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# Agent Orange and its associated dioxin: assessment of a controversy

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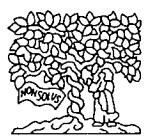

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# Preface

The controversy surrounding the use of the military herbicide Agent Orange in the Vietnam conflict has raged from the streets of cities in the United States and Australia to national capitals; from the headlines of national journals to television documentations and to the dockets of Federal and Supreme Courts; and from actions by Parliaments, Governors, Prime Ministers and Presidents to actions by legislatures. Yet after almost 20 years, the final resolution of this controversy is only now occurring.

Agent Orange has been more than just a herbicide used in military conflict. It has been the flagship of veteran and environmental groups demanding social changes. It has been the subject of a landmark lawsuit and of a Royal Commission inquiry leading to judgements that will influence litigation and legislative activities for decades to come. But above all, Agent Orange was a mixture of chemicals that have confronted and still challenge the scientific community to develop new chemical, analytical, biochemical, toxicological and clinical tools. The widespread appearance of the Agent Orange associated dioxin has proved to be of outstanding importance for the scientific world and is confronting the bodies in charge of protecting public health and the environment all over the world with unexpected and still poorly understood realities.

This book explores the numerous facets of the controversy and of its related dioxin problems written by the military men, doctors, scientists and lawyers whose lives intermingled with them.

Elsevier Science Publishers have to be commended for the optimism, hard work and solid organization which brought this book to light.

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## CHAPTER 4

# Assessment of the animal toxicologic data for TCDD

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*"The fact that TCDD is acutely toxic is not in dispute, the issues are the levels of exposure and species susceptibility"*

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## CHAPTER 3

# Historical overview of the controversy surrounding Agent Orange

G. REGGIANI

*"Agent Orange and its associated dioxin began as issues of chemicals in war and over time became controversies that impacted the human, scientific and financial resources of nations"*

A.L. Young and G.M. Reggiani (editors) Agent Orange and its associated dioxin: assessment of a controversy


## Introduction

Basically, the history of Agent Orange is the history of man's primary concern with health and its relation to chemicals in the environment. It is one example of man's ability to understand and estimate the hazards and implications of exposure to chemicals resulting from his activities or produced by him.

It is also the history of how the deficiency and limitations of our knowledge about toxic entities in our environment can create a wrong perception of risk and how research, information and education can change the same perception and the level of acceptability of risk.

The history of Agent Orange can be divided into two parts, the first one preceding and the second one following the time when the contaminant in the production of the herbicide, i.e., tetrachlorodibenzo-*p*-dioxin (TCDD), became a major issue.

## The beginning of the Agent Orange history

From a medical point of view, I am inclined to set the birthdate of the Agent Orange history as a matter of public concern in the fall of 1969 when the results of a study commissioned by the National Institute of Health to the Bionetics Research Laboratories of Bethesda, Maryland, became known, as shown in Table 1 [1].

The report presented by K.D. Courtney [2] and others supplied evidence that 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), one of the two components of Agent Orange, could cause malformations and stillbirths in mice when administered in high doses. Reports that herbicide Orange had produced birth defects in humans had been published in June, 1969, in Vietnamese newspapers [3, 4].

The results of the Bionetics studies on mice seemed therefore to support the assumption that Agent Orange could cause birth deformities and pose a probable threat to man. Later analysis [5 – 7] of the 2,4,5-T used by

Bionetics for its study revealed that the cause of the toxicity was a contaminant and that 2,4,5-T in itself is not teratogenic. Yet, the scientific community which was asked to examine the case had concluded at that moment that the use of 2,4,5-T represented a risk to human health which outweighed the benefits of the herbicide action [8].

The reaction caused by the disclosure of an embryotoxic effect in the animal experiment resulted in several surveys of South Vietnamese hospital records which were conducted independently by the institutions listed in Table 2.

Early in 1970, the Board of Directors of the American Association for the Advancement of Science (AAAS) [9] set up a commission which had the task of assessing the effects of large-scale use of herbicides on the ecology and on the population of South Vietnam. The commission was a four-man team composed of Prof. Matthew Meselson, Arthur Westing, Dr. John Constable

TABLE 1 *1969 – Birthdate of the Agent Orange history*

| |
|---|
| Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides and industrial chemicals |
| Vol. 2 – Teratogenic study in mice and rats, Bionetics Research Laboratories, Inc., National Technical Information Service |
| Doc. No. PB 223-160. |

TABLE 2 *Studies on birth defects in Vietnam*

| |
|---|
| Matthew S. Meselson et al.<br>Herbicide Assessment Commission of the American Association for the Advancement of Science<br>Preliminary Report, December 30, 1970 |
| R.K. Cutting et al.<br>Congenital Malformations and Still Births in the Republic of Vietnam, 1960 – 1969<br>(Department of Defense – U.S. Printing Office No. 903 – 233, 29 pp., 1970) |
| U.S. National Academy of Sciences:<br>Report on the Effects of Herbicides in South Vietnam, 1974 |
| To Thang Tung et al.<br>Clinical Effects of Massive and Continuous Use of Defoliants on Civilians<br>Vietnamese Studies 29: 53 – 81, 1971 |

of the Harvard Medical School and Robert Cook of Yale University [10]. During the summer and fall of 1970 they travelled extensively in South Vietnam, had access to important records and collected a large number of samples. In their report [11] to the AAAS in December, 1970, they said that their inspection had revealed not only that the herbicides sprayed in South Vietnam had destroyed the vegetation of the territory and the food which was needed by the civilian population, but also that there was the possibility that either or both 2,4,5-T and its associated dioxin had caused birth defects in the population of South Vietnam [12 – 14].

The second study was conducted by R.T. Cutting et al. [15] on behalf of the Ministry of Health of the Republic of South Vietnam and of the U.S. Military Assistance Command Vietnam. The maternity hospital records of 22 hospitals over the 10-year period from 1960 to 1970 were examined, covering therefore both the years preceding the spraying of herbicides and the years with a heavy spraying. No differences in the incidence and frequency of stillbirths and congenital malformations were found. However, the authors pointed out that the study had several biases because the birth records and consequently the rates of stillbirths and malformations were not reliable.

The third study was carried out by a committee appointed by the National Academy of Sciences [16]. Early in 1970, the United States Congress had directed the Secretary of Defense to request the National Academy of Sciences to conduct a comparative study and investigation to determine the ecological and biological dangers deriving from the use of herbicides and of the defoliation program carried out by the Department of Defense in South Vietnam. The National Academy of Sciences submitted its report on "*The Effects of Herbicides in South Vietnam*" to the government in February, 1974. On the question of teratogenicity and the use of herbicides, the report stated that, "Considerable attention was paid to the possibility suggested previously, of birth defects caused by herbicides or by contaminants in herbicide preparations; no evidence substantiating the occurrence of herbicide-induced defects was obtained. However, the potentially most definitive aspect of this examination has not yet been completed."

The fourth study was carried out by To Thang Tung, Director of the Viet Duc Hospital in Hanoi, North Vietnam, and published in 1971. Tung reported that in a group of 903 South Vietnamese who had been exposed to herbicide spraying and who were taking shelter in the North and hospitalized in Hanoi, a high frequency of Down syndrome and malformed children was found [17].

Similar findings during clinical examination of refugees from South Vietnam who claimed to have been sprayed with defoliants were reported also by others in subsequent years [18].

## Early opposition

The attention which was given in the years 1969 and 1970 to the safety of Agent Orange and to the consequences of its effects on nature and public health was not completely unexpected, as can be seen in Table 3. There had already been opposition to the herbicide program, which had been requested by the South Vietnamese government as a procedure for the achievement of immediate military targets as early as August, 1961. Its request had been agreed to by President Kennedy in November, 1961 [19], and the actual spraying as a limited experiment had been initiated in January, 1962 [20, 21]. The opposition was carried on initially by the Federation of American Scien-

TABLE 3 *Milestones in the history of Agent Orange*

| | |
|---|---|
| *August 1961*: South Vietnam government requests use of herbicide for military targets | *December 1968*: AAAS announces participation in the study |
| *November 1961*: U.S. Government agrees on actual spraying of herbicides as a limited experiment | *March 1969*: Society for Social Responsibility in Science provides funds to AAAS scientists for visit to Vietnam |
| *January 1962*: Initiation of Operation Ranch Hand (spraying mission) | *June 1969*: Council of AAAS directs officials to prepare specific plans for a field study on military use of herbicides in Vietnam |
| *March 1964*: Federation of American Scientists expresses concern about chemical and biological warfare | *Autumn 1969*: Officials of AAAS receive copy of teratology study performed by Bionetics Research Laboratories |
| *June 1966*: AAAS calls for investigation into herbicide spraying program | *October 1969*: White House science advisory committee is informed by council of AAAS about results of Bionetic study. Use of herbicides restricted to areas remote from population |
| *February 1967*: Petition signed by 5,000 scientists urging to stop use of herbicides in Vietnam | *December 1969*: Council of AAAS sets up herbicide assessment commission to prepare plan for one year and to conduct investigation |
| *June 1967*: Letter of AAAS to Secretary of Defense urging immediate investigation on use of herbicides in Vietnam | *February 1970*: AAAS herbicide assessment commission starts work in Vietnam |

TABLE 3 *(Continued)*

| | |
|---|---|
| *July 1967*: Department of Defense commissions study to Midwest Research Institute, Kansas City | *April 1970*: Hearings of senate committee on energy, natural resources and environment |
| *January 1968*: National Academy of Sciences reviews report of Midwest Research Institute | *April 1970*: Surgeon General announces governmental actions on use of herbicide 2,4,5-T |
| *July 1968*: AAAS recommends field study in Vietnam under auspices of United Nations | *April 1970*: Department of Health, Education and Welfare, Department of Interior, Department of Agriculture, announce immediate suspension of use of 2,4,5-T around homes, ponds, lakes, farms, food crops |
| *September 1968*: U.S. embassy in Saigon sets up committee to review spraying program | *April 1970*: Department of Defense suspends use of 2,4,5-T (Orange) in all military operations in Vietnam |

tists, which, as early as 1964, had opposed the use of herbicides in Vietnam on the grounds that their use was not discriminating between fighting forces and civilians, and it represented biological and chemical warfare [22].

In January, 1966, a group of scientists from Harvard University in Boston urged President Johnson to ban this practice. In December, 1966, the Council of the AAAS called for studies of the short- and long-term consequences of massive use of herbicides in Vietnam in a letter to the Secretary of Defense, Robert MacNamara [23 – 25].

In February, 1967, a second petition signed by more than 5,000 scientists, including 17 Nobel Prize laureates and 129 members of the U.S. National Academy of Sciences, was submitted to President Johnson urging him again to end the use of herbicides in Vietnam [26].

The Department of Defense reacted to the request by commissioning a non-governmental research institute to assess whether the use of the herbicides would have a long-term ecological impact and charged the National Academy of Sciences to review the study and to make appropriate recommendations. The study was performed by the Midwest Research Institute of Kansas City, Missouri. It was called "Assessment of Ecological Effects of Extensive or Repeated Use of Herbicides", and the final report was filed in December, 1967 [27].

## Decline and end of Ranch Hand

The report of the Midwest Research Institute was a thorough and painstaking collection of the scientific information available at that moment about herbicides. However, it did not provide the answers to two fundamental questions: the long-term effects on the ecological system and the effects of chronic exposure on the population [28]. Predictably, therefore, the Board of Directors of the AAAS called for further studies. It recommended in July, 1968, an international field study under the sponsorship of the United Nations to analyse the long-term effects of the use of the herbicides. The United Nations response was non-committal, but late in 1968 it passed a resolution asking the Secretary General to prepare a report on chemical, biological and bacteriological weapons and to endorse the Geneva Protocol of 1925, an international treaty which bans the use of chemical and bacteriological methods of warfare [29, 30].

However, the controversy over the use of herbicides continued, and the Council of the American Association for the Advancement of Science adopted a resolution which stated that recent studies had shown that both 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-T could cause birth deformities in experimental animals [31], thus supporting the conclusion that 2,4,5-T posed a threat to public health, while 2,4-D was a possible danger.

The consequences were that:

(1) On April 15, 1970, the Department of Health, Education and Welfare, the Department of the Interior and the Department of Agriculture decided on the immediate suspension of all use of 2,4,5-T, with the exception of carefully controlled and registered applications on non-crop land for such things as control of weeds and brush on range pasture and forests or on right-of-way and other non-agricultural land [32].
(2) On May 9, 1970, Ranch Hand flew its last defoliant mission of war in Vietnam [33].

This was the end of part one of the history of Agent Orange.

## The herbicides used in Vietnam

A few reflections are important for the understanding of the events which occurred in 1970 and those which followed between 1970 and 1980.

In South Vietnam, four different herbicides were used in the defoliant program (the so-called Ranch Hand Program). They were the two

chlorinated phenoxy acids, 2,4-D and 2,4,5-T, and the plant-growth regulators, cacodylic acid and picloram (Table 4).

All chemicals used for the production of Agent Orange were of common use in the chemical industry (Table 5).

None of these herbicides was of a new or experimental nature. They had all been used for several years in commercial agriculture both in the United States and in many other countries. Aerial spraying of them was a common procedure. In terms of research and experience accumulated in about a quarter of a century of extensive use throughout the world before their use in Vietnam, they could be considered as old materials [34 – 37]. Their acute toxicity (lethal dose) in laboratory animals was upwards of 300 mg/kg for the phenoxy acids. Long-term toxicity did not show proliferation of tissue damage (Table 6).

Toxicity of picloram and cacodylic acid is lower than that of 2,4-D and 2,4,5-T [38 – 41]. Their toxicity to vegetation was known with reasonable ac-

TABLE 4 *Herbicides used in Vietnam*

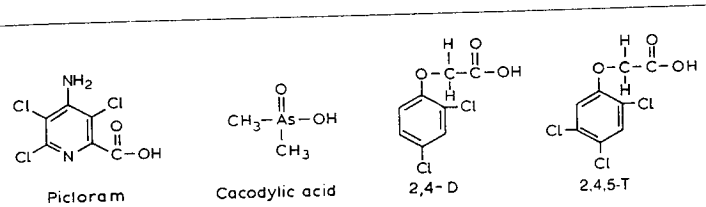



TABLE 5 *Major steps in the production of 2,4-D, 2,4,5-T and Agent Orange*

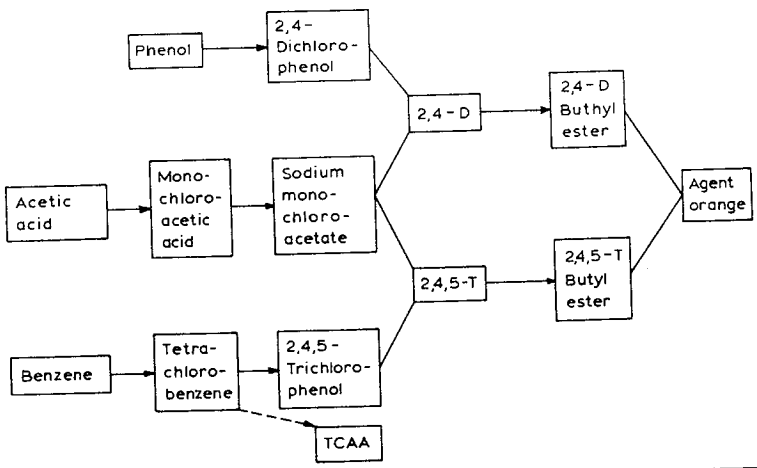


TABLE 6 *Single oral $LD_{50}$ values in mg/kg*

| Animals | 2,4-D | 2,4,5-T |
|---|---|---|
| Mice | 350 | 400 |
| Rats | 400 | 500 |
| Dogs | 100 | 100 |
| Guinea pigs | 500 | 400 |
| Chickens | 550 | 300 |

*Chronic toxicity*:

Signs of toxicity by chronic exposure duplicate those observed with a single dose. Long-term repeated administration does not produce either accumulation or proliferation of tissue damage.

curacy on hundreds of species of plants under a variety of conditions. The level of herbicide present in the environment as a result of normal use and under conditions representing possible misuse were also known for a wide variety of situations. The rate of their excretion from the body is rapid, and their persistence in the environment is limited because of rapid decomposition [42 – 44]. None of the herbicides used in Vietnam was known to produce significant dermal lesions other than temporary local irritation of some sensitive skin [45].

Toxic effects in man had been reported in the 1950's as well as in the early 1960's in the context of occupational exposure in the course of industrial chemical production or during application [46 – 48]. There have even been a very few cases of suicidal intake of large doses of one or the other of the four chemicals. The clinical symptomatology derived from these observations was known and was correctly related to quantities of the chemical and conditions of exposure which were completely different from those of the prescribed use [49].

All these chemicals fall into the medium class of toxicity: they are distinctly toxic but must be absorbed in quite substantial quantities to have any overt clinical effect. They are clearly much less toxic than many other chemicals of current use, including ordinary household materials, as can be seen in Table 7.

## Methods of detection for chloracnegenic chemicals

The manufacturers of trichlorophenol and of 2,4,5-T had been aware for many years that this class of compounds and particularly their impurities

produced a toxic reaction in humans which manifested itself with a condition known as chloracne, a skin disorder mostly prevalent on the face, neck and back.

To avoid this toxic reaction in humans and to detect chemicals having a chloracnegenic potential, the same manufacturers had developed, as early as 1941, a control test of the chemical batches which was a bioassay. This con-

TABLE 7 *Toxicity ratings of herbicide components compared to other substances*

| Herbicide | Component of agent | Toxicity rating class | Probable lethal dose (human) |
|---|---|---|---|
| Cacodylic acid | Blue | 3 | 500 mg – 5 g/kg |
| Picloram | White | 3 | 500 mg – 5 g/kg |
| 2,4-D | White-Orange | 4 | 50 – 500 mg/kg |
| 2,4,5-T | Orange | 4 | 50 – 500 mg/kg |
| *Comparative substances* | | | |
| Strychnine | | 6 | Less than 5 mg/kg |
| Arsenic | | 5 | 5 – 50 mg/kg |
| Aspirin | | 4 | 50 – 500 mg/kg |
| Caffeine | | 4 | 50 – 500 mg/kg |
| DDT | | 4 | 50 – 500 mg/kg |
| Diesel fuels | | 3 | 500 mg – 5 g/kg |
| Ethanol, ethyl alcohol | | 2 | 5 – 15 g/kg |
| Calcium carbonate | | 1 | About 15 g/kg |

TABLE 8 *Methods of detection for chloracnegenic chemicals*

| | |
|---|---|
| *1941* | Rabbit's ear test (limit of detection about 100 ppm) |
| *1965* | Gas chromatography (limit of detection: 1 – 20 ppm) |
| *1972* | Gas chromatography<br>Mass spectrometry (limit of detection: 50 ppb) |
| *1980* | Gas chromatography<br>Mass spectrometry (limit of detection: 100 ppt) |

sists of applying a solution of the material to the inner surface of a rabbit's ear and observing for the typical skin response, hyperkeratosis [50, 50a]. The bioassay has a sensitivity of about 50 – 100 ppm. In this way it was possible to monitor the production of the herbicide through purification of the impurities.

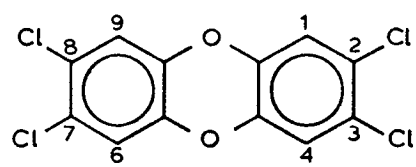
Advancements in technology permitted the detection of lower quantities of the contaminant and the improvement of the process of purification of the end product [51, 52], as can be seen in Table 8.

Around 1965, gas chromatography provided a valid substitute for the rabbit's ear bioassay with a chemical method of analysis with a detection limit of about 1 ppm for laboratory-grade products and 10 – 20 ppm for technical-grade products [53].

In the same year, the introduction of the molecule separator to interface the gas chromatography with the mass spectrometer marked a further advancement in toxicological analysis. The combination of gas chromatography and mass spectrometry in the 1970's increased the sensitivity and selectivity of the analysis [54]. In 1970, the lowest reported limit of detection of TCDD in some materials was around 50 ppb [55]. It was therefore possible for a manufacturer to detect even trace quantities of the contaminant in the herbicide and to provide regular production-grade material that was virtually safe. Animal experiments with this material and medical examination of people exposed to the herbicide showed no evidence of toxicity at the registered conditions of use.

There needed to be therefore other reasons for the drastic policy judgment of the Department of the Interior, of Agriculture and of Health, Education and Welfare in April, 1970. Analysis of the 2,4,5-T samples used by Bionetics Laboratories for the teratology study had revealed that they contained 30 ppm of 2,3,7,8-TCDD (Table 9). It could be shown that 2,4,5-T was not teratogenic if the content of the contaminant TCDD was much lower and that the toxicity attributed to 2,4,5-T was caused by the contaminant TCDD [56]. This finding is the beginning of the second phase in the history of Agent Orange.

TABLE 9 *Structure of 2,3,7,8-TCDD (according to Chemical Abstract system)*



## The dioxin problem

In the second part of the history of Agent Orange, attention was therefore directed toward two goals:

(1) Study of acute and chronic toxicity of TCDD, the contaminant of 2,4,5-T and of other dioxins, in experimental animals.
(2) Study of the effects on health in groups of persons who had been chronically exposed to these two chemicals during the process of production in the chemical industry or during the phase of their use and application.

TCDD was not completely unknown in the chemical industry. The first synthesis of this compound had been made in 1957 by Sandermann after other dioxins had been synthesized [57] (Table 10).

The first chlorinated dioxin, the octachlorinated compound, was prepared as far back as 1872 by two German chemists, Merz and Weith, but the structure of this product was not clear until 1957 (Merz and Weith 1872 [46]). In the 1930's, a Japanese group under Tomita started synthesizing chlorinated dioxins, but they did not prepare TCDD.

In 1957, Gilman and Dietrich reported that they had prepared the tetrabromodioxin (Gilman and Dietrich, 1957), and in the same year Sandermann published the first synthesis of TCDD. These two compounds were both prepared by halogenation of the unsubstituted dioxin, the amount of the toxic tetrachlorodioxin prepared being about 20 g [58].

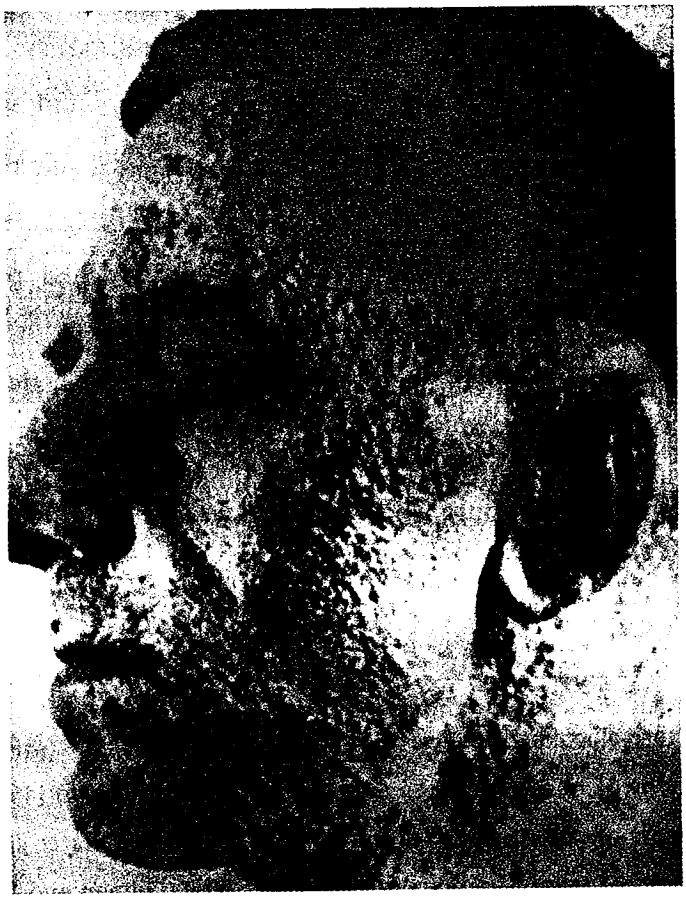
The association of TCDD with the skin disease called chloracne was purely coincidental. A laboratory technician of Sandermann in the Institute of Wood Chemistry in Hamburg who was working on the synthesis of the first 20 g of pure TCDD became contaminated on the face by a cloud of the substance when opening a dessicator. He soon developed very severe

TABLE 10 *Chlorinated dioxins*

| | |
|---|---|
| *1872* | Synthesis of octachlorodioxins. Structure elucidated only in 1957 (Merz and Weith) [46] |
| *1906* | Synthesis of non-chlorinated dioxins (Ullmann and Stein) [46] |
| *1932* | Synthesis of chlorinated dioxins but not TCDD (Tomita et al.) [46] |
| *1957* | Synthesis of tetrabromo dibenzodioxin (TBDD) (Gilman and Dietrich) [46] |
| *1957* | Synthesis of tetrachloro dibenzodioxin (TCDD) (Sandermann et al.) [57] |

TABLE 11 *Dioxin: development of research*

| | |
|---|---|
| *1971* | Meeting of the American Chemical Society, Washington, September, 1971.<br>Chlorodioxins – Origin and Fate |
| *1973* | Meeting of National Institute of Environmental Health Science. North Carolina, April, 1973.<br>Perspectives on Chlorinated Dibenzodioxins and Dibenzofurans |
| *1974* | U.S. National Academy of Sciences.<br>Report on the Effects of Herbicides in South Vietnam, February, 1974. |



FIGS. 1 and 2. *Skin chloracne lesions of the laboratory technichian who was working on the synthesis of TCDD. (Reproduced with permission from Prof. K.H. Schulz.)*

chloracne (Fig. 1). This simple coincidence gave the clue to the possible impurity in the chemical production of 2,4,5-T. Chloracne cases had, in fact, been observed in factory workers who had participated in the production of this compound in some plants in the States and in Europe [59, 60].

However, TCDD was previously unknown. Now, the chemist who made the synthesis and the dermatologist, K.H. Schulz, who treated the workers, were able to understand that TCDD could be the contaminant responsible for chloracne among the workers. Schulz also found that TCDD was highly active in producing hyperkeratosis on the rabbit ear and that 0.05 – 0.1 mg/kg b.w. (equivalent to 50 – 100 ppb) in the rabbit was lethal within 1 – 2 weeks and that the animal showed necrosis and fatty liver.*

Having shown that TCDD was a very potent chloracnegen, Schulz and Sandermann then demonstrated that this compound was formed during the synthesis of trichlorophenol. After the nature and identity of the toxic contaminant were established, a method of production was found which reduced the level of dioxin in the final product and reduced the exposure of

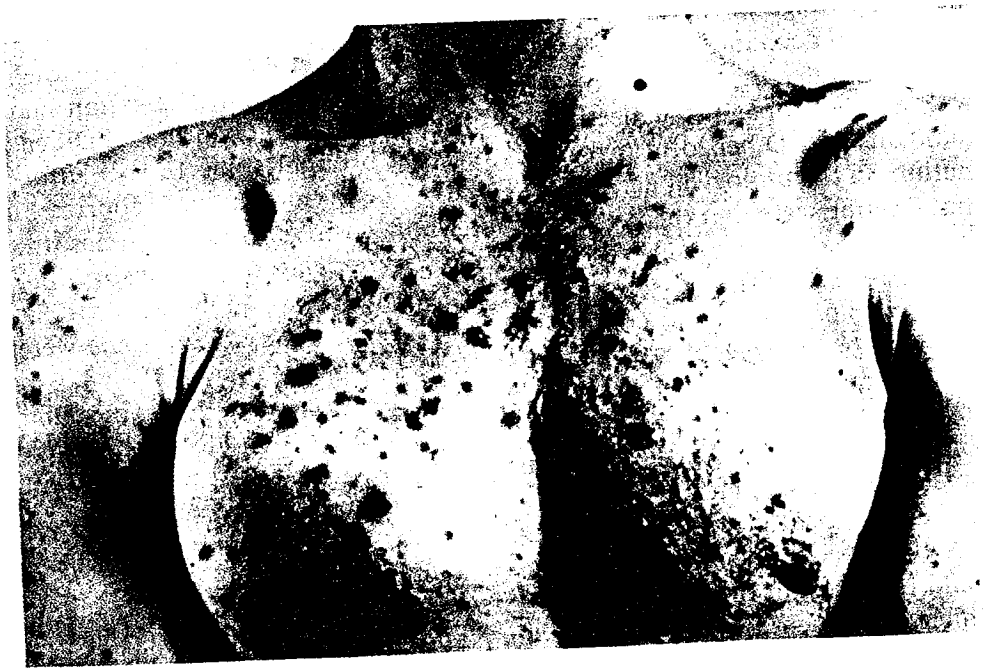


FIG. 2.

* Schulz applied 0.1 ml of a 0.005% (1 : 20,000, i.e. 50 ppm) and 0.01% (1 : 10,000, i.e. 100 ppm) TCDD solution on the skin of his left forearm. This corresponds to 5 – 10 μg of TCDD.

workers to whatever dioxin was present. This resulted in a substantial reduction in the incidence of chloracne [61, 62].

All these findings did not yet lead to any further research on TCDD. The substance existed only as an impurity of a well known and tolerated chemical which could be easily eliminated. It interfered only in very rare occasions and under special circumstances. As such, it was not a matter of concern. Concern for the possible hazards to humans exposed to 2,4,5-T was precipitated by the teratologic studies carried out by the Bionetics Research Institute.

The appearance of TCDD in trace quantities in some samples of the herbicide 2,4,5-T which could now be found owing to the extremely sensitive methods for detecting trace amounts of impurities stimulated research on the biological as well as the chemical and physical properties of TCDD (Table 11).

A first account of this research was presented in September, 1971, at a meeting of the American Chemical Society in Washington, D.C., under the item "Chlorodioxins – Origin and Fate". It was then reported that TCDD was the most toxic of all chlorodibenzodioxins studied, having an $LD_{50}$ in the $\mu g/kg$ range in the rat.

A second account of this research was presented in April, 1973, in North Carolina under the auspices of the Department of Health, Education and Welfare. The topic of the meeting was "Perspectives on Chlorinated Dibenzodioxins and Dibenzofurans". This meeting brought some further information on the biological activity of TCDD. The major findings reported at that meeting were that there was a variation of sensitivity among species, the liver was the target organ, the toxic effects were delayed after absorption, and the mechanism of teratogenesis was still incompletely understood. Moreover, patterns of absorption and of distribution among organs were beginning to emerge.

The same could be said for the effect of dioxin on cellular enzymes and on the lymphatic system (thymus, spleen and lymph nodes). However, nothing was reported on the human experience, which to a certain extent already existed at that time in cases of dioxin exposure. The understanding of the biological effects of this compound was still very limited.

A third account of the knowledge available at that time about TCDD could be found in the report on the effects of herbicides in South Vietnam which had been transmitted by the National Academy of Sciences in February, 1974, to the Department of Defense. The knowledge up to that time about the effects and fate of TCDD in animals, including man, was fairly summarized in this account. Special care was devoted to the experimental work on teratogenicity of TCDD and on the mechanism of embryotoxicity and teratogenicity.

TABLE 12 *Accidents in chemical plants involving the manufacture of chlorinated phenols*

| Date | Country | Manufacturer/location | Product | Cause of exposure | Personnel affected |
|---|---|---|---|---|---|
| 1949 | U.S. | Monsanto/Nitro, West Virginia | TCP | Explosion | 228 |
| 1949 | F.R.G. | Nordrhein-Westfalen | PCP, TCP | Occupational | 17 |
| 1952 | F.R.G. | Nordrhein-Westfalen | TCP | Occupational | 60 |
| 1952 – 1953 | F.R.G. | Boehringer | TCP | Occupational | 37 |
| 1953 | F.R.G. | BASF/Ludwigshafen | TCP | Explosion | 75 |
| 1953 – 1971 | France | Rhone-Poulenc/Grenoble | TCP | Occupational and explosion | 17 |
| 1954 | F.R.G. | Boehringer, Ingelheim/Hamburg | TCP, 2,4,5-T | Occupational | 31 |
| 1956 | U.S. | Diamond Alkalai/Newark, New Jersey | 2,4-D, 2,4,5-T | Occupational | 29 |
| 1956 | U.S. | Hooker/Niagara Falls, New York | TCP | Occupational | Many |
| 1959 | Italy | Industrie Chimiche Melegnanesi Saronno/Milan | TCP | Occupational | 5 |
| 1959 | U.S. | Thompson-Hayward/Kansas City, Kansas | TCP | Occupational | – |

TABLE 12 *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| 1960 | U.S. | Diamond Shamrock | TCP | Occupational | Many – 1 fatal |
| 1963 | Holland | Philips-Duphar/Amsterdam | TCP | Explosion | 106 |
| 1964 | USSR | | 2,4,5-T | Occupational | 128 |
| 1964 | U.S. | Dow Chemical/Midland, Michigan | 2,4,5-T | Occupational | 30 |
| 1964 – 1969 | Czechoslo-vakia | Spolana | TCP | Occupational | 80, 2 fatal |
| 1968 | U.K. | Coalite and Chemicals Products/ Bolsover, Derbyshire | TCP | Explosion | 90 |
| 1970 | U.K. | Coalite and Chemicals Products/ Hertfordshire | TCP | Occupational | 3 |
| 1970 | Japan | | 2,4,5-T | Occupational | 25 |
| 1972 | USSR | | TCP | Occupational | 1 |
| 1972 – 1973 | Austria | Linz Nitrogen Works | 2,4,5-T | Occupational | 50 |
| 1974 | F.R.G. | Bayer/Uerdingen | 2,4,5-T | Occupational | 5 |
| 1976 | Italy | ICMESA/Meda/Seveso | TCP | Explosion | |

Some of the 23 episodes of human exposure which had occurred during the production of trichlorophenol between 1910 and 1974 in Germany, the United States, France, Italy, Holland, the Soviet Union, Czechoslovakia, Great Britain and Austria were mentioned. The symptoms of the toxicity observed in man confirmed in each and all episodes the accurate description made by K.H. Schulz. The skin lesion called chloracne was present in practically all recorded cases.

## Accidents in chemical plants during manufacture of chlorinated phenols

Accidents in chemical plants involved in the manufacture of chlorinated phenolic compound are listed in Table 12. Their occurrence provides the opportunity to study the effects on man of these compounds. It should be stressed that all these cases involved exposure of plant workers either to TCP (2,4,5-trichlorophenol); to PCP (pentachlorophenol); to 2,4-D (2,4-dichlorophenoxy acetic acid); to 2,4,5-T (2,4,5-trichlorophenol acetic acid) or to mixtures of them. Furthermore, the same workers were often detailed to the production of other chemicals or had the opportunity of exposure to other chemicals manufactured in the factories where they worked. A further aspect to be considered is the fact that the actual concentration of the chemicals to which they were exposed is not known, and the presence and concentration of TCDD to which they were exposed has not been assessed.

However, this group of plant workers represents the largest known human population exposed to these chemicals and to the toxic contaminant TCDD. Exposure in all cases occurred either as a result of explosions in the reactor vessels housing the trichlorophenol mixture (acute exposure) or through poor hygiene and protective measures in the factory (chronic exposure) during the phase of purification of the mixture or disposal of the waste waters. Exposure affected the health conditions of many of these plant workers, and the symptoms and signs have been examined clinically. The laboratory tests and records of the clinical observations provide a picture which can be considered as the clinical feature of the toxic effects of TCDD on man.

The first accident occurred in 1949 at the West Virginia site of the Monsanto Chemical Company. As a result of a runaway reaction in the TCP plant, 122 workers were exposed to the chemical [62 – 64]. An additional 150 workers were exposed to and affected by TCDD in the routine handling of the herbicide 2,4,5-T. This second group was contaminated between 1949 and 1968.

A second group of accidents occurred between 1949 and 1952 at the Hamburg factory of Boehringer, West Germany, where 24 workers employed in the production of PCP and TCP were referred to the Dermatology Clinic

of the University of Hamburg with skin lesions which later provided the evidence for the identification of TCDD as their cause [65, 66]. Similar cases occurred in other plants of the same company involving a larger number of workers.

A third accident occurred in 1953 in the factory of BASF (Badische Anilin Soda Fabrik) at Ludwigshafen in West Germany. An exothermic reaction started in the reactor vessel during the production of TCP. Temperature and pressure rose rapidly until the vessel exploded. In the process of assessing and dealing with the damage, 42 workers were exposed. Others were later involved in the process of cleaning the installation and the building until the total number of workers exposed reached 75 [67, 68].

The fourth chemical company to be involved in the same type of accident was Philips-Duphar in Holland in 1963. Once again, an increase in temperature and pressure blew the safety valve of the reactor, ripping the lid off this time at the beginning of the process, rather than at the end as had been the case in the previous accidents. During the usual procedure of assessing the damage and reconstruction work, 44 factory workers were exposed. A second group of exposed persons worked for an outside contract cleaning firm. All were medically examined and treated. It was possible to measure the amount of dioxin formed during the accident, which was estimated to be between 20 and 200 g. The cleaning process could not decontaminate the plant, which eventually had to be demolished [73 – 75].

The fifth chemical company to be involved in an accident was the Fine Chemicals Unit of Coalite and Chemical Products at Bolsover, U.K., in 1968. Here, the trichlorophenol reactor exploded, killing the duty chemist during the night shift. He was one of the eight workers in the building at the time of the explosion; the other seven were hospitalized suffering from shock. The whole unit was closed in the wake of the accident, but, after clinical examination of the people involved did not reveal abnormalities, the work in the factory started again, with the TCP section sealed off for later cleaning and refitting. During the following 8 months [81], 79 workers and employees developed the typical skin lesions. The outbreak of chloracne forced the management to close the factory again. All workers were closely monitored.

The accidents that occurred in other chemical plants listed in Table 12, i.e Dow Chemical [88], Diamond Alkali [74], Hooker [80], Ind. Chim. Saronno, Milan [75], Thompson Hayward [73], Diamond Shamrock [73], Spolana [81 – 83], Rhone Poulenc, Grenoble [70] and in the USSR [79 – 87], present the same pattern as those previously described. About 1,000 people, most of whom were adult males working in the chemical plants, were involved in these episodes. All of them have been repeatedly clinically examined, and a wide variety of signs and symptoms have been recorded (see Table 13) in

medical literature in connection with the exposure. A causal association has been accepted for some of them.

Actually very few people have been exposed to TCDD alone. The only cases reported to have been exposed to pure TCDD are those described by Schulz [72], who reported on the laboratory technician who was exposed while drying crystals of the substance in 1955 and suffered from persistent chloracne at least until 1973 but continued his activity; by Rowe [89], who reported on the application in TCDD by D.R. Klingman onto the skin of 60 volunteers from the Holmesburg Prison in Lewisburg, Pennsylvania, who subsequently suffered from severe chloracne which lasted 4 – 7 months; and

TABLE 13 *Signs and symptoms reported in association with exposure to TCDD or mixtures containing TCDD*

| | |
|---|---|
| (A) | *Skin manifestations* |
| (1) | Chloracne |
| (2) | Hyperkeratosis |
| (3) | Hyperpigmentation |
| (4) | Hirsutism |
| (B) | *Systemic effects* |
| (1) | Mild fibrosis of liver |
| (2) | Raised transaminase values in blood |
| (3) | Hypercholesterolemia |
| (4) | Hypertriglyceridemia |
| (5) | Loss of appetite and weight loss |
| (6) | Digestive disorders (intolerance to alcohol or fatty food, flatulence, nausea, vomiting, diarrhoea) |
| (7) | Muscular aches and pains, joint pain, lower extremity weakness |
| (8) | Swollen lymph glands |
| (9) | Cardiovascular, urinary tract, respiratory and pancreatic disorders |
| (C) | *Neurological effects* |
| (1) | Sexual dysfunction |
| (2) | Headache |
| (3) | Neuropathy |
| (4) | Sight disturbance |
| (5) | Loss of hearing, taste and smell |
| (D) | *Psychiatric effects* |
| (1) | Sleep disturbance |
| (2) | Depression |
| (3) | Loss of energy and drive |
| (4) | Uncharacteristic bouts of anger |

by Oliver [85], who again prepared TCDD synthetically in 1975 and, together with two other scientists, suffered from typical chloracne.

In all other cases, the chemicals utilized for manufacturing TCP and its derivatives and PCP have most probably been part of the contamination and may have been the cause of many of these symptoms with or independently from TCDD. Furthermore, the cases were examined postexposure, and pre-existing diseases were often not known or not reported. No attempts have been made to assess whether the signs and symptoms reported in association with exposure to TCDD might have been merely concurrent or had an origin other than the chemical exposure.

Only some of the clinical symptoms reported in the literature can be retained as a constant, or almost constant, finding. These symptoms are:

(1) chloracne, which was present in practically all recorded cases;
(2) enlarged liver and impaired liver functions, frequently;
(3) peripheral neuropathy, occasionally.

All other signs and symptoms were inconstant and possibly not related to TCDD exposure.

However, all people involved in these episodes of exposure were adult males mostly in the prime of life, working in chemical plants and therefore in healthy conditions. There were no children, no newborn babies, no elderly people, no women, especially no pregnant women, among them. It was a population, therefore, which could hardly be compared with the one confronting the scientists in the next episode of exposure to dioxin, i.e. the Seveso accident, which occurred in Italy in July, 1976.

## The Seveso accident, July, 1976

In July, 1976, when an increase of pressure in a 2,4,5-T trichlorophenol reactor broke a security disk and drove part of the reactor's contents over the fields and houses close to the factory in Seveso, Italy, the people confronted with the public health problem caused by the accident had only the following information on which to make their decisions [90 – 92].

Laboratory experiment on animals had shown that TCDD caused death at extremely low doses, death occurred after a delay of several days to weeks, the mechanism of death was not understood; the chemical affected the immune system, enzymatic activity, fertility, the course of pregnancy and the formation and development of the newborn; it caused tumors to form, and it might affect the shape and behavior of future generations.

The few reports based on human observation from previous experience

available in the literature could not disprove the findings. Knowledge of the toxic effects of TCDD on humans was limited; and its long-term effects completely unknown. Thus, incomplete laboratory findings and spare and inadequate clinical findings shaped the decisions on the protective measures to be taken for the population, the attitude of experts, the opinion of the public, the reaction of the mass media, the decisions of the administrators, the program of medical survey, and the methods for the reclamation of the contaminated territory.

Chloracne occurred in some children who were exposed in the part of the territory with the highest contamination of TCDD in the soil (2 – 5 mg/m$^2$ or 20 – 50 ppb). In the most severe cases, the picture was very similar to the one observed by Schulz in the laboratory technician [93 – 95] (Fig. 2). The problem, however, was not how to deal medically with these cases, but what measures of protection and prevention to take for the population living in the contaminated territory and showing no biological signs of exposure.

The nature and cause of the Seveso accident, the extent of TCDD contamination, the assessment of the risk to humans, the program, methods, organization and results of 10 years of medical surveillance of the exposed population will be dealt with in a separate chapter of this book. The same report will also cover the program and the methods used for the rehabilitation of the contaminated area, the question of liability and its legal implications, and the compensation for the damages to the environment and property.

## The Vietnam veterans' health problems – 1977

The limitations of the ability of medical science to provide conclusive evidence of the real risk to human health posed by TCDD had repercussions not only on the people and institutions involved in the Seveso accident. When the spraying of Agent Orange in Vietnam was halted in 1970, the controversy concerning the herbicide also came to an end. The brief attention given the issue by concerned scientists and by the Senate hearings of 1970 was followed by a lull which lasted until the Seveso accident.

In 1977, veterans of the Vietnam war began to complain of serious health problems which they believed resulted from Agent Orange exposure in Vietnam. Press accounts of the possibility that these problems could be in fact related to Agent Orange provided the early basis for the veterans' belief [96 – 98].

Any attempt to refute this charge simply spread the suspicions wider and wider. Armed with little more than preliminary and confusing information and a belief that their health problems were unusual and unlikely to have

been caused by natural events, the veterans began to press their claims before the Veterans Administration. As had to be expected, the Veterans Administration took the firm position that Agent Orange had caused no health problems.

This answer did not satisfy the veterans of certain regions who believed that they had health problems in common which were the results of some common experience. They urged the Veterans Administration to conduct a serious investigation to follow up their deeply felt assumption. They were able to involve and gain the support of other groups of Vietnam veterans already concerned with other issues deriving from the war, such as less than honorable discharge, education benefits, psychological readjustment, amnesty, vocational counselling, etc. All these groups and coalitions became increasingly active with the Agent Orange controversy, which very soon became the central issue and much more important than all the other problems that had prompted their action.

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*" [99]. In this way the public became aware of the magnitude of the veterans' 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 the matter.

## The response of the Veterans Administration and of the Environmental Protection Agency

The gaps in medical information which had so strongly shaped the measures of protection for the people in Seveso and of prevention of potential damage to their health was now hampering the actions of the Veterans Administration [100 – 102]. The Veterans Administration reasonably argued that admittedly the effects on laboratory test animals had been studied; however, long-term health effects on humans were still largely unknown. It allowed, therefore, no compensation claims solely on the basis of Agent Orange exposure. Furthermore, because specific records on herbicide exposure were not readily available, the Veterans Administration was having difficulties in identifying veterans who actually had been exposed to Agent Orange. However, it was decided to examine any veteran concerned about the exposure and to have retrospective and prospective epidemiological studies of Vietnam veterans and of their families to evaluate and establish the likelihood of a relationship between recurrent health problems in the veterans and the spraying of Agent Orange [103 – 106].

The Environmental Protection Agency took completely different action with respect, not to Agent Orange, but to its component 2,4,5-T, carrying the contaminant TCDD [107 – 112]. Already in 1971, as soon as the newly formed Agency took over the regulation of pesticides and herbicides, and solely on the basis of the then available laboratory evidence, the Agency had placed a firm restriction on the use of the herbicides. Ignoring a report of the scientific advisory panel which had found that the herbicide did not create any significant health hazard, the Agency enforced a cancellation order on some use of the herbicide [113 – 115].

This decision did not remain unchallenged. The manufacturers of the herbicide 2,4,5-T and members of the scientific community contended that the restriction of the use of 2,4,5-T was based on experimental findings which incorrectly imputed toxic properties to this substance. Even when, later, following the publicity of the Oregon studies on spontaneous abortions, ill-founded allegations on the relationship to 2,4,5-T spraying precipitated new restrictive orders by the Environmental Protection Agency, the stand of the above-mentioned manufacturers and scientists did not change. They maintained that there was no valid medical or scientific evidence that 2,4,5-T herbicides are harmful to humans, animals or the environment if they are used in the recommended way and for the recommended purposes. They fought their case in judicial and administrative courts and virtually succeeded [116 – 121].

## The U.S. Government response – the Interagency Work Group

The research efforts and activities at the experimental, epidemiological and clinical levels going on at the time in different agencies of the government and in many public and private scientific institutions had reached an extent that obviously required assistance from and guidance by a central body of experts.

In 1979, the White House established an "Interagency Work Group" to study the possible long-term health effects of phenoxy herbicides and contaminants (Table 14).

The group was chaired by the General Counsel of the Department of Health and Human Services and included representatives of the Department of Defense, the Department of Health, the Veterans Administration, the Environmental Protection Agency, the Department of Agriculture, the White House Office of Science and Technology Policy and the Congressional Office of Technology Assessment [122, 123]. The Interagency Work Group pledged to conduct a thorough, objective and scientifically impeccable examination of the possible health effects of exposure to phenoxy herbicides,

TABLE 14 *Interagency Work Group to study the possible long-term health effects of phenoxy herbicides and contaminants*

| |
|---|
| Department of Health and Human Service (Chair) |
| Department of Defense |
| Department of Agriculture |
| Department of Labor |
| Congressional Office of Technology Assessment |
| Environmental Protection Agency |
| Veterans Administration |
| White House Office of Science and Technology Policy |

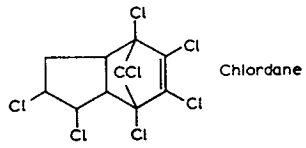
including Agent Orange. It made provisions for all possible epidemiological studies of the veterans and their families. It also organized supporting experimental research and analysis to fill the still existing gaps in our knowledge.

It warned, however, that the task of finding a causal relationship between veterans' health problems and the spraying of Agent Orange might be beyond the capability of medical science, owing to circumstances of exposure and to the very high number of factors which might have influenced the exposure [124 – 127]. Among other problems was the fact that the veterans had been exposed not only to Agent Orange, but also to a variety of other toxic chemicals and physical agents such as other herbicides (Blue and White), pesticides like chlordane and malathion and anti-malarial drugs like dapsone (Table 15).

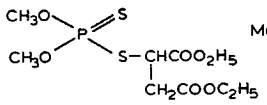
The short-term effects of all these substances resemble those of Agent Orange, but the long-term effects, especially the combination of the toxicity and their interaction, was and remains unknown. Very soon, therefore, the Work Group cautioned against the belief that the outcome of their activities would be quickly conclusive.

There have been some who have disliked or rejected the deliberate, experimental approach of the Interagency Work Group, feeling that it implied an unsympathetic or even a malevolent disposition towards the Vietnam veterans. Nothing could be more mistaken than this assumption. In fact, the group always stressed that organizing its studies in a way that could be of value to itself and to others did not in the least touch the ethical and human aspects of the Vietnam veterans' predicament. However, the mandate of the group was not to answer moral and ethical questions but to assess whether the health problems of the Vietnam veterans were related to an exposure to certain chemicals.

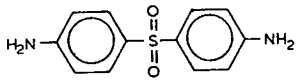
TABLE 15 *Chlordane, malathion and dapsone: chemicals regularly used during the Vietnam war operations*




Chlordane




Malathion




Dapsone

The research efforts and the studies related to the Agent Orange issue are in fact still going on today, and other chapters in this book will report on that part. To give the issue even more significance, in August, 1981, an "Agent Orange Work Group" was instituted at the White House and raised to Cabinet Council level.

## Long-term effects and epidemiologic studies of cases exposed to dioxin

The scientific panel of the Interagency Work Group gave priority to the concerns of Vietnam veterans related to the possible exposure to Agent Orange. This issue prompted the gathering of medical and scientific knowledge on the long-term effects on populations associated with occupational or accidental contamination with dioxin.

The signs and symptoms of acute exposure had been reported by physicians who had observed people exposed to dioxin, and the clinical features of the poisoning by the chemical have been described. There was, however, a lack of data describing the persistence or disappearance of such clinical findings for some years after the exposure or the appearance of symptoms or syndromes occurring only years after the exposure.

The scientific panel of the Interagency Work Group decided to move on two courses for gathering medical knowledge on this issue. One course would be to identify among the Vietnam veterans those who had been exposed and to conduct appropriate medical studies on this cohort [128 – 132].

The second course would be to endorse any follow-up studies on people of the private sector who had been exposed during their occupational life or accidentally to dioxin.

The U.S. government initiated, therefore, 10 epidemiologic studies of Vietnam veterans and five health surveillance projects, as can be seen in Tables 16 and 17. The intermediate evaluation of the mortality rate among Air Force personnel who conducted aerial herbicide spraying missions in Vietnam (Operation Ranch Hand) showed that the mortality rate of the Ranch Hand group is nearly identical to that of its comparison matched group. The same conclusion was reached after analysis of the data of the morbidity study. There was no evidence to support a cause-and-effect relationship between herbicide exposure and adverse health findings in the Ranch Hand group at the time of the examination. Both mortality and morbidity studies of this group will be updated annually for the next 20 years.

The private sector also took up the re-examination and follow-up of the many cases of exposure reported in Table 12. The mortality, the morbidity and the reproductivity of several of them have been adequately studied during the last 5 years and are providing very valuable information on the long-term effects of dioxin exposure. Keeping in mind that all the people involved in the accidents listed in Table 12 suffered from chloracne and that this skin lesion is the most obvious symptom of the human exposure to dioxin, they offer the best conditions for studying long-term effects [133].

Today, the results of these studies are available for the workers involved in the accidents of Monsanto (1949), Boehringer (1952 – 1954), BASF (1953), Philips-Duphar (1963), Dow Chemical (1964) and Coalite and Chemical Products (1968). Based on the data provided by these studies, it can be concluded that exposure to dioxin has not modified the mortality rate and pattern of these people. At some stages of the evaluation, it was thought that the dioxin exposure had exposed the victims to increased risk of mortality from cardiovascular diseases, mediated through an effect on blood lipids. Due to lack of supporting evidence in the data currently available, this hypothesis has been abandoned [134 – 142].

Interest shifted then to the possible consequences of dioxin exposure on human reproduction. Studies in this area indicate that up to now there are no discernible effects on human reproduction which are paternally mediated. A comprehensive evaluation of maternal exposure is still going on, but the data available to date do not support a causal association between dioxin exposure and any adverse reproduction outcomes [143 – 155].

The biological marker of the dioxin exposure, the dermatological condition chloracne, has, in many cases, completely or partially disappeared, but in some cases is still persistent 30 years and more after exposure, even if the severity and extent of the lesions have diminished. Toxicological research,

TABLE 16 *The 10 major epidemiologic studies of U.S. Vietnam veterans, Agent Orange and TCDD exposure, and Vietnam experience currently ongoing in the United States*

| Title | Responsible Federal Agency and study location | Type of study | Total study population size | Completion date |
|---|---|---|---|---|
| Air Force Health Study | United States Air Force School of Aerospace Medicine, San Antonio, Texas | Matched cohort study of Ranch Hand personnel and controls, mortality, morbidity and reproduction | 2,500 | (a) Baueline Reports 1983, 1984; (b) Long-term follow-up planned |
| VA Mortality Study | Veterans Administration Agent Orange Projects Office, Washington, D.C. | Mortality study of Vietnam-era veterans | 60,000 | Mid-1985 |
| Vietnam Experience Twin Study | Veterans Administration Medical Center, St. Louis, Missouri | Morbidity study of identical twins | 1,200 | 1986 |
| Birth Defects Study | Centers for Disease Control, Atlanta, Georgia | Case-control study of anatomical birth defects | 8,400 | August 1984 |
| Agent Orange Epidemiologic Study of Ground Troops | Centers for Disease Control, Atlanta, Georgia | Three-cohort morbidity study of Vietnam veterans | 18,000 | 1988 |

TABLE 16 *(Continued)*

| | | | | |
|---|---|---|---|---|
| Vietnam Experience Epidemiologic Study | Centers for Disease Control, Atlanta Georgia | Matched cohort morbidity Study of Vietnam and non-Vietnam veterans | 12,000 | 1987 |
| VA/AFIP Soft Tissue Sarcoma Study | Veterans Administration Agent Orange Projects Office, Washington, D.C. | Case-control study of soft tissue sarcoma | 250 Cases 750 Controls | Late 1986 |
| NIOSH Dioxin Registry | National Institute for Occupational Safety and Health, Cincinnati, Ohio | Mortality study of workers at 12 production sites where dioxin-containing products were manufactured | 6,000 | 1985 |
| NIOSH Industrial Morbidity Study | National Institute for Occupational Safety and Health, Cincinnati, Ohio | Morbidity study of 2 production sites where dioxin containing products were manufactured | 500 | 1986 |
| NCI Kansas Soft Tissue Sarcoma Study | National Cancer Institute, Bethesda, Maryland | Case-control of soft tissue sarcoma | 100 Cases 300 Controls | Early 1985 |

TABLE 17 *The five major current health surveillance projects of U.S. Vietnam veterans, Agent Orange and TCDD exposure, and Vietnam experience*

| Title | Responsible Federal Agency and study location | Type of surveillance | Target population | Status |
|---|---|---|---|---|
| VA Patient Treatment File Review | Veterans Administration Agent Orange Projects Office, Washington, D.C. | Review of VA hospital inpatient medical records | Vietnam era veterans who have been hospitalized in VA medical facilities | On-going |
| Agent Orange Register Review | Veterans Administration Agent Orange Projects Office, Washington, D.C. | Review of the records of the medical examinations at VA hospitals | Vietnam veterans who who have reported to VA hospitals for an Agent Orange examination | On-going |
| A Review of the Soft Tissue sarcoma Cases in Patient Treatment File for Vietnam Era Veterans | Veterans Administration Agent Orange Projects Office, Washington, D.C. | Review of pathology reports and the tissue specimens of patients diagnosed as having International Classification of Diseases ICD-171 | Vietnam era veterans who have been hospitalized in VA medical facilities | On-going |
| AFIP Agent Orange Registry | Armed Forces Institute of Pathology, Washington, D.C. | Review of tissue specimens | Vietnam era veterans | On-going |
| VA/EPA Adipose Tissue Study | Veterans Administration and the Environmental Protection Agency, Washington, D.C. | 500 Samples of human fats | U.S. Vietnam era males | 1986 |

a series of epidemiology studies from Europe and a small number of case reports from the United States have shifted the attention toward cancer, especially liver and stomach cancer, malignant lymphoma and a broad group of tumors known as soft tissue sarcomas [156 – 163, 173].

An evaluation of the scientific publications on the carcinogenicity of the chemicals that were constituents of Agent Orange toward man shows that in the case where a direct relationship is postulated between soft tissue sarcomas, i.e. malignant lymphoma, and TCDD, as happened in Sweden, the studies have a common design (case control studies), and one author (Hardell) appears in all publications. The criteria of definition of exposure have been fairly permissive, and exposure in one paper was to phenoxy herbicides that do not contain TCDD and to 2,4,5-T and 2,4-D in another paper in which the possible role of TCDD cannot be discounted.

Evidence provided by independent verification of these findings in Sweden and in other countries has meanwhile accumulated to negate a link between soft tissue sarcoma and exposure to the phenoxy herbicides. However, other studies have recently pointed out a possible implication of another rare form of cancer. The studies by Hoar [182] and Woods [183] suggested an association (as an increased risk) between exposure to the phenoxy herbicides and a group of tumors which are put together today in the category of non-Hodgkins lymphomas. As is the case with this type of illness, the non-Hodgkins lymphomas have unclear etiology but the evidence so far collected hints to several potential factors which seems to be associated with its occurrence such as rural versus urban habitation, exposure to radiation, various drugs, organ transplants and most recently viral infections. It is therefore too early to reach a consensus of the relationship of non-Hodgkins lymphomas and phenoxy herbicides.

In the case of the association of exposure to herbicides with stomach cancer [147, 160], the interpretation is very tenuous due to the size of the cohorts examined and the possible bias of familial or genetic relationship. The same reservations can be offered for the observations of similar cases reported in the United States [169, 170, 173, 174]. Independent studies on the same issue have been conducted in Finland and New Zealand, and neither an excess mortality for cancer nor an excess incidence of this type of tumor have been found [164 – 168, 171].

Genotoxic effects after exposure to crude 2,4,5-T have been suspected, and a study was performed in two groups of workers (BASF, 1953, and Coalite and Chemical Products, 1968) to look for chromosome irregularity as indication of such effect. Chromosome aberration and sister chromatid exchange rate might be increased in people exposed to substantial quantities of chemical mutagenic or clastogenic agents. Both groups showed no significant deviation from that expected by chance [149, 157].

## Determining the dioxin risk

Parallel to the above-mentioned studies and partially independently, research on dioxin continued and became more and more important. Motivated by the Seveso accident in Europe and by the controversy on Agent Orange and 2,4,5-T in the U.S.A., scientists gathered at international meetings to report and discuss their findings and to look for a cue to their overwhelming questions.

Under the heading "Chlorinated Dioxins and Related Compounds", a series of workshops for scientists of different disciplines was organized (Table 18).

The first took place in Rome in October, 1980; the second in Arlington, Virginia, in 1981; the third in Salzburg, Austria, in 1982; the fourth in Ottawa, Canada, in 1984; the fifth in Bayreuth, Germany, in September, 1985; the sixth in Fukuoka, Japan, in September, 1986, the seventh in Las Vegas, Nevada, in October 1987 and the eight in Umeå, Sweden, in August 1988.

The structure of the meetings has been the same for all of them. Each one has been divided into the following sections:

Sources, combustion, incineration
Analytical methodology
Environmental fate and levels
Waste disposal and reclamation methods
Biochemical toxicology and metabolism
Animal toxicology
Observations in man.

*Risk assessment*

This structure has allowed scientists belonging to completely different disciplines to interact with each other and to understand the complexity of the problems created by this group of compounds.

TABLE 18 *Workshops on chlorinated dioxins and related compounds*

| | | |
|---|---|---|
| 1st | Rome, Italy | October 1980 |
| 2nd | Arlington, Virginia | October 1981 |
| 3rd | Salzburg, Austria | October 1982 |
| 4th | Ottawa, Canada | October 1984 |
| 5th | Bayreuth, Germany | September 1985 |
| 6th | Fukuoka, Japan | September 1986 |
| 7th | Las Vegas, Nevada, U.S.A. | October 1987 |
| 8th | Umeå, Sweden | August 1988 |

One event which brought together widely different members of the scientific community was a new development in the research of the polychlorinated compounds. Agent Orange, the 2,4,5-T herbicides, the Seveso accident and other episodes of dioxin exposure are no longer the major issue of the research on dioxin. Something new and unexpected was found which has changed completely the perspective of this history.

## Evolution in the risk perception: trace chemistries of fire hypothesis

In 1979, while attempting to determine the source of dioxin in some biological samples, chemists found that a large number of combustion sources emit dioxins into the environment. They found them in the smoke of cigarettes and of refuse incinerators, of car and truck mufflers and in charcoal grilled steaks. These findings led the chemists to conclude that dioxins are ubiquitous, and this is due to a natural phenomenon: the trace chemistries of fire. During the last 8 years, the attention of the scientific world and in its wake of politicians and the public has moved, therefore, in another direction, and the former perception of risk has evolved to a completely different dimension [175].

Polychlorinated benzodioxins and benzofurans had been already detected in 1977 in fly ash and flue ashes of some municipal incinerators in The Netherlands [178 – 180]. Investigations carried out in various parts of the world confirmed the early findings and were soon able to quantify the amounts of those compounds as well as of other chemicals originated by the combustion of the waste materials [181] (Tables 19 and 20). These findings have confronted the scientific community, the bodies in charge of protecting

TABLE 19 *Emissions from a large municipal incinerator**

| Substance | Emission rate (g/year) |
|---|---|
| Total phenols | 2,700 |
| Trichlorobenzenes | 500 |
| Phenanthrene | 200 |
| Fluoranthrene | 40 |
| PCBs | 20 |
| Total PCDDs | 30 |
| Total PCDFs | 350 |

* U.S. Environmental Protection Agency. Chemical Exposure Monitoring Program, July 1982.

TABLE 20 *Residues of dioxins and furans observed in flue gas of a muncipal waste combustion facility**

| Isomer groups | Mean concentrations (ng/cubic m) | Mean quantities emitted ($\mu g$/h) |
|---|---|---|
| TRI-CDD | 13 | 1,100 |
| TRI-CDF | 300 | 26,000 |
| TETRA-CDD | 6.3 | 540 |
| 2,3,7,8-TCDD | 0.4 | 34 |
| 2,3,7,8-CDF | 90 | 7,600 |
| HEXA-CDD | 16 | 1,400 |
| HEXA-CDF | 62 | 5,200 |
| HEPTA-CDD | 7.6 | 640 |
| HEPTA-CDF | 7.5 | 640 |
| OCTA-CDD | 2.5 | 220 |
| OCTA-CDF | 0.6 | 52 |

* U.S. Environmental Protection Agency. Chemical Exposure Monitoring Program, July 1982.

TABLE 21 *Evolution in the risk perception*

| | |
|---|---|
| *1970*: | There is no such thing as a safe exposure to any amount of a carcinogen<br>Primary prevention of chemical carcinogenicity<br>Exposure is the biological plausibility of a logical opportunity for contact with the chemical |
| *1980*: | Since these chemicals are widespread in the environment and since we can detect them down to very low levels, we must assume that life now takes place in a minefield of risks from perhaps thousands of substances |

public health and the environment, and the public with a completely different situation.

In the 1970's, a tendency prevailed in the scientific community to set the level of concern at which political action and regulatory response are required at the moment when the risk is not yet obviously demonstrated but when it is simply plausible. What it comes down to is that one should not demand that scientists prove the cause of the risk but simply show that it might be related to the assumed cause [176].

In this way, one would prevent that man be exposed to chemicals whose

effects may appear only after many years of use in the form of cancer, birth defects or mutations and where it is very difficult to prove unequivocally a cause-and-effect relationship between exposure and toxic effects, particularly when there is a long delay between the two events.

This way of thinking is contrary to the scientific tradition of research that requires unequivocal proof of cause-and-effect relationships in its experimental models. Political decisions may, however, be taken on the principle of so-called "primary prevention", provided that one can factually prevent the introduction of man-made pollutants into the environment.

Today the evolution in the risk perception might be best summed up by the following statement: "Since these substances are widespread in the environment and since we can detect them down to very low levels, we must assume that life now takes place in a minefield of risks from perhaps thousands of substances. No more can we tell the public: you are home free with an adequate margin of safety" (Table 21).

This was formulated by the administrator of the Environmental Protection Agency in 1984 during his second term in office [177]. This is, however, another story and not the story of Agent Orange. Even so, it is a pertinent one because it has given the Agent Orange issue a different dimension.

I have not related the history of Agent Orange as a witness but as an outsider. It is well known that history is made by man, but man does not know the history he is making. The history of Agent Orange is not an exception to that rule. We are still seeking the truth, and it seems that truth can be found only in controversy. Agent Orange has been and still is to a certain extent a controversial issue.

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