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ABSTRACT

Objectives. The largest known dioxin contamination occurred between 1962 and 1970, when 12 million gallons of Agent Orange, a defoliant mixture contaminated with a form of the most toxic dioxin, were sprayed over southern and central Vietnam. Studies were performed to determine if elevated dioxin levels persist in Vietnamese living in the south of Vietnam.

Methods. With gas chromatography and mass spectroscopy, human milk, adipose tissue, and blood from Vietnamese living in sprayed and unsprayed areas were analyzed, some individually and some pooled, for dioxins and the closely related dibenzofurans.

Results. One hundred sixty dioxin analyses of tissue from 3243 persons were performed. Elevated 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) levels as high as 1832 ppt were found in milk lipid collected from southern Vietnam in 1970, and levels up to 103 ppt were found in adipose tissue in the 1980s. Pooled blood collected from southern Vietnam in 1991/92 also showed elevated TCDD up to 33 ppt, whereas tissue from northern Vietnam (where Agent Orange was not used) revealed TCDD levels at or below 2.9 ppt.

Conclusions. Although most Agent Orange studies have focused on American veterans, many Vietnamese had greater exposure. Because health consequences of dioxin contamination are more likely to be found in Vietnamese living in Vietnam than in any other populations, Vietnam provides a unique setting for dioxin studies. (*Am J Public Health*. 1995;85:516-522)

Agent Orange and the Vietnamese: The Persistence of Elevated Dioxin Levels in Human Tissues

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Introduction

Studies of Agent Orange and its dioxin contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), commonly referred to as "dioxin," have focused mainly on American veterans.¹ The health consequences for the Vietnamese have seldom been considered. This paper summarizes the assessments of exposure conducted from 1970 to 1974 and from 1983 to 1994.

Of the herbicides sprayed during the Vietnam War (known in Vietnam as the Second Indochina War), Agent Orange was by far the most abundant.^{1,2} Throughout the course of that war, which ended in 1975, American and South Vietnamese fixed-wing aircraft sprayed more than 12 million gallons of Agent Orange over about 10% of what was then South Vietnam, the area below the 17th parallel. Additional spraying was conducted from helicopters, from back-packs, and from boats. Spraying began in 1962, intensified in 1967, and is believed to have ended in 1971. This phenoxyherbicide defoliant, named for the orange coding stripes on the 55-gal barrels in which it was stored, consisted of 50% 2,4-dichlorophenoxyacetic acid (2,4-D) and 50% 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in an n-butyl ester formulation. The latter was contaminated with the most toxic dioxin congener, 2,3,7,8-TCDD, which is believed to have been present in Agent Orange at an average level of 3 ppm. In Agent Purple, a related herbicide, TCDD contamination averaged 30 ppm.

Because TCDD is very persistent in human tissue and the environment,¹⁻⁴ the potential health effects of Agent Orange are of particular concern to the Vietnamese people, some of whom have been at risk

since the spraying began in 1962. Eighty percent of the population live in rural areas. They traditionally wear open sandals or walk barefoot while working in the fields; they eat food grown on contaminated soil; and they consume water from contaminated areas. By contrast, American veterans generally served in Vietnam for only 1 year and consumed US-supplied food.

Exposure to Agent Orange can best be assessed by identifying tissue levels of 2,3,7,8-TCDD, the dioxin characteristic of

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Agent Orange.⁵⁻⁷ The studies described here use relatively new analytic techniques to demonstrate exposure in Vietnamese populations. These techniques should help correct the weaknesses of exposure assessments noted by many authors and seen in some Agent Orange, dioxin, or herbicide studies published to date.⁸⁻²⁴ The resultant exposure data may prove useful in developing clinical and epidemiological studies of Agent Orange health consequences in Vietnam; they may also aid in determining the number and locations of persons exposed to Agent Orange in Vietnam. Such information is crucial in formulating a rational public health policy in Vietnam for the large numbers of men, women, and children living in the south of Vietnam who were exposed to dioxin-contaminated Agent Orange.

Methods

Patient Selection

Initially, volunteers were selected who reported that they had been sprayed with Agent Orange or were living in herbicide-sprayed areas. Herbicide spraying could be recognized by the subsequent defoliation, and Agent Orange was the defoliant most commonly used.¹² Vietnamese health teams of physicians and nurses interviewed volunteers extensively before sampling human tissue. Informed consent documents approved by an American Institutional Review Board were explained in Vietnamese by Vietnam health workers and were signed by patients and health workers. Dioxins are found at a parts-per-trillion level in the lipid portion of blood and at a parts-per-quadrillion level in whole blood. Since most Vietnamese strongly object to contributing more than a few milliliters of blood, leftover hospital samples were also collected and pooled.

Samples of human tissue from Vietnam were obtained in two separate periods. In 1970 and 1973, milk was collected from nursing mothers living in areas heavily sprayed with Agent Orange, and in control areas that were not sprayed, by J. Constable, M. Meselson, and colleagues, a team sponsored by the American Association for the Advancement of Science. The samples were then analyzed by R. Baughman in Meselson's laboratory at Harvard University. (This was the first measurement of dioxins in biological specimens.) Additionally, beginning in 1983 and once or twice yearly since then, samples of human adipose tissue,

TABLE 1—Range and Weighted Mean (Lipid Basis, Parts per Trillion) of 2,3,7,8-TCDD in Human Blood, Milk, and Adipose Tissue Samples from Areas Sprayed with Agent Orange (Southern and Central Vietnam) and Unsprayed Areas (Northern Vietnam), 1984 to 1992

	Sprayed Areas (n = 896)			Unsprayed Areas (n = 144)		
	Blood (n = 716) ^a	Milk (n = 90) ^b	Adipose (n = 90) ^c	Blood (n = 82) ^d	Milk (n = 36) ^e	Adipose (n = 26) ^f
Weighted mean	12.6	7.5	14.7	2.2	1.9	0.6
Minimum	3.4	ND (1)	ND (2)	ND (1)	ND (1)	ND (1)
Maximum	32	17	103	2.9	2.1	1.4

Note. ND = not detected, with detection limits in parentheses.

^a13 pools, n = 50; 2 pools, n = 33.

^b6 pools, n = 2; 4 pools, n = 3; 6 pools, n = 4; 1 pool, n = 7; 1 pool, n = 8; 1 pool, n = 12; 1 pool, n = 15.

^c90 individual analyses.

^d1 pool, n = 32; 1 pool, n = 50.

^e1 pool, n = 2; 2 pools, n = 3; 1 pool, n = 28.

^f16 individual analyses; 1 pool, n = 10.

milk, and blood from various Vietnamese populations have been collected by Constable, A. Schecter, and Vietnamese colleagues.

Sample Collection and Storage

Human tissue was collected in chemically clean glass containers at hospitals or clinics and frozen immediately. Because electrical supply is episodic in Vietnam and rare in rural areas, frozen "blue ice" packs were frequently used to preserve specimens. The samples were then moved, stored in freezers at tertiary care hospitals, and kept frozen with dry ice during hand transport to the United States, where they were then stored in freezers at -20°C and shipped on dry ice to the cooperating dioxin laboratories. At least 100 mL of blood was required for each dioxin analysis.

Chemical Analysis

In the 1970s, analysis was performed by gas chromatography and mass spectrometry.^{25,26} In late 1984, archived specimens from the 1970s, preserved at Harvard University in a freezer at -70°C , were reanalyzed using improved techniques then available.²⁷ TCDD levels measured in aliquots of these archived samples proved to be almost identical to the values reported originally from the same samples. The current analytic techniques used by each of the participating dioxin laboratories of meticulous specimen cleanup, high-resolution capillary column gas chromatographic separation, and high-resolution mass spectrometric determination with the use of known standards have been found to meet World Health Organization "certification" standards and will

not be further described.²⁸⁻³³ They are similar to those techniques now used at the Centers for Disease Control and Prevention³⁴ and elsewhere.³⁵ Because dioxins are lipid soluble, tissue lipids are determined gravimetrically and dioxin levels are reported on a lipid basis.

Reporting

Dioxin data are reported in two ways. The first is by measured levels of the individual dioxin (PCDD) and dibenzofuran (PCDF) congeners. The second is by calculating "dioxin toxic equivalents" to reflect estimated dioxin toxicity. Individual dioxins vary quantitatively but not qualitatively in toxicity.

It has been experimentally validated that each dioxin can be represented by a numerical toxic potency factor relative to the most toxic dioxin, 2,3,7,8-TCDD, which is defined as equal to one, and that since there is a common mechanism of action for the dioxins, which vary only in relative toxicity, there is additivity of effect. The toxic dioxin and dibenzofuran congeners each have a dioxin "toxic equivalency factor," which can be as low as 0.001. The total dioxin toxicity value of a mixture is derived by multiplying the measured amount of each congener by its toxic equivalency factor and adding the sum for all the congeners.³⁶⁻³⁹

Results

Table 1 summarizes the weighted mean levels of 2,3,7,8-TCDD for 106 individual and 42 pooled human tissue samples collected from 1984 to 1992 from 1043 Vietnamese adults (899 from the

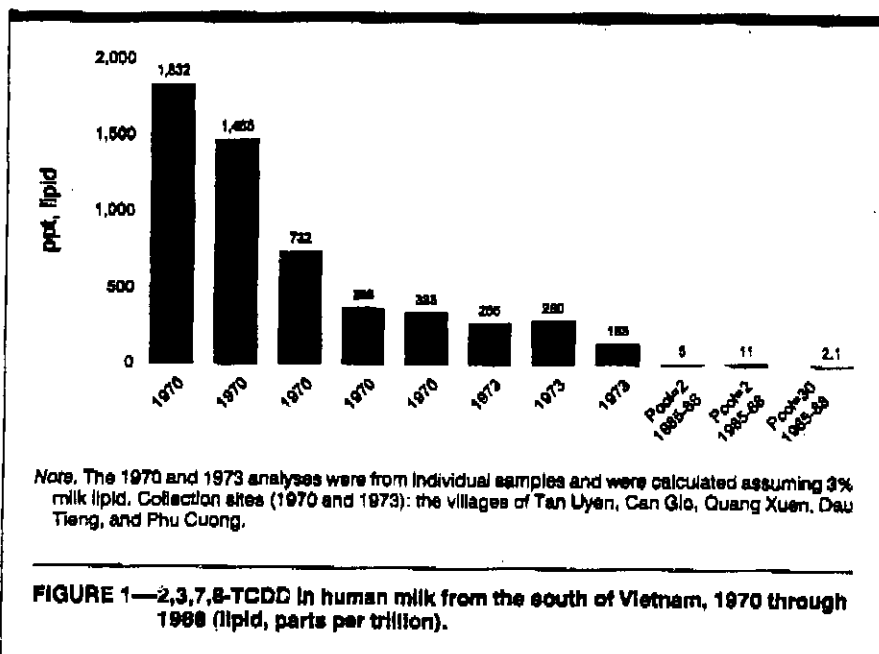


FIGURE 1—2,3,7,8-TCDD in human milk from the south of Vietnam, 1970 through 1989 (lipid, parts per trillion).

TABLE 2—Congener-Specific Dioxin Levels and Dioxin Toxic Equivalents (Lipid Basis, Parts per Trillion) for Pooled Vietnamese Blood, by Geographic Region, 1991 through 1992 Samples

Congener	TEF	South (n = 433)		Central (n = 183)		North (n = 82)	
		Measured Level	TEq	Measured Level	TEq	Measured Level	TEq
Dioxins (PCDDs)							
2,3,7,8-TCDD	1.0	12.9	12.9	13.2	13.2	2.2	2.2
1,2,3,7,8-PeCDD	0.5	8.0	4.0	16.3	8.2	4.1	2.1
1,2,3,4,7,8-HxCDD	0.1	6.6	0.7	13.0	1.3	3.7	0.4
1,2,3,6,7,8-HxCDD	0.1	29.9	2.9	48.2	4.8	13.4	1.3
1,2,3,7,8,9-HxCDD	0.1	8.3	0.8	13.4	1.3	4.8	0.5
1,2,3,4,6,7,8-HpCDD	0.01	77.2	0.8	78.1	0.8	25.5	0.3
OCDD	0.001	616.1	0.6	751.0	0.8	132.1	0.1
Dibenzofurans (PCDFs)							
2,3,7,8-TCDF	0.1	2.1	0.2	2.9	0.3	4.6	0.5
1,2,3,7,8-PeCDF	0.05	1.8	0.09	2.2	0.1	1.7	0.09
2,3,4,7,8-PeCDF	0.5	8.3	4.2	14.9	7.5	7.6	3.8
1,2,3,4,7,8-HxCDF	0.1	21.1	2.1	87.4	8.7	20.6	2.1
1,2,3,6,7,8-HxCDF	0.1	13.0	1.3	40.0	4.0	11.1	1.1
1,2,3,7,8,9-HxCDF	0.1	0.7	0.1	0.7	0.1	0.5	0.1
2,3,4,6,7,8-HxCDF	0.1	2.3	0.2	3.0	0.3	2.2	0.2
1,2,3,4,6,7,8-HpCDF	0.01	37.8	0.4	75.7	0.8	48.7	0.5
1,2,3,4,7,8,9-HpCDF	0.01	3.4	0.03	1.9	0.02	1.9	0.02
OCDF	0.001	3.9	0.004	5.1	0.005	4.2	0.004
Dioxins and dibenzofurans							
Total PCDDs		759.0	22.7	931.2	30.2	185.8	6.9
Total PCDFs		94.4	8.6	213.8	19.8	101.1	8.4
Total PCDD/Fs		853.4	31.3	1145.0	50	286.9	15.3

Note. TEF = dioxin toxic equivalency factor (toxicity relative to TCDD); TEq = dioxin toxic equivalent (measured dioxin level × TEF); n = number of pooled samples.

1.9, and 0.6 ppt, respectively). In southern specimens from the 1980s, the highest individual TCDD level was 103 ppt. In a pooled adipose tissue sample from 10 northern soldiers who had served for many years in Agent Orange-sprayed jungles in the south, the TCDD level was 8.1 ppt (not shown on Table 1). In the northern samples from the general population, the highest level was 2.9 ppt.

Figure 1 illustrates TCDD levels in human milk over time. During the period in which fixed-wing aircraft sprayed Agent Orange and just after it ended in 1970, these levels were quite high; they then gradually declined. The highest dioxin level in 1970 specimens was approximately 1832 ppt, lipid.²⁵ Of individual samples from five women in 1970, positive levels shown varied from approximately 333 to 1832 ppt. There were also several samples in which TCDD was not detected. In three human milk samples obtained in 1973, TCDD levels ranged from 133 to 280 ppt, lipid. Several other samples had undetectable levels. Aliquots taken from 1973 archived milk previously analyzed by Baughman were found to contain TCDD levels between 77 and 230 ppt when analyzed by Ryan; these results were similar to the original data.

Table 2 shows dioxin contamination from Agent Orange as well as from other sources. In contrast to TCDD, found in Agent Orange, higher chlorinated dioxins and dibenzofurans with five to eight chlorines are found in chlorinated phenols used as wood preservatives and in agriculture. The mean results of pooled blood analyses by specific dioxin or dibenzofuran congener and by geographic region are presented for the first 698 patients in our pooled-blood series of 1991/92. These results are converted to dioxin toxic equivalents, reflecting total dioxin toxicity using "international" weighting toxic equivalency factors.²⁷⁻³⁰ As previously noted, these factors range from 1.0 for 2,3,7,8-TCDD to 0.001 for octachlorodibenzo dioxin. Here, mean TCDD level varies from 2.2 ppt in the north to 12.9 ppt and 13.2 ppt in the south and central regions, respectively. Total measured blood PCDDs and PCDFs, reflecting dioxins (and dibenzofurans) from industrial sources⁴⁰⁻⁴⁴ as well as Agent Orange, averaged 853 ppt in the south, 1145 ppt in the central region, and 287 ppt in the north. Total PCDD and PCDF dioxin toxic equivalents averaged 31.3, 50, and 15.3 in these blood samples.

Table 3 presents TCDD levels and total dioxin toxic equivalents in the 43

southern and central areas of Vietnam and 144 from the north).

In the southern samples, mean TCDD levels in blood, milk, and adipose

tissue are relatively similar (12.6, 7.5, and 14.7 ppt, lipid, respectively). In samples from the north, mean levels for blood, milk, and adipose tissue are lower (2.2,

TABLE 3—2,3,7,8-TCDD and Dioxin Toxic Equivalents (Lipid Basis, Parts per Trillion) in Pooled Blood from Vietnam, Collected 1991 through 1992, by Location

	Collection Date	Number Sampled	Mean Age, y	TCDD	TEq	Range of TCDD/TEq for Each Geographic Region	
Northern Vietnam (n = 168)							
Hanoi, Hospital 103	3/91	33	45	1.2	12.0	TCDD 1.2–2.9 (6.1) ^b TEq 12–18 (40.3) ^b	
Tay Nguyen (veterans) ^a	11/91	35	48	6.1	40.3		
Quang Binh, Dong Hoi	1/91	50	47	2.9	17.2		
Than Hoa	11/91	50	55	2.9	18.0		
Central Vietnam (n = 490)							
Thua Thien, Hue	1/91	30	57	11.0	57.0	TCDD 2.9–19.0 TEq 23–118.2	
Quang Tri, Quang Tri	1/91	50	51	9.5	34.0		
Da Nang, Da Nang	2/91	49	59	18.0	77.0		
Thua Thien, A Luoi	1/91	35	52	15.0	23.0		
Kh. Hoa, Nha Trang	1/92	50	49	4.1	29.5		
Phu Yen, Phu Yen	1/92	43	51	6.2	26.4		
Ninh Thuan, Phan Rang	1/92	33	56	2.9	31.7		
Da Nang, Da Nang (18–40 y)	8/92	100	30	14.0	98.3		
Da Nang, Da Nang (>40 y)	8/92	100	58	19.0	118.2		
Southern Vietnam (n = 2062)							
Dong Nai, Tri An (Ma Da Forest)	3/91	50	47	12.0	19.0		TCDD 1.0–33.0 TEq 8.7–104.6
Cuu Long, Vinh Long	8/91	51	59	4.3	16.9		
Dong Nai, Bien Hoa	3/91	50	51	28.0	47.0		
Ben Tre, Giong Trom	8/91	34	55	10.2	29.0		
Kien Giang, Go Quao	8/91	37	58	10.9	27.5		
Kien Giang, Rach Gia	8/91	48	58	4.9	17.3		
Minh Hai, Ca Mau	8/91	52	69	7.2	19.9		
Song Be, Song Be	3/91	47	47	9.0	48.0		
Song Be, Tan Uyen	3/91	48	54	32.0	55.0		
Tay Ninh, Tan Bien	2/91	50	60	5.3	25.0		
Tay Ninh, Tay Ninh	3/91	60	53	6.8	16.0		
Cuu Long, Tra Vinh	8/91	48	57	7.2	27.7		
Hau Giang, Can Tho	8/91	52	61	4.8	16.4		
An Giang, Long Xuyen	8/91	49	62	2.2	10.5		
An Giang, Chau Doc	6/91	46	56	3.5	16.6		
Ho Chi Minh, Cho Ray Hospital	2/91	48	54	10.8	30.0		
Minh Hai, Bac Lieu	8/91	50	60	10.3	34.6		
Gia Lai, Pleiku	1/91	50	57	4.2	34.2		
Tay Ninh, Chan Thanh	8/92	100	54	4.6	19.4		
Tra Noc, Can Tho	8/92	102	51	33.0	104.6		
Song Be, Tan Uyen (18–40 y)	8/92	100	32	9.4	25.4		
Song Be, Tan Uyen (>40 y)	8/92	100	51	5.7	18.9		
Song Be, Ben Cat	8/92	100	53	12.0	49.8		
Dong Nai (18–40 y)	8/92	100	31	14.0	61.0		
Dong Nai (>40 y)	8/92	100	53	19.0	53.7		
Tay Ninh, Hoa Thanh	8/92	100	50	1.0	38.6		
Song Be, Dong Xoai	8/92	100	50	3.1	8.7		
Tay Ninh, D.M. Chan	5/92	100	50	7.0	35.3		
Dong Nai, Bien Hoa (18–40 y)	5/92	100	47	7.3	22.6		
Dong Nai, Bien Hoa (>40 y)	5/92	100	N/A	12.0	49.0		

Note. N/A = not available; TCDD = 2,3,7,8-TCDD; TEq = total dioxin toxic equivalent.

^aAlthough hospital is located in the north, elevated TCDD was found in veterans stationed in the south during the period of Agent Orange spraying.

^bFigures for Tay Nguyen only, not included in range amounts.

1991/92 pooled-blood analyses completed to date from 2720 persons. TCDD makes a lesser contribution to the total dioxin toxicity in most of these samples than it does to toxicity in samples obtained at or near the time of spraying. The highest dioxin toxic equivalent value found is 118.2 from Da Nang in Da Nang province; the highest TCDD level is 33 ppt from Tra

Noc in Can Tho province, followed by 32 ppt from Tan Uyen village in Song Be province, and 28 ppt from Bien Hoa in Dong Nai province.

Discussion

In this paper, we present TCDD levels in blood, milk, and fat tissue

interchangeably because it has been demonstrated that levels of this dioxin congener in these tissues are almost identical when reported on a lipid basis.^{21,45–47} It is now common to use these tissue levels interchangeably when reporting on a lipid-normalized level for purposes of estimating exposure and relative body burden.

These studies in Vietnam were conducted under less than ideal circumstances. During the early period, the country was involved in military conflicts, first with the United States (ending in 1975) and then with Cambodia and China. From 1978 to 1994, the country was under a US-imposed economic embargo. But even under these difficult conditions, the various human tissue samples, collected opportunistically and sporadically, clearly document elevated levels of 2,3,7,8-TCDD, the only dioxin contaminant of Agent Orange, at much higher levels in persons living in areas sprayed in southern Vietnam than in persons living in the unsprayed north, above the 17th parallel, where we find some of the lowest dioxin tissue levels reported worldwide to date.^{31,43}

In milk samples collected from nursing women in 1970, during the time of spraying, we found the highest dioxin levels reported in milk to date: approximately 1832 ppt TCDD.²⁴⁸ In samples collected in 1973, three years after the spraying of Agent Orange is thought to have ended, somewhat lower but also markedly elevated levels of dioxin were still found in milk. At present, levels in milk from the southern samples are declining to levels similar to those found in industrial countries, although they are still higher than those found in the north of Vietnam. In the United States, for example, TCDD levels are 3 to 6 ppt in the general population and total dioxin toxic equivalents are between 20 and 40 ppt, lipid.^{4,49}

Dioxins originate from many sources. These include municipal waste or toxic waste incineration, paper and pulp bleaching using chlorine, chlorinated phenols used as fungicides, wood preservatives and pesticides, feed stocks used in chemical production, herbicides, and polychlorinated biphenyl transformer fires.⁴⁰⁻⁴⁴ There is a characteristic pattern of dioxins and dibenzofurans from each of these sources, as there is for Agent Orange, where only TCDD is characteristic.

As noted previously, total dioxin toxicity, characterized by dioxin toxic equivalents from all congeners, is higher than toxicity of TCDD alone. This will become even more the case as dioxins, dibenzofurans, and dioxin-like polychlorinated biphenyls from industrial processes and agricultural use add to the human body burden of dioxin-like chemicals. Thus, accurate exposure assessments, whether for environmental fate, risk assessment, or dioxin health studies, need to

consider all dioxins present and total dioxin toxic equivalents, not just 2,3,7,8-TCDD. Blood values of TCDD may be elevated but total dioxin toxicity may not be, or the reverse might be the case. Both scenarios are seen in Table 3. Thus, total dioxin toxicity is not always proportionate to Agent Orange exposure.

Mapping the geographic areas where TCDD elevation in Vietnamese tissue reflects the presence and bioavailability of dioxin from Agent Orange can be helpful to others besides the Vietnamese. With areas of likely intake identified, large numbers of individual blood dioxin analyses of Vietnam veterans from the United States, Korea, and Australia might not be necessary.

Cost is an important consideration in planning research studies. Complete dioxin analyses of blood performed by one of the less than 30 World Health Organization certified laboratories currently cost up to \$2000 each. Collection, shipping, and medical interpretation further increase the cost. Studies using pooled blood data can rapidly and economically provide public health information on average population dioxin levels, despite certain methodological limitations.

Now that Vietnamese-US scientific teams are in place and have years of experience working together, environmental mapping of Agent Orange in Vietnam that uses 2,3,7,8-TCDD elevation relative to other dioxins in blood as a marker can be completed relatively quickly, given sufficient funding. This should pave the way for the important Agent Orange- and dioxin-related studies of health outcomes in Vietnam.

Understanding the health effects of dioxin exposure in Vietnam will be valuable, not only for the almost forgotten Vietnamese, but also for the United States and other industrialized nations that seek to evaluate the health risks of widespread exposure to TCDD and other PCDDs/PCDFs. The health of American veterans exposed to Agent Orange is of concern, as is the health of Vietnamese in the south, the population most at risk. In addition, there are about 1 million immigrants from Vietnam, Laos, and Cambodia now living in the United States; these persons might also benefit from research in Vietnam since they too are potentially at risk for adverse health effects of dioxins.

The US Environmental Protection Agency Draft Dioxin Reassessment Documents^{50,51} (released for public and scientific review in late 1994 and awaiting

finalization from the Science Advisory Board of EPA) conclude from an extensive review of dioxins' toxicity and of human exposure that levels of dioxins found in the general US population may be at or close to levels that have consequences for health. Possible consequences are increased risk for cancers, adverse reproductive and developmental effects, immune deficiency, endocrine disruption, neurological damage including cognitive and behavioral damage from in utero exposure, and other health effects.⁵² Since the dioxin levels shown here in Vietnam often exceed US levels, this suggests that health consequences are all the more likely to be expected in Agent Orange-exposed Vietnamese. □

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