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## REVIEW ARTICLE

# AGENT ORANGE USE IN VIETNAM AND ALLEGED HEALTH IMPACTS: A REVIEW

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**Abstract**

Physicians and other members of the medical community frequently are asked about “Agent Orange” and potentially “associated” health issues. The Vietnam War officially ended in 1975, but concerns over the legacy of Agent Orange linger to this day. Under the Agent Orange Act of 1991, the United States Department of Veterans Affairs (DVA) recognizes 14 diseases associated with alleged exposure to Agent Orange, its associated dioxin (TCDD) contaminant, and other tactical herbicides used in combat operations in Vietnam during the war. The medical community needs to understand why Agent Orange has become a national public health issue, and be prepared to respond to questions by veterans and the public. Although the Institute of Medicine (IOM) provided recommendations to DVA on the medical issues, they were directed by the Act to develop “statistical associations” for human diseases rather than to establish cause and effect relationships. No IOM report determined a consistent, coherent, and credible evidence of a causal connection between a disease and exposure to Agent Orange. The reality is that the current Agent Orange Policy is based on politics driven by public, media, veteran and congressional actions. Special evaluations and considerations must be given to the numerous health studies of our Vietnam Era veterans and what they have indicated. Perhaps we could have been fairer to all Vietnam veterans with a program of 'Vietnam experience' benefits rather than Agent Orange benefits. Greater efforts should have been made to study how societal pressures and politics have played a larger role than the efforts of the scientific and medical communities in providing health answers for our Vietnam veterans and the Vietnamese, all who now continue to suffer the lasting effects of war.

**Keywords:** Vietnam War, Agent Orange, Agent Orange Act of 1991, tactical herbicides, dioxin/TCDD, veteran health effects, environmental fate, Veterans Administration

**1. Situation**

Most of the present members of the Medical Community likely entered graduate school and/or medical school many years after the Vietnam War was over. Nevertheless, these physicians and health providers likely have been asked about the

health impacts of the tactical herbicide “Agent Orange” that was used as a defoliant in the Vietnam War. Beginning with the Agent Orange Act of 1991, the United States Department of Veterans Affairs (DVA or alternatively VA, Veterans Administration) determined that veterans who were exposed

to Agent Orange or other tactical herbicides during military service may be eligible for a variety of VA benefits, including health care and disability compensation for diseases associated with alleged exposure [1]. VA and federal law assumes that certain diseases are a result of exposure to these herbicides. This “presumptive policy” simplifies the process for receiving health care and compensation for these diseases since VA foregoes the normal requirements of proving that an illness began during or was worsened by military service.

### **1.1. Veterans’ Diseases Associated with Agent Orange**

The Veterans Administration has recognized the following cancers and other health problems as presumptive diseases associated with exposure to Agent Orange or other herbicides during military service [1]:

- AL Amyloidosis,
- Chronic B-cell Leukemias,
- Chloracne,
- Diabetes Mellitus Type 2,
- Hodgkin’s Disease,
- Ischemic Heart Disease,
- Multiple Myeloma,
- Non-Hodgkins’s Lymphoma,
- Parkinson’s Disease,
- Peripheral Neuropathy, Early-Onset,
- Porphyria Cutanea Tarda,
- Prostate Cancer,
- Respiratory Cancers, and,
- Soft Tissue Sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi’s sarcoma, or mesothelioma).

Additionally, VA presumes certain birth defects in children of Vietnam veterans, specifically Spina Bifida [2].

### **1.2. Procedure for Determining Associated Diseases**

The Agent Orange Act of 1991 established procedures that the Department of Veterans Affairs must follow in deciding whether to create presumptions of service connection for disabilities suffered by Vietnam veterans that may be associated with exposure to Agent Orange or other tactical herbicides in Vietnam [3]. The procedure required that the DVA contract with the National Academy of Sciences’ Institute of Medicine (IOM) to conduct reviews of the scientific literature on the health effects of exposure to the contaminant TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), Agent Orange, and the other tactical herbicides [3]. From 1994 through 2014, IOM conducted 10 biennial updates of the scientific literature [3]. For the DVA, the determination of whether a disease (the above currently fourteen) should be service connected is not based on determination of causation or proof of exposure, nor is it primarily based on studies of veterans who served in Vietnam [4]. Rather, it is based on whether the evidence, as judged following the periodic reviews of the scientific literature by IOM, is sufficient to conclude there is a positive association [4]. In making the final decision on whether an association exists, the Secretary of DVA must apply the standard, as mandated by Congress and the courts, that any resolution of doubt favors Vietnam veterans [4].

### **1.3. Expansion of Eligibility**

The Agent Orange Act of 1991 originally identified veterans with “Service in Vietnam” as eligible for benefits, i.e., Vietnam veterans “who set foot in Vietnam”. This applied to veterans who served in Vietnam between January 9, 1962 and May

7, 1975 [1]. In the past 20 years, eligibility has been subsequently expanded to include veterans who briefly visited ashore in Vietnam; served aboard a ship that operated on the inland waterways of Vietnam; served in or near the Korean demilitarized zone anytime between April 1, 1968 and August 31, 1971; served on or near the perimeters of military bases in Thailand during the Vietnam Era; served where herbicides were tested and stored outside of Vietnam; applied to Air Force Reserve veterans who were crew members on UC-123 defoliation aircraft flown after the Vietnam war; and veterans who were associated with Department of Defense projects to test, dispose of, or store herbicides in the United States (US) [5].

#### **1.4. What is Problematic with the Agent Orange Policy?**

##### **1.4.1. The Failure to Establish “Cause and Effect”**

The first reported concerns by Vietnam veterans about Agent Orange occurred in 1978 in a television documentary by the Columbia Broadcasting System (CBS) entitled “Agent Orange: Vietnam’s Deadly Fog” [6]. This documentary was widely distributed throughout the nation, with a special showing to members of Congress [7]. On December 11, 1979, the Executive Office of the President (President Jimmy Carter) established an “Interagency Work Group to Study the Possible Long-term Health Effects of Phenoxy Herbicides and Contaminants” (IWG) [7].” In August 1981, President Reagan expanded and elevated the IWG to become the Agent Orange Working Group (AOWG) at the Cabinet Council level; Agent Orange had reached the dimensions of a national public health problem [7]. For the next 12 years, the AOWG guided and monitored all federal research into the possible adverse effects of Agent Orange

and similar chemicals on humans, with a focus on the health of Vietnam veterans [7]. The results from 17 major studies failed to clearly establish “cause and effect”, i.e., never confirming that the herbicides or associated dioxin had caused health problems in Vietnam veterans [7].

##### **1.4.2. A Political Solution: The Agent Orange Act of 1991**

The fact that scientific studies did not establish “cause and effect” relationships resulted in the Congress of the United States and the President taking political action to address veterans’ concerns by passage of Public Law 102-4, the Agent Orange Act of 1991. For the Vietnam veteran, the political route resolved the debate of whether the government would assume responsibilities for health-related diseases that might of been caused by exposure to Agent Orange or other military herbicides while on duty in Vietnam [3, 7].

##### **1.4.3. The Limitations of the IOM Reviews**

The Institute of Medicine’s reports of linkages between herbicides or TCDD and human disease are NOT based on cause and effect relationships, but rather on “statistical associations.” The term “statistical association” was not defined, but was interpreted by IOM committees as evidence of an increased risk in as little as one study for which bias, confounding and chance could be reasonably dismissed without weighing contrary or conflicting evidence [3]. No IOM report has ever reported an actual causal relationship between a disease and herbicide/TCDD exposure, i.e., a consistent, coherent, and credible evidence of a causal connection between exposure and dose to a disease [8]. In the case of TCDD, the IOM relied on the *precautionary principle* since the magnitude of the potential damage that it may cause in humans was uncertain [3].

#### **1.4.4. The Failure to Understand Exposure and Risk in Establishing Eligibility**

Today, we have millions of Vietnam Era veterans who can potentially seek health care and compensation through the DVA as alleged “victims” of Agent Orange. A careful evaluation of the military records of the Vietnam Era have confirmed that Agent Orange was never sent to military bases in Thailand, or used or tested on Okinawa, Guam, or applied by US Veterans on the Korean DMZ, yet all these are alleged locations by Vietnam Era veterans where they were exposed to Agent Orange and its associated TCDD [9, 10, 11, 12]. The records and scientific studies also question how more than 2.6 million military men and women who served in Vietnam could have been exposed to tactical herbicides and the associated TCDD. As noted by IOM, the lack of adequate exposure data has made it difficult to estimate the degree of increased risk of disease in Vietnam veterans as a group or individually [3].

The following section is intended to familiarize the medical community with a brief history concerning the Vietnam War, and why the uses of defoliants were deployed in combat operations. In addition, the above problematic issues will be further discussed.

## **2. A Brief History of the Vietnam War**

The United States Military met an unusually complex challenge in the Vietnam War. In conjunction with the United States Military Forces and Allied Forces, the goal was to support a national policy of assisting an emerging nation to develop governmental processes of its own choosing, free of outside coercion [13]. The usual problems of waging armed conflict in Vietnam, also required superimposing the immensely sophisticated tasks of a modern military

upon environments of extreme topography, climate, and vegetation while dealing with the frustrations of antiguerrilla operations, and conducting conventional campaigns against well-trained and determined regular units of North Vietnam [13].

Five nations provided combat troops, i.e., Allied Forces, to support the Republic of Vietnam (RVN, South Vietnam), 1962 – 1973. Australia/New Zealand deployed 46,850 combat troops. The government of Thailand contributed 11,790 military personnel to include Naval, Army, and Air Force units. The Republic of Korea (South Korea) deployed 312,850 combat troops, and 2,644,000 military personnel from the United States served within the borders of South Vietnam [13, 14, 15]. No figures were available on either the number of troops deployed by the Republic of Vietnam (RVN, South Vietnam) as Allied Forces, or the Viet Cong Insurgency Forces or the Democratic Republic of Vietnam (North Vietnam; now the Socialist Republic of Vietnam), but the numbers were likely also in the millions [7, 16]. All of these nations have taken the position that Agent Orange and the associated TCDD have impacted the health of their veterans and their families, or in the case of Vietnam, rural populations.

A large body of historical records and other data exist on the use of Agent Orange in Vietnam. Many of these primary historical records are now openly available through the United States National Archives and military repositories, and they permit a comprehensive assessment of the procedures and supporting historical data related to spraying of tactical herbicides in Vietnam [7]. Extensive collections of publications and reports on environmental data have been assembled on Agent Orange and its associated dioxin [7]. These data also provide insight into the mechanisms of dissipation and degradation as they relate to the distribution and bioavailability of the

herbicides and dioxin in the environment, i.e., issues related to human exposure. Procurement records from the United States Air Force and Defense Supply Agency, complemented by records from the chemical companies that produced the tactical herbicides, and from the National Institute for Occupational Safety and Health, have permitted new estimates on both the quantities of tactical herbicides sprayed in Vietnam and on the level of dioxin in those inventories. Lastly, workshops between the United States Department of Defense and Vietnam's Ministry of National Defense have opened a dialogue on how the two governments can work together to resolve the remaining controversies over Agent Orange, "dioxin hot spots", and potential health issues in Southern Vietnam [15].

### **3. Use of Tactical Herbicides in Southeast Asia**

#### **3.1. Historical Setting for the Use of Herbicides in Vietnam**

The jungles and swamps of Vietnam presented challenges of not just hiding the enemy, but were commonly known as "walking nightmares" providing an environment of biting insects carrying malaria, dengue fever, and encephalitis. Rodents carried fleas and the constant threat of plague, as well as serving as a reservoir of other pathogenic organisms. There were multiple varieties of poisonous plants and snakes, giant centipedes and scorpions. The deployed US and Allied military personnel suffered in the jungle from hornet stings, leeches, trench foot, and biting ants [16, 17]. US Advisors reasoned that the effective control of the vegetation would significantly reduce many of these problems and at the same time lessen the number of ambushes around military camps and bases [18]. Indeed, controlling ambushes was critical to the Allied Military mission. Abundant rainfall and high year-round temperatures

gave much of South Vietnam a 12-month growing season that resulted in almost impenetrable stands of vegetation [19]. These conditions/situations convinced... "US military leaders that Agent Orange was the most appropriate tactical method that would save the lives of American soldiers in Vietnam" [20].

#### **3.2. The Tactical Herbicides Used in Vietnam**

There exists significant confusion as to how herbicides were selected by the US military to be subsequently used in the defoliation program in Vietnam, 1962 – 1971. The belief that commercially available herbicides were simply purchased from the chemical companies and deployed directly to Vietnam is incorrect and contrary to historical records. Tactical herbicides were herbicides developed specifically by the United States Department of Defense to be used in "combat operations" [21].

Approximately 74,176,000 liters (19.6 million gallons) of tactical herbicides were used in defoliation and crop destruction missions in Vietnam, from November 1961 through October 1972. Approximately 58% of the total was Agent Orange and was used from 1965 – 1970; and approximately 63% of all tactical herbicides contained 2,4,5-T, and hence TCDD, and expanding the period from 1961 – 1972 [7].

#### **3.3. The Aerial and Ground Spraying of Commercial and Tactical Herbicides**

The Department of Army's Chemical Corps was responsible for the helicopter or ground application of tactical herbicides *outside base perimeters*, and for selective use in crop destruction and defoliation operations surrounding airfields and fuel depots [22]. Twenty-two US Army Chemical Corps units (approximately 2,900 men) were assigned to South Vietnam

during the period 1965 to 1973. The United States 7<sup>th</sup> Air Force was responsible for Operation RANCH HAND, the aerial defoliation operation involving the spraying of tactical herbicides using 46 specially modified UC-123B/K aircraft from January 1962 through January 1971 (approximately 1,260 men). RANCH HAND aircraft sprayed 95% of the tactical herbicides used in Vietnam with the remainder applied by the Army's Chemical Corps and other Allied Forces [22].

#### **4. The Toxicology and Environmental Fate of the Herbicides**

##### **4.1. The Herbicide 2,4,5-T**

From its use as an herbicide in 1945 through 1978, an extremely large amount of research data, demonstration, and experience of using 2,4,5-T herbicide (2,4,5-trichlorophenoxyacetic acid) had been accumulated including toxicity in animals and man and vegetation control recommendations under field conditions [23]. In 1969, however, the herbicide came under extreme scrutiny since it was discovered that 2,4,5-T was contaminated with TCDD, a teratogen in laboratory animals. The concern about 2,4,5-T was intensified by the fact that it was a major component of Agent Orange [23, 24].

Researchers have repeatedly summarized the toxicological, medical, and environmental information available on 2,4,5-T [23, 24, 25, 26]. The oral LD<sub>50</sub> for 2,4,5-T is 390 mg/kg. None of the reports reviewed suggested that there was a serious level of human risk resulting from the application of 2,4,5-T in forestry, rangelands, or on rights-of-way. Moreover, these studies found that the intake, i.e., dose of 2,4,5-T, was restricted to those individuals directly involved in the operations, and hence exposed to the liquid. These studies showed that any significant dose was rapidly (days) excreted unchanged in the urine [24].

##### **4.2. The Herbicides 2,4-D, Picloram, and Cacodylic Acid**

Since 1994, the Institute of Medicine of the National Academies of Science has published biennial updates of their publication: *Veterans and Agent Orange: Health Effects of Herbicides used in Vietnam* [3]. The last update was published in 2014. The following information summarizes the massive amounts of literature reviewed on 2,4-D, picloram, and cacodylic acid. None of these three herbicides contained TCDD.

The herbicide 2,4-D (2,4-dichlorophenoxyacetic acid) was a major component of three of the four major tactical herbicides used throughout South Vietnam [7]. After rigorous biomonitoring and scientific studies spanning over more than five decades, there was no evidence of cancer in animal tests, no evidence of reproductive toxicity, nor any evidence of birth defects. The oral LD<sub>50</sub> for 2,4-D is 375 mg/kg. It does not metabolize in the human body, but rather it is rapidly (days) excreted in the urine. It is not considered a human carcinogen, and the epidemiological data provide no convincing or consistent evidence of any chronic adverse effects of 2,4-D in humans [3].

The herbicide cacodylic acid (dimethylarsinic acid), the major component of Agent Blue, was an organic arsenical herbicide extensively used in crop destruction programs and control of grassy and dense vegetation around base perimeters and on enemy encampments in the grasslands and savannas of South Vietnam [7]. The toxicity of the active ingredients, the acid and sodium salt of cacodylic acid, is considered low [27]. In man, these active ingredients are rapidly excreted unchanged in the urine. When combined with the toxicological data (i.e., LD<sub>50</sub> >2,000 mg/kg) cacodylic acid did not pose a threat to human health [27]. Reviews by IOM of studies of cacodylic acid have concluded

that it was unlikely to be a carcinogen, teratogen or a mutagen in laboratory animals or man [3].

The herbicide picloram (4-amino-3,5,6-trichloropicolinic acid), a component of Agent White was sprayed from 1966 to 1972 in the Vietnam War [7]. In human trials, picloram, because of its rapid excretion, had a low potential to accumulate in man during repeated or prolonged exposures. When combined with the toxicological data (i.e.,  $LD_{50} > 8,000$  mg/kg) picloram did not pose a threat to human health [3, 26]. Reviews by the IOM concluded that in humans, picloram was unlikely to be a carcinogen, mutagen or teratogen [3].

### **4.3. The Environmental Fate of the Herbicides**

The phenoxy herbicides 2,4-D and 2,4,5-T, as well as the herbicides picloram and cacodylic acid, were used for decades in agricultural and forestry programs worldwide. In the case of 2,4-D and picloram, their use continues today [21]. A large amount of data were available on their environmental fate and how those data have provided a better understanding of human exposure to these herbicides [24, 25, 26, 27].

The extensive available data indicated that both 2,4-D and 2,4,5-T had short persistence time in the environment (days), and when combined with the toxicological data did not pose a threat to human health. The uptake of a measurable dose was possible only when handling the actual liquid [25]. The extensive available data on the environmental fate of picloram provided ample evidence that it was rapidly taken up by the vegetation and although more persistent in the soil, its availability for human uptake was minimal [26]. The extensive available data on the environmental fate of cacodylic provided ample evidence that it was rapidly taken up

and bound by the vegetation [27]. When in contact with soil, the organic form of arsenic rapidly became bound and immobile due to the mineral content of the soil. Its slow disappearance was due to conversion to the volatile alkyl arsine [27].

In summary, a large preponderance of scientific studies and publications on the environmental fate of 2,4-D, 2,4,5-T, picloram, and cacodylic acid have provided ample evidence that within days after these herbicides were sprayed into the environment, the lack of bioavailability, even at application rates used in Vietnam, would have minimized human exposure. The question remained, what exposures to 2,4,5-T and its associated TCDD occurred in Vietnam resulting from the wide-scale application of 2,4,5-T-containing tactical herbicides for defoliation and crop destruction?

### **5. The TCDD Contaminant in 2,4,5-T-Containing Tactical Herbicides**

Much of the concern about the use of Agent Orange, and the other 2,4,5-T-based tactical herbicides, has arisen from the highly toxic TCDD -- often simply called dioxin -- that was a contaminant only in the 2,4,5-T component [23, 24]. Since 1970, TCDD has been one of the most studied chemical molecules. Thousands of scientific papers have been published on TCDD and other members of the dioxin family. Despite such extensive research, there continues to be much debate about how the human responds to the presence of TCDD [14]. The media's coverage of the controversy surrounding Agent Orange and the Vietnam War has unfortunately too often placed TCDD in the political arena divorced from the science. The media's substantial reliance on anecdotal stories, often disconnected with the results of studies published in the medical and scientific literature, have influenced negatively the public's

understanding of the relative risk to human health posed by exposure to dioxin. Dioxin's effects on human health can only be determined by careful consideration of pertinent medical and scientific evidence of the relationships between various serum TCDD levels and human health effects [14]. Testing of serum dioxin levels has been widely regarded as the gold standard of exposure assessment for epidemiological studies since its development in the late 1980s. Its superior predictive power is the best evidence of dose absorbed resulting from exposure. This has been confirmed repeatedly; for example, in the observation of chloracne, the "hallmark" of exposure in humans to TCDD [28]. Other than chloracne, there is no clear and convincing evidence to suggest that the miniscule concentrations of TCDD in our environment cause any serious harm to man [28].

### **5.1. TCDD Concentrations in Agent Orange**

In 2007, an effort was undertaken with the objective of providing a statistically valid measure of the amount of TCDD that contaminated 2,4,5-T-containing tactical herbicides shipped and sprayed or spilled in Vietnam from 1962 (start of Operation RANCH HAND) to 1972 (completion of Operation PACER IVY, the removal of remaining Agent Orange in Vietnam) [15]. Data from the analyses of 1,083 samples of Agent Orange or archived 2,4,5-T established that the mean concentration of TCDD in Agent Orange as 1.88 ppm (parts per million). Considering the concentrations in the other 2,4,5-T-containing tactical herbicides, it was estimated that the total amount of TCDD released in Vietnam was 130 kg (~290 lbs.) (this figure did not include the TCDD in the 2.3 million gallons of Agent Orange returned to the United States in Operation PACER IVY, 1971-1972) [15].

### **5.2. The Likely Distribution of the TCDD During the Vietnam War**

In preparation for the 2<sup>nd</sup> Agent Orange and Dioxin Workshop in Hanoi, Viet Nam, in June 2007, information was gathered on where the USAF, the Army of the Republic of Vietnam (ARVN), the US Army Chemical Corps and Allied units temporarily stored and maintained inventories of tactical herbicides used in Operation RANCH HAND [15]. The records confirmed that the USAF sprayed 95% of the tactical herbicides in Operation RANCH HAND. The remaining 5% was primarily sprayed from helicopters belonging to the US Army Chemical Corps (4%) and Combat Engineers belonging to Australian, Korean, or ARVN units (1%) [14, 15]. Moreover, of the 130 kg of TCDD estimated to have been present in the tactical herbicides, it was likely that at least 96% to 98% of the TCDD was aurally sprayed over the jungles and mangroves of Southern Vietnam [14, 15]. The remaining 2% to 4% likely remained in what has been labeled as "hot spots", i.e., locations where the Agent Orange was spilled during storage or when loaded on to RANCH HAND aircraft and Army Chemical Corps helicopters [15].

### **5.4. The Environmental Fate of TCDD**

In 2004, scientists knowledgeable of the environmental fate and toxicology of 2,4,5-T herbicide and the associated dioxin contaminant TCDD conducted a critical review of hundreds of scientific studies and assessed the likelihood of environmental fate, persistence, and bioavailability of Agent Orange and its associated dioxin on potential exposure during the Vietnam War [29]. The conclusion of this review was that the prospect of widespread prolonged exposure to TCDD from tactical herbicides in ground troops or Vietnamese civilians in Vietnam entering defoliated areas was

unlikely because of the environmental dissipation via photodegradation of TCDD (days), little bioavailability, and the properties of the tactical herbicides and circumstances of application that occurred [29].

### **5.5. Operational Issues that influenced Exposure to Agent Orange/TCDD**

In 2004, three military historians who were in Vietnam during the war or after the war and were intimately familiar with the use of contemporary military records, assessed possible exposure of ground troops and civilians to tactical herbicides [30]. They noted that the historical military records did not support the hundreds of examples of anecdotal information by individuals who claimed they were exposed to tactical herbicides and TCDD. Historical records documented that RANCH HAND spray missions were flown at tree top level and consequently were exposed to frequent and intense hostile fire. Thus, the conclusion was that through detailed policies and procedures, the circumstances in which spraying of combat troops and non-combat civilians with tactical herbicides in Vietnam was closely managed to minimize this exposure [30, 31].

### **5.6. Operation FLYSWATTER**

Vietnam War veterans and Vietnamese civilians often reported sightings of RANCH HAND aircraft spraying Allied Bases and associated Vietnamese communities. In late 1966, the USAF was instructed to modify RANCH HAND UC-123 aircraft to an insecticide-spray configuration. Operation FLYSWATTER commenced on 6 March 1967 [32]. From that date through February 1972, from one to three UC-123 aircraft and crews were used to spray malathion, an organo-phosphate insecticide, for mosquito and malaria control. The low-flying insecticide-spraying aircraft were commonly

called the ‘Silver Bug Birds’ because they normally were not camouflaged [32]. By 1970, malathion treatment was being applied to 14 airbases and their adjacent South Vietnamese cities, and the re-spray interval had been reduced from every fourteen days to every nine days. Between 1966 and 1972, more than 3.5 million liters of malathion insecticide were sprayed on approximately 6 million hectares of Southern Vietnam [32]. Anecdotal reports of direct spraying of troops and civilians in Vietnam likely reflected the RANCH HAND missions supporting Operation FLYSWATTER.

### **6. The Analysis of TCDD as the Gold Standard of Measuring Exposure and Dose**

The development of increasingly sophisticated methods for monitoring low levels of TCDD in human tissue is regarded as one of the premier achievements of environmental science and is considered the “gold standard” for assessing actual received doses in persons exposed to environmental TCDD [28]. Exposure is the opportunity for physical contact with a chemical, in this case TCDD, in the environment. For exposure to occur, it is necessary for the TCDD to have been released from its source in a form in which it is possible to reach a portal of entry into the human body (dermal, absorption, inhalation or ingestion). Dose is the amount of TCDD that enters the body and is transported to target tissues, often by means of the blood stream. In the case of TCDD, analyses have been performed on body fat, blood serum and breast milk. While epidemiological studies of Vietnam veterans and Vietnamese have attracted considerable attention over the years, the questions of exposure and actual absorbed dose were of less importance because of the inability to measure the TCDD at parts per trillion (ppt), a situation that has now become possible [14].

### 6.1. The Family Named Dioxin

The name “dioxin” has been confusing. The popular media calls 2,3,7,8-tetrachlorodibenzo-*p*-dioxin simply “dioxin”. However, scientists abbreviate the molecule as 2,3,7,8-TCDD or just TCDD. The reality is that there are 75 possible “isomers” or congeners in the dioxin family [33]. The most toxic of these have the chlorines in the 2,3,7,8 position on the molecule. Thus, there are 22 tetrachloros molecules with the chlorine atoms in various positions on the molecule, e.g., 1,4,7,8-tetrachlorodibenzo-*p*-dioxin, but only one with the chlorine atoms on 2,3,7,8 positions on the molecule. There are penta, hexa, and octa dioxins and again the most toxic have the chlorine in the 2,3,7,8 position within the molecule. The “furans” are dioxin cousins, where instead of two oxygen atoms joining two benzene rings, there is only one. There are 135 furan congeners. Again, there are tetrachloros furans available, as well penta, hexa, and octa all having the 2,3,7,8 position. *Why is all this chemistry important?* An analytical chemist using high-resolution gas chromatography (HRGC) and high-resolution mass spectrometry (HRMS) found that in the human body fat and blood serum there were potentially seven polychlorinated dibenzo-*p*-dioxins (PCDDs), all having chlorine atoms in the 2,3,7,8 positions on the molecules, and ten polychlorinated dibenzofurans (PCDFs), all having chlorine atoms in the 2,3,7,8 positions on the molecules [33]. It was found that human fat tissues retained these 17 molecules because of their highly lipophilic nature. It was subsequently found that there were many environmental sources where PCDDs and PCDFs could be found [33]. For monitoring purposes, it was found that the half-life for TCDD was 5-7 years in the human body [33].

### 6.2. Sources of PCDDs and PCDFs in Vietnam

The first measurements of TCDD concentrations in Vietnam were of very limited value in determining the relative concentration of potential sources of dioxins. The biomonitoring work of Baughman and Meselson in 1973 inferred that the “dioxin source” in fish and crustaceans collected in fishing villages along the Dong Nai and Sai Gon Rivers was primarily attributed to Agent Orange [34]. In the years between 1970 and 1991, many potential sources for PCDDs/PCDFs occurred in Southern Vietnam including large discharges of PCB-contaminated oil and untreated wastes into rivers and lakes from industrial zones, including wastes from paper, plastic, electronic and chemical industries containing TCDD [35]. The author noted that in 1995 an estimated 9,100 cubic meters of garbage were generated daily in Vietnam, and 90% of the garbage in Ho Chi Minh City (formerly Saigon) was either burned or dumped in rivers, lakes and ponds [35].

Starting in the mid-1980s, when foreign scientists were again permitted to conduct research in Vietnam, and continuing through 1990s, Schechter and associates began an ongoing series of studies on human adipose tissues and later blood serum samples that addressed dioxins and furans in the environment, food sources, and in the Vietnamese population [36, 37]. The seventeen congeners previously discussed were generally found in all samples. Schechter et al focused much of the research first on the collection of human adipose tissue from Vietnamese volunteers and later pooled human serum samples from Vietnamese hospitals. Adipose tissues studies identified TCDD concentrations that ranged from 7.3 to 33 ppt [36], while blood serum studies ranged from 6.1 to 56.1 ppt [37].

In 1991, Kang et al reported concentrations of PCDDs and PCDFs in adipose tissue from 36 US Vietnam veterans, a similar group of 79 non-Vietnam veterans, and 80 civilians [38]. Tissue samples were selected from the 8,000 archived tissues collected from the non-institutional US general population by the US Environmental Protection Agency, 1971-1987. The arithmetic means and standard deviations for concentrations of TCDD in adipose tissue of US Vietnam veterans, non-Vietnam veterans, and civilian controls were 13.4 ( $\pm$  7.4), 12.5 ( $\pm$  7.2), and 15.8 ( $\pm$  14.8) ppt on a lipid weight basis, respectively. The large standard deviation of the civilian controls was attributed to an outlier with a value of 106 ppt. Mean concentrations were not significantly different among the three groups with or without adjustment for individuals' age, body mass index, and specimen collection year. In addition, none of the surrogate measures of Agent Orange exposure such as military branch or troop location in relation to recorded Agent Orange spray were associated with concentrations of TCDD in adipose tissue of US Vietnam veterans [38]. A comparison of congener profiles with the Schecter et al data for concentrations of the 17 PCDDs and PCDFs congeners known to be found in human tissue from industrialized countries, revealed that both the absolute and relative concentrations of these congeners were consistent among the three groups and similar concentrations and patterns in adipose tissues in Vietnamese [36]. These data suggested that much of the adipose TCDD levels in Vietnamese and Americans may not have been just related to exposure to Agent Orange, but rather to the progress of industrialization. Southern Vietnam became industrialized before and during the Vietnam War, while Northern Vietnam entered a rapid industrialization beginning in the late 1980s.

Most recently, there has been renewed interest in serum levels of PCDDs and PCDFs in Vietnamese residents living at or near contaminated sites, i.e., "hot spots", at the former US bases at Bien Hoa, Da Nang, and Phu Cat [37]. In general, fish farming and other water-related activities at or near the hot spots increased the risk of exposure to TCDD [39]. An additional study determined the levels of PCDD and PCDF in breast milk of 143 primiparae living around the same three "hot spots" [40]. The TCDD concentrations ranged from 0.5 to 27 ppt in breast milk, with the highest level found at Bien Hoa [40]. No results were presented with respect to the health of mothers or infants. Interestingly, Schecter et al compared mean PCDDs levels found in breast milk in Cambodia (77 ppt), Thailand (82 ppt), Hanoi (104 ppt), Germany (289 ppt), United States (327 ppt), and Da Nang (406 ppt) [41]. Dates of collections, numbers of samples, and different analytical laboratories involved limit the confidence of the findings. The authors however conclude that the variation in data by location represented the degree of industrialization [41]. Again, there was an absence of health-related data.

Despite evidence that most of the TCDD detected in human tissues probably came from other sources, exposure to Agent Orange continues to be identified as the source for bioaccumulation in Vietnamese. In large measure, this reflects the international notoriety associated with Agent Orange and its associated TCDD. It also reflects the reality that quantitative inventories for non-Agent Orange sources of PCDDs and PCDFs to which Vietnamese are potentially exposed, makes it difficult to accurately assess exposure and risk.

## 7. Results of the Numerous Health Studies of Vietnam Veterans

Our awareness of its toxicity, persistence in biological tissue, and environmental fate of TCDD now spans at least 35 years [41, 42]. In that span of time, thousands of articles have been published on TCDD making it not only a chemical of intense regulatory interest but also one of the most researched molecules worldwide.

While the major epidemiological studies of Vietnam veterans and Agent Orange have attracted considerable attention over the years, the important question of exposure and actual absorbed dose remains elusive. A pathway that would have represented a primary exposure to Agent Orange and its associated TCDD would have been a direct exposure to the liquid herbicide. A “secondary exposure” would have been through secondary pathways such as the consumption of contaminated food, or the drinking of water with contaminated sediments. These are called “environmental exposures” and represent an indirect exposure [42].

An excellent example of Vietnam veterans allegedly receiving environmental exposures was conducted by CDC in 1988 [42]. This study compared the blood serum TCDD levels in 646 ground combat troops who served in heavily sprayed areas of Vietnam against 97 veterans who did not serve in Vietnam. The 646 combat veterans had served at least one tour in III Corps, a heavily sprayed part of Vietnam near Saigon. Exposure estimates were based on military records and on self-reporting [42]. For the Vietnam veterans, the fact that military records appeared to validate that they were exposed, coincided with their own perception of being exposed. However, the concentration of TCDD levels in Vietnam and non-Vietnam veterans were nearly identical, ~ 4 ppt. To the Vietnam veterans in this study, the perception of exposure and

the reality of exposure were not the same, and the use of military records to determine locations of combat veterans in relation to RANCH HAND missions were also not good indicators for validating exposure to Agent Orange [42].

An excellent example of a study of Vietnam veterans where exposure to the liquid Agent Orange was documented by extensive TCDD analysis was the Air Force Health Study (AFHS) [43]. In 1982, the USAF initiated the AFHS, a study of the men of Operation RANCH HAND, the US-Vietnam allied program for the aerial application of tactical herbicides from the UC-123 aircraft during the Vietnam War. For the 20-year study, there were two cohorts; one cohort included 1,261 RANCH HAND veterans, and the other cohort represented the comparison group that consisted of 19,109 veterans who flew C-130s in Vietnam. The protocol used a matched retrospective cohort design intended to independently determine mortality, morbidity, and reproductive health [43]. The strength of AFHS was enhanced during the second physical examination in 1987 with the development of TCDD determination in blood serum at the ppt level. Of the 995 RANCH HAND who were fully compliant in 1987 for the physical examination, 932 had serum specimens analyzed by CDC. The serum values for TCDD ranged from less than 10 ppt (considered “background”) to 618 ppt. The highest values were found in the maintenance personnel who came into direct contact with the liquid herbicide, and who were responsible for loading the herbicide into the planes, cleaning the spray equipment and repairing the aircraft. During the six examinations conducted over the 20 years, the AFHS investigated over 300 health endpoints on multiple occasions. The results of the AFHS did not provide evidence of disease in the RANCH HAND veterans caused by their elevated levels of exposure

to Agent Orange and its associated TCDD contaminant [43]. Despite these results, DVA granted presumption for the Air Force Reserve personnel who flew the same RANCH HAND UC-123 aircraft after they had been returned to the United States, cleaned and re-fitted [5].

In 2006, the Veterans Health Administration, DVA, published a report on *“Health Status of Army Chemical Corps Vietnam Veterans Who Sprayed Defoliant in Vietnam”* [44]. As previously noted, the US Army Chemical Corps veterans also handled and sprayed tactical herbicides in Vietnam potentially resulting in exposure to Agent Orange and TCDD. The study was a health survey of 1,499 Vietnam veterans and a group of 1,428 non-Vietnam veterans, and was conducted using a computer-assisted telephone interview. Serum specimens were obtained from a sample of 897 veterans for TCDD analysis. The mean blood serum concentration of TCDD in the Vietnam veterans was 4.3 ppt (0.5 – 85.8) and for non-Vietnam veterans 3.1 ppt (0.8 – 9.6). The authors concluded that Army Chemical Corps veterans who were occupationally exposed to tactical herbicides in Vietnam, experienced higher risks of several chronic medical conditions relative to non-Vietnam veterans [44].

A 30-year post service mortality study by CDC of a cohort of 9,324 male US Army veterans who had served in Vietnam, and whose presumption of exposure would have been consistent with the DVA policy [45]. The Vietnam veteran cohort was matched with a cohort of 8,989 male non-Vietnam veterans. The conclusion as reported in 2004 was that death rates from disease-related conditions, including cancers and circulatory diseases, did not differ between Vietnam veterans and their peers, despite the increasing age of the cohort (mean age, 53) and the longer follow-up (average, 30 years)” [45].

As noted earlier, Australia also provided military personnel supporting the conflict in Vietnam [13, 14]. In a study of long-term disabilities supported by the Australian Department of Veterans’ Affairs, 60,228 military personnel who served in the Australian Army, Navy, and Air Force in Vietnam, or in the waters adjacent between May 1962 and April 1975 were identified for participation from the Nominal Roll of Vietnam Veterans in Australia [46]. The control group consisted of 82,877 military personnel who had at least 3 years of peacetime service in the Australian Defense Force between 1972 and 1994, but who had no evidence of deployment overseas. There were significant causes of disability between the two cohorts. In the Vietnam veteran group, the most common reasons for disability were eye and ear disorders and mental health conditions (each around 48%) and musculoskeletal and connective tissue disorders 18%. In the control group, the leading causes of disability were eye and ear disorders (11%), musculoskeletal and connective tissue disorders (10%), and injury (5%). The conclusions of the study were that long-term effects of deployment into military conflicts are substantial, and likelihood of war-related disability is associated with service history” [46].

The results of recent research studies sponsored by the US Department of Veterans Affairs at DVA Medical Centers continue to be limited by the determination of the Vietnam veteran’s exposure to Agent Orange. Indeed, in these studies the investigators depended on the selection of participants that were identified in the Department’s Agent Orange Health Registry [47]. The claims process for the Vietnam veteran begins with the Agent Orange Health Registry Examination administered through the VA. If the participant is found to have a medical condition that is associated by the VA to possible exposure to herbicides in Vietnam, that individual is provided with

a follow up examination and is automatically included in the Agent Orange Health Registry and thus, presumed to be exposed to Agent Orange [47].

How has this Registry been applied? In a 2016 study to determine if exposure to Agent Orange was a risk factor for hepatocellular cancer (HCC), the investigators used the Agent Orange Health Registry to determine Vietnam veteran exposure to Agent Orange [48]. The retrospective study reviewed 390 patients with confirmed chronic hepatitis C-related cirrhosis (CHC) between 2000 and 2013. The mean age of the cohort was 51 years, with the majority being male (98.5%). Seventy-nine (79) of 390 patients (20.2%) developed HCC, diagnosed on average 8 years after diagnosis of CHC. The conclusions were that there was no significant association between exposure to Agent Orange and HCC, although larger studies were needed in the US military veteran population to confirm these findings [48].

The authors of a review of skin diseases associated with Agent Orange and presumably TCDD exposure, recognized that in many long-term health studies skin diseases are not comprehensively assessed, and this represented an important gap for patients presenting cutaneous findings [49]. The hallmark of dioxin/TCDD exposure is chloracne [49]. Chloracne typically presents with the development of numerous noninflammatory comedo-like lesions interspersed with straw-colored cysts in a distribution most commonly involving the malar crescent surrounding the eyes and periauricular areas with occasional genital and truncal involvement. The results of a review of organochlorine exposures in 25 Vietnam War veterans found:

*“Vietnam veterans have self-reported a higher frequency of chloracne and other skin ailments and communicate*

*many current concerns about those skin problems, yet dermatologic examination findings over 20 years after possible herbicide exposure often do not support the self-reported symptoms. The studies have also shown an increase in “symptom complex” scale scores that quantify self-assessed disease severity among veterans who served in Southeast Asia and claimed they handled herbicides directly” [49].*

The diseases most concerning to the Vietnam veteran are those of the various cancers allegedly associated with exposure to phenoxy herbicides, i.e., components of Agent Orange, and its associated TCDD [50]. A 1989 study of “Phenoxy Herbicides and Cancers” concluded that there was insufficient epidemiologic evidence of causation [51]. This concern of TCDD causing cancer was updated in 2011 in a critical review of the available epidemiological studies [52]. This critical analysis concluded:

*“Recent epidemiological evidence falls far short of conclusively demonstrating a causal link between TCDD and cancer risks in humans. The emphasis on results for overall cancer risk – rather than risk for specific neoplasms – is not justified on epidemiologic grounds and is not a reason for ignoring the weakness of the available evidence” [52].*

Perhaps the most extensive study of selected cancers in veterans with service in Vietnam was conducted by the CDC and reported in 1990 [53]. The Selected Cancers Study was undertaken by CDC to assess the effects of military service in Vietnam and exposure to herbicides on the subsequent health of American veterans of that conflict. In a population-based, case-control study, the risks were examined for (1) non-Hodgkin’s lymphoma, (2) soft tissue and

other sarcomas, (3) Hodgkin's disease, (4) nasal, (5) nasopharyngeal, and (6) primary liver cancer among Vietnam veterans [53]. The conclusions of the study:

*“An increased risk was found of non-Hodgkin's lymphoma (NHL) among Vietnam veterans relative to men who did not serve in Vietnam, but no increased risk for the other five cancers. After accounting for other factors that might influence the development of NHL among Vietnam veterans, a roughly 50% increased risk was found for these men. The data suggested a higher relative risk for veterans who had served a longer time in Vietnam, although the results were not statistically significant. Risks different slightly by dates of service, age at entry on duty in Vietnam, rank, or type of unit the veteran served in (combat, combat support, or support) but lacked statistical significance. No evidence that the increased risk of NHL might be related to Agent Orange in Vietnam”* [53].

Vietnam veterans have also expressed great concern over the issue of birth defects. The CDC in its “Vietnam Experience Study” in 1988 conducted a random sample of enlisted men who entered the US Army from 1965 through 1971, 7,924 Vietnam and 7,364 non-Vietnam veterans participated in a telephone interview [54]. A random subsample of 2,490 Vietnam and 1,972 non-Vietnam veterans also underwent a comprehensive medical examination [54]. The results:

*“During the telephone interview, Vietnam veterans reported more adverse reproductive and child health outcomes than did non-Vietnam veterans. However, children of Vietnam veterans were not more likely to have birth defects recorded on hospital birth records than were*

*children of non-Vietnam veterans. The rates of total, major, minor, and suspected defects were similar among children of Vietnam and non-Vietnam veterans. These results are consistent with the findings of three epidemiologic studies conducted since 1981 on the relationship of Vietnam service and birth defects in children of male veterans”* [54].

The 2014 IOM Committee responsible for reviewing studies on birth defects concluded that there was inadequate or insufficient evidence to conclude that the components of the tactical herbicides or the associated TCDD caused birth defects in human populations [3].

Most recently, a 2016 study was published by a group of Chinese, Japanese, and Vietnamese scientists and physicians examining the influence of dioxin exposure upon levels of prostate-specific antigen and steroid hormones in Vietnamese men [55]. The study was in response to DVA's decision to include prostate cancer in the list of diseases “associated” with Agent Orange exposure. The study consisted of comparing blood chemistry from 97 men who had resided in a “dioxin hotspot” to men from a non-sprayed region of Vietnam. The findings suggested that PSA levels in Vietnamese men were not associated with levels of dioxins, furans or steroid hormones in these two regions of Vietnam [55].

## 8. Conclusions

The extensive medical and scientific studies of Agent Orange and associated TCDD and the critical examination of historical records over the last thirty-five years, tell us that most veterans were not exposed to Agent Orange, and those that were exposed, received only negligible doses. Nevertheless, as Vietnam veterans have aged, the presence of prostate cancer and diabetes have increased and

compensation provided [56]. It is unlikely that those who received compensation will have had their diabetes or prostate cancer caused by exposure to Agent Orange [56]. Studies have shown that even those with measurable exposure, i.e. TCDD in blood serum, have not suffered ill effects [43, 44, 45]. But we should also acknowledge that many Vietnam veterans do appear to be at risk for a range of diseases and health problems perhaps due to the 'Vietnam experience', and those studies are underway [8, 57]. It is appropriate that there are strong societal concerns, intense media reporting, and public policies favoring our veterans. But our scientific principles ought not favor or disfavor anyone. Why artificially focus on Agent Orange instead of on providing treatment and benefits for all those veterans that served in Vietnam and have health issues? As scientists and health providers, we cannot ignore the societal, emotional, or legal issues influencing public policies, because in today's environment those policies shape the research agenda, and of course funding. However, we have the responsibility to ensure that our research results are not tainted by politics or emotion.

In hindsight, after all the years of controversy over Agent Orange, perhaps we could have been fairer to all Vietnam veterans with a program of 'Vietnam experience' benefits rather than Agent Orange benefits. What was really needed was scientific studies of effects of the Vietnam experience on all veterans rather than studies seeking to 'link' more diseases to Agent Orange. It is our hope that ongoing public dialogue can result in a more reasoned policy for our Vietnam veterans.

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