CHAPTER 5

AGENT ORANGE AND ITS DIOXIN CONTAMINATION

Much of the concern over the widespread military use of tactical herbicides in South Vietnam, especially the use of Agent Orange, stemmed from the dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD) contaminant in the 2,4,5-T herbicide. Our awareness of its toxicity, persistence in biological tissue, and environmental fate now spans at least 35 years. 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. The Department of Defense (DOD) has expended hundreds of million dollars in the conduct of the Air Force Health Study, on the disposal of Agent Orange (Operation PACER HO), and on the numerous remediation and environmental monitoring programs conducted at the former sites where Agent Orange was stored in Mississippi and Johnston Island. This Chapter explores the history of Agent Orange and its dioxin contaminant. It also describes the analytical studies on the quantities of TCDD contained in the 2,4,5-T herbicides and the subsequent Agent Orange production, and the conflict that exists between science and social concern.

5 The Significance of the Dioxin Contaminant in Agent Orange

It is likely that the expenditures related to the development and use of tactical herbicides by the Department of Defense will however be dwarfed by the costs that will eventually be incurred by the United States Department of Veterans Affairs (DVA) on the Congressionally-mandated Agent Orange Act of 1991. This act established procedures that the DVA must follow in deciding whether to create new presumptions of service connection for disabilities suffered by Vietnam veterans that may be associated with exposure to Agent Orange and other herbicides in Vietnam [IOM 1994]. For the DVA, the determination of whether a disease (currently eleven) should be service connected is not based on determination of causation or proof of exposure, nor is it based on studies of veterans who served in Vietnam. Rather, it is based on whether the evidence, as judged following periodic reviews of the scientific literature by the National Academy of Sciences' Institute of Medicine, is sufficient to conclude there is a positive association [IOM 1994]. 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 favor the Vietnam veteran [IOM 1994; Young 2002].

Vietnam, Agent Orange, and its associated dioxin are intense societal, emotional, legal, and public policy issues as much as medical and scientific issues – perhaps more so. There are strong societal concerns and public policies favoring our veterans, and rightly so. But our scientific principles ought not favor or disfavor anyone. However, as scientists, we cannot ignore the societal, emotional, or legal issues influencing public policies, because in today's environment those policies shape the research agenda (and hence funding), and if we are not careful, may affect even the research results [Young 2004; Young 2008].

Thus, it is appropriate to ask the question "How did we get ourselves into this situation?" This Chapter explores the history of Agent Orange and its dioxin contaminant and the conflict that exists between science and social concern.

5.1 Formation of the TCDD Contaminant

Polychlorodibenzo-*p*-dioxins may be contaminants of any of the chemical products that use chlorophenols in the manufacturing process [Young 1980]. The presence of 2,3,7,8-TCDD (and its concentration) was dependent upon the industrial process used in the manufacture of the basic chlorophenol, in this case, the production of sodium 2,4,5-trichlorophenate. The most common industrial process that was used for the production of 2,4,5-T herbicide is shown in **Figure 5.1**.

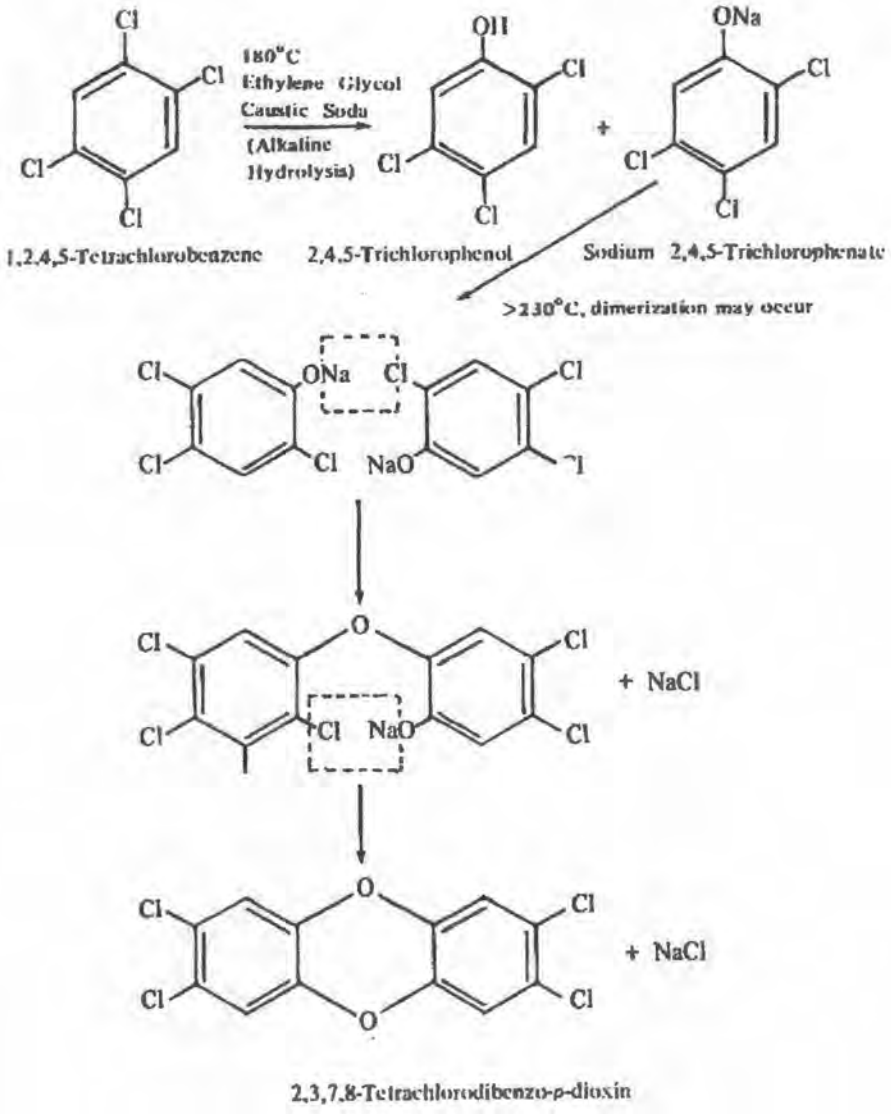

Figure 5.1 Formation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin by the alkaline hydrolysis and subsequent dimerization of sodium 2,4,5-trichlorophenate [Young 1980]

The process of making 2,4,5-trichlorophenate by the hydrolysis of hexachlorobenzene was a process developed by Dow Chemical Company and was known as the 'Dow Process' [Plimmer 1973]. The reaction temperatures during the Dow Process had to be carefully maintained. If the temperature of the hydrolysate rose above the normal 180° C, an exothermic reaction occurred

after any residual solvent, e.g., glycol, was removed by distillation. This reaction, attributed to the decomposition of sodium-2-hydroxethoxide, started at a temperature of 230° C and continued to 410° C. The heat generated by this reaction assisted in the formation of TCDD through the dimerization of two molecules of sodium trichlorophenate [Plimmer 1973; Young 1980]. The rapid temperature increase in the reaction vessel, results in a pressure increase; failure to release this pressure resulted in the Seveso accident of 1976 [Reggiani 1988]. In this case, the dimerization resulted in a 1% yield of 2,3,7,8-TCDD [Reggiani 1988].

The capability for accurately assessing the levels of TCDD in herbicide formulations did not exist in the years during the use of Agent Orange in Vietnam. Furthermore, no mention was made in the early scientific literature that dioxins might occur as contaminants in the commercial chlorinated phenols until 1959 [Julia and Baillarge 1959]. In 1962, the first description of the acnegenic potency of TCDD was published in the article: ***A technique for testing acnegenic potency in rabbits, applied to the potent acnegen 2,3,7,8-tetrachlorodibenzo-p-dioxin*** [Jones and Krizek 1962]. It is interesting to note that much controversy surrounded the preparation, properties, and identification of high purity samples of 2,3,7,8-TCDD that could be used as standards for analytical studies. The National Cancer Institute (NCI) took the lead in preparing purified standards, conducting studies of the chemistry, and searching for possible sources for human exposure. The NCI 4-volume publication "***Evaluation of the Carcinogenic, Tetragenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals***" was released in 1967 [NCI 1967].

Dr. Warren Crummett (a Dow Analytical Chemist) reported that the analytical limit of detection of 2,3,7,8-TCDD in herbicide formulations was 1 ppm in 1965, but the procedure for doing this analysis required rigorous cleanup and purification of the analyte, often using the rabbit ear test to validate TCDD [Crummett 2002]. It was not until late 1969 that 2,3,7,8-TCDD could be positively identified and quantified in herbicide formulations by the use of gas chromatography-mass spectroscopy [Crummett 2002]. Subsequently in 1970, they were able to confirm levels of 0.050 ppm with some consistency. However, it was not until 1974 that Dow Analytical Services was able to detect 0.001 ppm in ester, amine, and acid formulations of 2,4,5-T herbicide [Crummet 2002]. Buser of Switzerland reported the same level of detection that same year, indicating the global search that was occurring for methods of detection of the dioxins and furans [Buser 1974]. By 1975, the ability to detect TCDD in biological tissues and in other environmental samples had reached the limit of 10 parts-per-trillion, ppt (picograms/gram), but the cost of doing one analysis exceeded $1000/sample [Young 1980]. Today the capability to detect 0.01 ppt of various dioxins and furans is common. However, as Crummett noted:

> *"Chemists seeking to measure small numbers of molecules will continue to develop more sensitive and specific instrumentation for doing so. Eventually, they will reach the ultimate limit – single molecule detection. And what will that mean in a practical sense? Nothing, of course! But as a point of interest, it may mean that at least one molecule of every substance that has ever existed in nature will be present in a glass of drinking water"* [Crummett 2002].

In 1972, the United States Agricultural Research Service published data on the analysis of additional samples of 2,4,5-T herbicide [Woolson et al 1972]. Of 42 samples of 2,4,5-T, 22 samples contained less than 0.5 ppm TCDD. Of the 20 samples containing more than 0.5 ppm of TCDD, 15 were obtained for the yearly survey of one manufacturer. The samples were from 1966 – 1970, with four samples usually collected each year. There was a 10-fold drop in TCDD

content by this manufacturer between 1968 and 1969. However, their technical grade 2,4,5-T still contained 2 – 3 ppm of TCDD in 1970. The 1970 technical samples from another manufacturer contained less than 0.5 ppm [Woolson et al 1972]. Technical grade 2,4,5-T manufactured as a formulation for use in agricultural products, typically contained 90 – 92% 2,4,5-T (as the acid) and 8 – 10 % impurities; suggesting that the sample noted above, when made into a commercial form of 2,4,5-T herbicide, probably contained between 1 and 1.5 ppm TCDD [Bovey 1980]. Edmunds, Lee, and Nickels [1973] subsequently reported on 55 samples of butyl and octyl esters of 2,4,5-T from lots manufactured in the late 1960s and early 1970s. The mean concentration of TCDD in the 55 samples was 0.31 ppm.

In 1971, in a report on 2,4,5-T prepared by the President's Science Advisory Committee [MacLoed 1971] obtained data on TCDD levels in technical grade 2,4,5-T from one manufacturer for samples analyzed from 1958 to 1969. These data were provided in **Table 5.1.**

Table 5.1 The history of TCDD concentrations, ppm, in technical grade 2,4,5-T acid manufactured by one company [MacLoed 1971]

Parts-per-Million, ppm, 2,3,7,8-TCDD in Technical Grade 2,4,5-T Manufactured by One Company	
1958	11
1959	11
1960	8
1961	5
1962	10
1963	11
1964	12
1965	5—32
1966	3—18
1967	1—25
1968	1—25
1969	<1

The data in **Table 5.1** represented only one of the seven major companies that produced 2,4,5-T for use in formulating Agent Orange. All seven companies simultaneously provided 2,4,5-T commercial formulations for US and international agriculture [WSSA]. Both the demand for 2,4,5-T for military and commercial uses increased during the period 1965-1970, at the same time that improvements were occurring in the industrial process and in the analytical methodology for the detection of the TCDD in the herbicide formulations.

5.2 Establishing Agent Orange and Its Contaminant as a Major Public Health Issue

The relationship between TCDD and Agent Orange first became a matter of public concern in the fall of 1969 when the results of a study commissioned by the National Institutes of Health to the Bionetics Research Laboratories of Bethesda, Maryland, became known [Bionetics 1968; Reggiani 1988]. A portion of that report described the teratogenicity of 2,4,5-T in laboratory mice

was subsequently published in Science Magazine in 1970 [Courtney et al 1970]. However, in June 1969 reports that Herbicide Orange had produced birth defects in humans had already appeared in Vietnamese newspapers [MacLeod 1971]. A subsequent analysis of the 2,4,5-T used by Bionetics revealed that the cause of the toxicity was the TCDD contaminant and that 2,4,5-T in itself was not teratogenic [Reggiani 1988; Crummett 2002]. The members of the scientific community that had been asked to examine the Bionetics data and the reports coming out of Vietnam concluded that the use of 2,4,5-T represented a potential risk to human health that outweighed the benefits of its use domestically, or by the Department of Defense in Vietnam [Nelson 1969; DuBridge 1970].

In 1970, the United States Congress directed the Secretary of Defense to request that the National Academy of Sciences (NAS) conduct studies assessing the ecological and biological impact of the military use of herbicides in Vietnam [NRC, 1974]. A committee of the National Research Council (NRC) published their report "***The Effects of Herbicides in South Vietnam***" in February 1974 [NRC 1974]. Due to insufficient data it had not been possible to assess the potential impact of TCDD in Vietnam. For the next decade, studies funded by the US Federal Government and other governments on the toxicity, sources, environmental fate, and human risks of TCDD were debated and published in hundreds of forums [Young and Reggiani 1988; IOM 1994; Young 2002]. The public was bombarded by stories of the horror of dioxin (see **Figure 1**).

Figure 5.1 A cartoon critizing the US Forest Service for its continued use of 2,4,5-T herbicide. Published by *The Daily Utah Chronicle*; Thursday, May 20, 1976, page 3

A large volume of toxicological data on 2,4,5-T and 2,4-D were available during the final years of US involvement in Vietnam, but woefully inadequate toxicological and environmental data on TCDD. Although scientists in 1969 had recognized that TCDD as acutely toxic and teratogenic (birth deforming) in laboratory animals, no studies were available on the effects of chronic, long-term, low-level exposures in lower mammalian species. Furthermore, numerous occupational exposures to TCDD were reported during the industrial production, but epidemiological studies were not available despite documented exposures as early as 1949 [Young et al 1978].

Reggiani [Reggiani 1988] described how the issue of TCDD and Agent Orange was refocused for the public:

"In 1978, with the help of a reporter from the Columbia Broadcasting system, Bill Kurtis, the issue of Agent Orange and its potential effects on human health was presented to the nation in a television documentary entitled "Agent Orange: Vietnam's Deadly Fog". In this way the public became aware of the magnitude of the veteran's concern, and Agent Orange reached the dimensions of a public health problem. Thus, the public turned its attention to the scientific and policy decisions the government had taken or intended to take regarding this matter".

In response to the documentary and numerous inquiries from Vietnam veterans, the United States Air Force's Occupational and Environmental Health Laboratory (OEHL), Brooks Air Force Base, Texas published as a technical report a comprehensive review of "***The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and Its Associated Dioxin***" [Young et al 1978]. The significance of the document was that both historical and scientific analyses were available in a single publication on the tactical herbicides used in Vietnam and the dioxin contaminant. Of particular value was the assessment of how much herbicide had been procured and disseminated in Vietnam, and how much of the TCDD contaminant had likely been disseminated with the 2,4,5-T herbicide.

Once the public was alerted to the controversy surrounding Agent Orange, it was only a matter of time before the US Congress and the Executive Office of the President expressed interest in taking action. Indeed, the importance to the Federal Government in resolving veteran health issues and addressing the potential risks of dioxin were demonstrated in December 11, 1979, when the Executive Office of the President (President Jimmy Carter) directed the establishment of an "***Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants***" [Eizenstat 1980]. Members of Interagency Work Group (IWG) included representatives from the Departments of Agriculture, Defense, Health and Human Services, Housing and Urban Development, and Labor, and representatives from the Environmental Protection Agency, Veterans Affairs, Office of Management and Budget, Council of Economic Advisors, and Office of Science and Technology Policy. In August 1981, the IWG was expanded and elevated to become the **Agent Orange Working Group (AOWG)** at the Cabinet Council level by President Ronald Reagan. The task assigned to the AOWG was..."*to guide and monitor all Federal research into the possible adverse health effects of Agent Orange and similar chemicals on humans, with a particular focus on the health of Vietnam veterans*" [Bowen 1988]. Secretary of Health and Human Services was appointed Chair of the AOWG, and the Director of the Centers for Disease Control was appointed Chair of the AOWG Science Panel. The Congressional Office of Technology Assessment and the General Accounting Office were invited to become observers and advisors to the Group.

The AOWG undertook a massive research effort encouraging, supporting, and monitoring studies conducted by VA, DOD (the Air Force Health Study of RANCH HAND personnel), the Centers for Disease Control and Prevention (CDC), other Federal Agencies, and the international community (e.g., Australia and New Zealand) [Davis 1983]. Subcommittees were formed to examine the use of TCDD as a bio-indicator of exposure to Agent Orange [Rall 1981], and the Science Panel of the AOWG undertook a comprehensive assessment of the feasibility of conducting the major study of ground troops [Beach 1984].

The major issue facing all of the government-supported research was the confirmation of

exposure to the phenoxy herbicides and the associated TCDD. The 1988 study released by the 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 those of 97 Vietnam-era veterans who had not served in Vietnam [CDC 1988]. The distribution of TCDD levels were 'nearly identical' in the two groups, both having means and medians of about 4 ppt, which was well within the range of background at that time [CDC 1988]. The CDC concluded that neither military and spraying records nor self-reported history of exposure could reliably identify high or low exposure groups, and "*most US Army ground troops who served in Vietnam were not heavily exposed to TCDD, except perhaps men whose jobs involved handling herbicides*" [CDC 1988]. These results were consistent with other studies and so clear cut that a planned epidemiological study of ground troops and Agent Orange was discontinued as infeasible [Young 2004].

Subsequent publications by Buckingham [1982], Cecil [1986], and Young and Reggiani [1988] provided more insight into the details of Operation RANCH HAND. Publications by Westing [Westing, 1976, Westing, 1984] provided appraisals of the ecological impact of the use of herbicides in Southeast Asia. All of these publications became the primary sources of information on Agent Orange and RANCH HAND for the National Academy of Sciences' Institute of Medicine's publication in the 1994 on "***Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam***" [IOM 1994].

Disregarding the eight years of research conducted by the Federal Agencies in the United States, and the conclusion based upon that science, the Congress moved to find a "political solution" to Agent Orange [Hanson 1987]. The Congressionally-mandated (and signed by the President) Agent Orange Act of 1991, Public Law 102-4, established procedures that the Department of Veterans Affairs (DVA) must follow in deciding presumptive compensation; that is, whether to create new presumptions of service connection for disabilities suffered by Vietnam veterans that may be associated with exposure to Agent Orange and other herbicides in Vietnam. The procedures required that the DVA contract with the National Academy of Sciences' Institute of Medicine to conduct reviews every two years of the scientific literature on the health effects of herbicides and TCDD [IOM 1994]. In response to the DVA, the IOM noted in its first report:

> *"Controversy has surrounded the study of Agent Orange since the first questions of herbicide-related health effects in Vietnam veterans were raised more than 20 years ago. In the course of its work, the Committee heard allegations of scientific misconduct and claims of government conspiracy to suppress information on health effects, as well as serious disagreements among scientists about the interpretation of laboratory and clinical data. The Committee was not charged with investigating or resolving these controversies, and it did not attempt to do so... Although the conclusions and recommendations presented here will not end the controversy surrounding this issue, it is the Committee's hope that this report will crystallize the current scientific information on this important topic and prompt further research to answer the remaining questions being asked by veterans and their families, the Department of Veterans Affairs, and Congress"* [IOM 1994].

The Academy's Institute of Medicine has now issued seven comprehensive reports [IOM 1994; IOM 1996; IOM 1998; IOM 2000; IOM 2002; IOM 2004; IOM 2006]. In accordance with their findings, DVA has prepared a list of conditions that are presumed to be service connected based

on herbicide and/or TCDD exposure [DVA 2007]. The issue of whether a veteran was actually exposed to Agent Orange, and presumably dioxin, is irrelevant for establishing presumption. For any veteran who served in Vietnam between 9 January 1962 and 7 May 1975, and has one of the eleven diseases on that list, DVA must presume that they were exposed to herbicides (and associated TCDD) and their disease is service connected [DVA 2007].

5.3 Composition of Agent Orange and Associated Contaminants

In order to determine the quantity of TCDD that may have been present in the 2,4,5-T containing tactical herbicides, data on the TCDD contamination of the 2,4,5-T stocks used in formulating Agent Orange must first be gathered. Orange Herbicide was procured from numerous chemical companies. The USAF procured Orange under Purchase Description AFPID 6840-1, dated 23 February 1968, and Amendment 1, dated 11 April 1968. The Orange Purchase Description containing the changes and additions of Amendment I was published in the Final Environmental Statement on the "Disposition of Orange Herbicide by Incineration [Department of Air Force, 1974]. Since the most recent purchase description for "Herbicide Orange" was dated 11 April 1968, no reference was made of the TCDD contaminant. **Table 5.2** was the procurement specification for Herbicide Orange.

Table 5.2 The Military Procurement Specification for Herbicide Orange [Department of the Air Force 1974]

1. SCOPE: This purchase description prescribes requirements for a herbicide identified as Orange. The material is used as a systemic growth regulator to kill and defoliate vegetation.
2. APPLICABLE DOCUMENTS:
   PPP-D-729, Drums: Metal 55-gallon, for shipment of non-corrosive material.
   MIL-H-51148, Herbicide N-Butyl 2,4,5-Trichlorophenoxyacetate.
   MIL-H-51147, Herbicide N-Butyl 2,4-Dichlorophenoxyacetate.
   MIL-STD-105, Sampling Procedure and Tables for Inspection of Attributes
   MIL-I-45208, Inspection Systems Requirements
3. REQUIREMENTS
   3.1 Materials. The herbicide shall be composed of the following two ingredient materials.
      a. N-Butyl 2,4,5-Trichlorophenoxyacetate
      b. N-Butyl 2,4-Dichlorophenoxyacetate
         3.1.1 The ingredient materials shall meet the following specifications:
            a. Specification MIL-H-51148, N-Butyl 2,4,5-Trichlorophenoxy-acetate, except free acid will be 0.5% by weight.
            b. Specification MIL-H-51147, N-Butyl 2,4-Dichlorophenoxyacetate except composition (purity) shall be 98% minimum by weight, acid equivalent shall not be less than 79.0% nor more than 80.0% and free acid shall be 0.5% maximum by weight.

   3.2 Finished Mixture (Orange)
      3.2.1 Composition
         a. 50% by volume N-Butyl 2,4,5-Trichlorophenoxyacetate
         b. 50% by volume N-Butyl 2,4-Dichlorophenoxyacetate
      3.2.2 Tolerance. Tolerance range for amount of each composition ingredient contained in the final mixture will be ± 1.5% including the precision allowance for the analytical method used.

         a. Range for N-Butyl 2,4,5-Trichlorophenoxyacetate is 48.5 to 51.5% by volume.
         b. Range for N-Butyl 2,4-Dichlorophenoxyacetate is 48.5 to 51.5% by volume.