Department of Dermatology at the University of Vienna Medical School in Austria [3–5]. In addition, because of the widespread attention given to Agent Orange exposure during the Vietnam War, data for TCDD serum levels in United States Vietnam veterans have been collected. Table 1 summarizes data comparing the levels of TCDD for industrial populations, the 1976 Seveso, Italy, accident, the poisoning episodes, and levels reported for US veterans of

**Table 1:** Serum TCDD levels for varying exposure scenarios

Statistic	TCDD Level (ppt)	N	Population Studied
Mean (range)	233 (2–3,400)	253	Industrial workers at contaminated site [3]
Mean	7	79	Industrial worker control group [3]
Mean	418	119	Industrial workers with more than 1 year exposure [3]
Range	828–56,000	10	Seveso residents with severe chloracne [5]
Observed value	144,000	1	Woman #1 investigated by Geusau et al. [6]
Observed value	26,000	1	Woman #2 investigated by Geusau et al. [6]
Observed value	100,000	1	Viktor Yushchenko [1]
Mean	4	743	646 US Ground troops serving in Vietnam, 97 not serving in Vietnam (no significant difference between the two groups) [7]
Median (range)	12.7 (0.4–617)	872	RANCH HAND personnel [8]
Median (range)	4.2 (0.6–54.8)	1,060	RANCH HAND control group [8]
Mean (range)	3.63 (0.55–5.80)	332	US Army Chemical Corps personnel serving in Vietnam [11]
Mean	2.2	53	US Army Chemical Corps control group [11]

the Vietnam War. Order of magnitude differences are evident in the TCDD concentrations in blood serum. It is evident that the highest TCDD concentrations have occurred from poisoning incidents, whether intentional or inadvertent, which have resulted in levels 10 to 1,000 times higher than those of other exposures.

## 2 Discussion of Serum Levels

The highest level of serum TCDD reported in an industrial setting was 3,400 ppt [3]. However, the mean serum TCDD level in a sample of 253 workers employed in industrial processes involving TCDD contamination was 233 ppt with a range of 2 to 3,400 ppt. A mean level of 7 ppt was found in the control group, while the mean for 119 workers with one year or more of exposure was 418 ppt. Because all of these workers had received their last occupational exposures 15 to 37 years earlier [3], it is impossible to establish the actual serum levels immediately following the last exposure. Some investigators have extrapolated the level at the time of last employment using an estimate of the long half-life in serum, which often results in estimates in the thousands to tens of thousands of ppt dioxin, while others have developed a job-exposure matrix to estimate exposure for job specific production workers [4].

The studies conducted of 200 residents from environmental exposures after the 1976 Seveso, Italy accidental release of TCDD into the atmosphere as a result of an uncontrolled chemical reaction during the industrial production of trichlorophenol provide data about chloracne and its association with serum TCDD levels [5]. Analyses of blood serum samples collected from Zone A residents immediately after the accident, but analyzed years later, revealed that for those individuals with severe chloracne (N = 10) the serum TCDD levels ranged from 828 to 56,000 ppt [5]. Until recently, the serum level of 56,000 ppt (56 ppb) reported in a child by Mocarelli et al in 1991 was the highest human concentration recorded in the scientific literature [5].

However, in 2001, Geusau et al published the results from a 2-year follow-up study of two women, 30 and 27 years of

age, who suffered from chloracne due to "severe TCDD intoxication" of unknown origin [6]. One patient had a blood serum level of 144,000 ppt (144 ppb) TCDD, and developed severe generalized chloracne. The second patient had a blood serum level of 26,000 ppt (26 ppb) and exhibited only mild facial acne lesions.

A search of the worldwide web for information on Agent Orange provides extensive anecdotal information from individual Vietnam veterans who believe they were exposed to Agent Orange, and hence TCDD (**the contaminant by-product in the military herbicide Agent Orange**). Typically, TCDD serum values were not available for those individuals. Systematic analysis of TCDD serum, on the other hand, has been conducted for a representative subset of US Army ground troops. In addition, TCDD serum studies with control groups have been conducted for US Air Force personnel and US Army Chemical Corps personnel, the primary individuals who handled and had direct contact with the liquid herbicide.

A 1988 serum dioxin study by the Centers for Disease Control and Prevention (CDC) compared levels of serum TCDD in 646 US Army veterans who served as ground troops in the most heavily sprayed regions of Vietnam with a control group of 97 Vietnam-era veterans who did not serve in Vietnam [7]. The frequency distributions of TCDD levels were nearly identical in the two groups, both having means and medians of about 4 ppt of TCDD, which was within the range of background at that time. The CDC conducted an extensive analysis of self-reported exposure histories, herbicide spraying records, and military records (five different computed Agent Orange exposure scores using dates and map coordinates of herbicide sprays, military unit locations, and dates of service for each Vietnam veteran) and failed to find a relationship between these surrogates of exposure and the measured serum TCDD levels in the Vietnam ground troops. In fact, the serum TCDD results reported in the 1988 study by the CDC indicated that "most US Army ground troops who served in Vietnam were not heavily exposed to TCDD, except perhaps men whose jobs involved handling herbicides" [7].

Investigators, in fact, have identified elevated levels of serum TCDD in some of the US Air Force *Operation RANCH HAND* veterans responsible for the fixed-wing aerial spraying of herbicides in Vietnam from 1962–1971 [8,9]. RANCH HAND veterans were exposed to herbicides, and hence TCDD, during loading, flight operations, and maintenance of the aircraft and spray equipment. Approximately 1,000 RANCH HANDs and a control group of 1,300 veterans were examined, and medical records for each veteran, his spouse and his children were retrieved and coded in 1982, 1985, 1987, 1992, 1997, and 2002. The Air Force has collaborated with CDC since 1986 to measure dioxin in serum samples from these veterans. The median dioxin level in 872 RANCH HANDs in 1987 was 12.7 ppt with a range of 0.4 to 617 ppt. The median level in 1,060 controls was 4.2 ppt, and the range was 0.6 to 54.8 ppt. Ninety-nine percent of the RANCH HAND dioxin levels were less than 200 ppt and 99 percent of the Comparison group's levels were less than 13 ppt [8]. Although data from the 2002 examination have yet to be reported, the data from the 1997 and previous physical examination cycles lead to the following:

1. No chloracne in any of the RANCH HAND participants;
2. As dioxin levels increased, the presence and severity of adult-onset diabetes increased, although there were no significant differences between RANCH HAND and Comparison Vietnam veterans;
3. Cardiovascular (heart and blood vessels) findings were inconsistent, but an increased risk of cardiovascular deaths in the RANCH HAND enlisted ground crew (those most heavily exposed to TCDD) was observed;
4. The occurrence of signs of neurological abnormalities (peripheral polyneuropathy) appeared to be greater in RANCH HANDs than Comparisons but there was no increase in diagnosable neurological disease;
5. Several blood tests that measured liver function and lipids were slightly elevated, and tended to increase with dioxin level; and,
6. At the end of 15 years of follow-up, RANCH HANDs as a group exhibited a statistically insignificant (i.e., the most likely explanation for variation was chance) six percent increase in the risk of cancer relative to their Comparisons [9]. A recent analysis that breaks with the original design of the study suggests an increased cancer risk among RANCH HAND veterans but introduces bias by using different controls and severely restricts the data on which the analysis is based [10].

In 1994, the Institute of Medicine of the National Academy of Sciences recommended to the Department of Veterans Affairs that a health study be conducted of US Army Chemical Corps veterans who were responsible for storing, preparing, and spraying herbicides around base camp perimeters and aerial spraying from helicopters in Vietnam and of an appropriate control group [11]. Individuals in the Vietnam veterans group were on active duty for a minimum of 18 months with a permanent tour of duty that involved chemical operations during the period from July 1965 to March 1973, a period during which there was a significant US military combat involvement in Vietnam. The non-Vietnam veteran controls consisted of men who had similar characteristics as the Vietnam group except for a tour of duty in Vietnam. Of the 385 dioxin assessments, 332 were for Viet-

nam veterans and 53 were for non-Vietnam veterans. The mean serum TCDD concentration among Vietnam veterans was 3.63 ppt, with a range from 0.55 to 85.80 ppt. The mean serum concentration for the non-Vietnam veterans was 2.20 ppt. A t-test of the means showed that the differences in the means were statistically significant ( $p < 0.05$ ). Of six health conditions examined between the veterans groups, only diabetes was found to be statistically significantly elevated between the high TCDD Vietnam veterans group compared to the low TCDD Vietnam veterans group [11]. Interestingly enough, while the WHO has listed dioxin as a known human carcinogen [12], cancer incidence was lower among high TCDD concentration Vietnam veterans compared to low TCDD concentration Vietnam veterans.

### 3 Health Effects from Elevated TCDD Exposure

What are the health consequences of massive TCDD exposure? In the case of Viktor Yushchenko, he complained of a headache about three hours after the dinner (5 September 2004), and by the next day he had developed an acute stomachache. He later developed pancreatitis and gastrointestinal pain, as well as a severe backache [1]. About three weeks after his first symptoms, Yushchenko reportedly developed lesions suggestive of chloracne, the hallmark of dioxin poisoning [1]. The duration of Yushchenko's illness and his future health effects are uncertain.

The 2-year follow-up of the two women exposed to severely elevated TCDD levels in 1997 provides an encouraging near-term assessment [6]. Despite the high TCDD levels, apart from chloracne, only few clinical and biochemical health effects were observed within the first 2 years after TCDD intoxication [6]. Moreover, through the use of olestra and methylprednisolone to enhance the fecal excretion of TCDD, the blood serum levels of TCDD in October 2000 decreased to 30,300 ppt and 10,100 ppt, respectively for the two women [13]. Nonetheless, one should exercise extreme caution in making inferences based on just two cases.

Fingerhut et al [3] examined long-term health consequences of exposure to dioxin by conducting a retrospective cohort study of mortality involving 5,172 workers at 12 industrial plants in the United States that produced chemicals contaminated with TCDD. As previously noted, serum TCDD levels ranged from 2 to 3,400 ppt in workers whose last occupational exposure to TCDD was 15 to 37 years earlier. Despite the more than 20 years of latency, this study of mortality among workers with occupational exposure to TCDD did not confirm high relative risks for cancers. Indeed, mortality from all cancers combined was slightly increased, but the authors could not rule out the confounding by smoking or other occupational carcinogens. Using a retrospective job exposure matrix for estimating exposure to TCDD and extending the follow-up of the cohort through 1993, a re-analysis of exposure-response has been conducted [14]. The new analyses suggested that high TCDD resulted in an excess of all cancers combined without any marked specificity. However, excess cancer was limited to the high-

est exposed workers with exposures 100–1,000 times higher than those experienced by the general population [14]. The investigators noted that it was possible that other chemicals acted as confounders and were responsible for increases in cancer rates in this cohort [14]. Indeed, Dr. Dimitrios Trichopoulos, Professor of Epidemiology, Harvard University School of Public Health, has suggested that "there is persuasive evidence that TCDD at low levels is not carcinogenic to humans and that it may not be carcinogenic even at high levels" [15].

A 20-year follow-up study of the population exposed to dioxin after the Seveso, Italy, industrial accident failed to reveal an overall increase in all-cause and all-cancer mortality [16]. However, it suggested that those residents living in the highly contaminated territory were at increased cancer risk from some causes, e.g., brain cancer and leukemia. Mortality from non-cancer deaths exhibited some unusual features. For example, an increase in *Diabetes mellitus* was present among females in all exposure zones, and the increase was suggestively time-related. This finding should be interpreted with caution because the diagnostic accuracy of death certificates for this condition was poor. A more in-depth analysis of the relationship of serum TCDD concentrations and age at exposure of female residents of Seveso has recently been published [17].

#### 4 Conclusion

The medical and scientific evidence about serum TCDD levels derived from a wide range of settings have provided examples of how humans may have been adversely affected by exposure to elevated concentrations of TCDD. The extensive data from the retrospective cohort studies of workers at 12 US industrial plants, the Seveso studies, and the studies of Vietnam veterans suggest a possible association between elevated levels of dioxin in the body and some adverse health effects associated with the highest levels of dioxin, but no conclusive evidence of harm with the exception of chloracne. Fortunately, documented cases of highly elevated levels of TCDD serum in humans, such as the Yushchenko case, are extremely rare. On balance, the most serious cases tend to be associated with deliberate poisoning with TCDD, as a consequence of industrial accidents, or due to occupational exposures. The serum data for Vietnam veterans suggest that they were not exposed to Agent Orange and TCDD at the elevated levels experienced by industrial workers or victims of intentional poisoning. Moreover, recognition that exposure to elevated TCDD levels may be associated with adverse health outcomes has resulted in risk management programs that are likely to minimize the potential for non-intentional exposure, as contrasted with the apparently intentional poisoning of Mr. Yushchenko. In fact, the application of rigorous 'medical forensics' in the Yushchenko case underscores the importance of relying on objective, weight-of-the-evidence evaluations grounded in medical and scientific studies as a basis for making public policy decisions in the field of human health.

#### References

- [1] Ross E (2004): Yushchenko Poisoned with Pure TCDD <<http://www.suntimes.com/output/news/cst-nws-ukraine18.htm>>
- [2] Young AL (2004): TCDD Biomonitoring and Exposure to Agent Orange: Still the Gold Standard. *ESPR – Environ Sci & Pollut Res* 11 (3) 143–146
- [3] Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steenland K, Suruda AJ (1991): Cancer Mortality in Workers Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. *N Engl J Med* 324 (4) 212–218
- [4] Piacitelli L, Marlow D, Fingerhut M, Steenland, Sweeney MH (2000): A Retrospective Job Exposure Matrix for Estimating Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. *Am J Ind Med* 38: 28–39
- [5] Mocarelli P, Needham LL, Marocchi A, Patterson DG Jr, Brambilla P, Gerthoux PM, Meazza L, Carreri V (1991): Serum Concentrations of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Test Results from Selected Residents of Seveso, Italy. *J Toxicol Environ Health* 32: 357–366
- [6] Geusau A, Abraham K, Geissler K, Sator MO, Stingl G, Tschachler E (2001): Severe 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Intoxication: Clinical and Laboratory Effects. *Environ Health Perspect* 109 (8) 865–869
- [7] Centers for Disease Control (1988): Serum 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Levels in US Army Vietnam Era Veterans. *JAMA* 260: 1249–1254
- [8] Michalek JE, Akhtar FZ, Ketchum NS, Jackson WG Jr (2001): The Air Force Health Study: A Summary of Results. *Organohalogen Compounds* 54: 396–399
- [9] The Air Force Health Study – Final Report (2000): Executive Summary, pp xxxviii – xiv. Prepared by SAIC for the Air Force Research Laboratory, Brooks City-Base, TX <<http://www.brooks.af.mil/AFRI/HED/hedb.afhs.afhs.html>>
- [10] Akhtar FZ, Garabrant DH, Ketchum NS, Michalek JE (2004): Cancer in US Air Force Veterans of the Vietnam War. *JOEM* 46 (2) 123–136
- [11] Kang HK, Dalager NA, Needham LL, Patterson DG, Lees PSL (2001): Health Status of US Army Chemical Corps Vietnam-Era Veterans Relative to Current Serum Dioxin Concentrations. *Organohalogen Compounds* 54: 392–395
- [12] World Health Organization (1999): Dioxins and their effects on human health. Fact sheet No. 225. Geneva, Switzerland: WHO
- [13] Abraham K, Geusau A, Tosun Y, Helge H, Bauer S, Brockmoller J (2002): Severe 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Intoxication: Insights into Measurement of Hepatic Cytochrome P450 1A2 Induction. *Clin Pharmacol Ther* 72 (2) 163–174
- [14] Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI (1999): Cancer, Heart Disease, and Diabetes in Workers Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. *J Natl Cancer Inst* 91 (9) 779–786
- [15] Trichopoulos D (2001): No Evidence That Dioxin is a Human Carcinogen. *Organohalogen Compounds* 54: 409
- [16] Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C, Pesatori A (2001): Health Effects of Dioxin Exposure: A 20-Year Mortality Study. *Am J Epidemiol* 153 (11) 1031–1044
- [17] Eskenazi B, Mocarelli P, Warner M, Needham L, Patterson DG Jr, Samuels S, Turner W, Gerthoux PM, Brambilla P (2004): Relationship of Serum TCDD Concentrations and Age at Exposure of Female Residents of Seveso, Italy. *Environ Health Perspect* 112 (1) 22–27

Received: December 20th, 2004

Accepted: December 24th, 2004

OnlineFirst: December 24th, 2004