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Synopsis of Scientific Literature on Phenoxy Herbicides and Associated Dioxins

No. 3 - (Volumes VII and VIII)

Department of
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SYNOPSIS OF SCIENTIFIC LITERATURE ON PHENOXY HERBICIDES AND ASSOCIATED DIOXINS No. 3 - (Volumes VII and VIII)

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PREFACE

This synopsis is the third in a series of lay language summaries of the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. Synopsis No. 1 of Volumes I-IV was published in July 1985 and Synopsis No. 2 of Volumes V and VI was published in October 1985.

This current synopsis, a review of Volumes VII and VIII, continues the effort of the Veterans Administration to provide for the general public a summary in laymen's terms, of the scientific literature published during 1985 related to the possible health effects of exposure to phenoxy herbicides and dioxins.

Agent Orange Projects Office
Veterans Administration
Washington, D.C.
October 1986

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1. Introduction

In April 1986, Clement Associates, a research firm in Arlington, Virginia, completed a review of the literature published during 1985 on the health effects of Agent Orange and related compounds. A critical review and an annotated bibliography of this literature have been published as Volumes VII and VIII of the ongoing *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. The present synopsis summarizes the key new information that became available during 1985.

Phenoxy herbicides are a group of structurally related chemicals that have been used to kill plants and trees. Historically, the ones most frequently used have been 2,4-D and 2,4,5-T. Several herbicidal preparations were used from 1963 to 1971 during the military action in Vietnam, primarily to remove the leaves from jungle trees. The herbicide spraying operation conducted by the U.S. Air Force was known as Operation Ranch Hand. Agent Orange, a mixture with equal parts of 2,4-D and 2,4,5-T, was the herbicide that was used most frequently.

Commercial phenoxy herbicides manufactured in the past contained small but variable quantities of contaminating impurities known as chlorinated dibenzodioxins. The term "dioxins" has frequently been used as shorthand for these compounds. It is known that very small amounts of one of these dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), were present in the 2,4,5-T portion of the Agent Orange used in Vietnam; it was not present in 2,4-D. The effects of TCDD have been extensively studied in experimental animals. Some other herbicides that were used in Vietnam are cacodylic acid and picloram. However, they were used in much smaller quantities and were not contaminated with dioxins.

2. Description of the literature published during 1985

Approximately 250 new documents describing scientific research on the health effects of phenoxy herbicides and chlorinated dibenzodioxins were published during 1985. The annual rate of publication was approximately the same during the two preceding years. However, there are some important differences between the literature published in 1985 and that from the several preceding years.

More than half of the documents published during 1985 were either review articles that did not contain any new information or abstracts, which are short summaries of studies that are published as full-length articles elsewhere. A majority of the remaining documents describe the results of basic research into the mechanisms by which TCDD causes adverse effects in experimental animals. At present, these studies are of limited use in trying to assess the effects on human health of exposure to TCDD or to phenoxy herbicides contaminated with dioxins.

Relatively few of the documents published in 1985 reported the unpublished results of studies of people exposed to phenoxy herbicides or their dioxin impurities. Nor were there many studies in experimental animals that can be directly used to predict or explain potential human health effects. One notable aspect of the literature published in 1985 is that almost no studies on the health effects of 2,4,5-T, picloram, or cacodylic acid were published. In the case of 2,4,5-T, this probably reflects the fact that this herbicide is no longer manufactured or used.

3. Cancer

The results of two epidemiological studies designed to investigate a possible association between cancer and military service in Vietnam were contradictory. The Veterans Administration (VA) and the Armed Forces Institute of Pathology conducted one study of 214 cases of cancer of connective or other soft-tissues (soft-tissue sarcomas) in veterans. They concluded that veterans with soft-tissue sarcomas were no more likely to have served in Vietnam than veterans treated for any other condition at VA hospitals. However, a second study in Massachusetts examined the causes of death among white males who might have been in the military during the Vietnam era (that is, they were in the appropriate age group). It revealed a statistically significant increase in the number of deaths from soft-tissue sarcoma among veterans who had served in Vietnam, compared both to veterans who did not serve in Vietnam and to nonveterans. Although this study indicated that there might be a link between service in Vietnam and soft-tissue sarcoma, a very similar study conducted in New York State and reviewed in an earlier volume of this series, showed that actually fewer Vietnam veterans died from soft-tissue sarcoma than did other veterans or nonveterans.

Both the VA and the Massachusetts studies used military service in Vietnam as the sole criterion for identifying individuals potentially exposed to phenoxy herbicides. It is clear that many individuals who served in Vietnam experienced little or no exposure to phenoxy herbicides, whereas individuals who never served in Vietnam may have been exposed to phenoxy herbicides either on the job or in the environment. In addition, there were other weaknesses in these studies. In the Massachusetts study, for example, inadequate verfication of the causes of death, the specific type of cancer and possible selection bias. Consequently, neither of these studies can be considered to offer strong support for any hypothesis regarding an association between soft-tissue sarcoma and exposure to Agent Orange in Vietnam.

Another epidemiological study examined the incidence of cancer among men employed in manufacturing phenoxy herbicides in Denmark between 1947 and 1982. The number of soft-tissue sarcomas among these men was significantly higher than the incidence of this cancer among all Danish males of similar ages. There were five cases of soft-tissue sarcoma among these workers. However, one person had been hired less than ten years before the cancer was diagnosed, and three had been employed in herbicide manufacturing for less than three months. Since no soft-tissue sarcomas were diagnosed among the workers with the longest and most intense exposure to phenoxy herbicides during its manufacture, it is not reasonable to conclude from this study that exposure during employment in phenoxy herbicide manufacturing causes soft-tissue sarcoma.

Case-control epidemiological studies conducted in Sweden in the late 1970s suggest that there may be an association between exposure to phenoxy herbicides and another form of cancer, malignant lymphoma. To investigate this possibility, two studies of malignant lymphoma were conducted by scientists in New Zealand, a country with a history of relatively extensive use of phenoxy herbicides. The results were published during 1985. In the first study, the investigators compared individuals with malignant lymphoma or multiple myeloma to those with other types of cancer. They found that the former were significantly more likely at the time of diagnosis to have been employed in agriculture or forestry, occupations with the

potential for herbicide exposure. In the second study, these same authors looked at 83 men who were diagnosed as having non-Hodgkin's lymphoma, a specific type of malignant lymphoma. They found that these men were no more likely to have been exposed to phenoxy herbicides than were 168 men with other forms of cancer. Thus, the apparent association seen in the first, relatively crude study disappeared when it was examined more rigorously in the second study.

Several studies published during 1985 looked at the relationship between soft-tissue sarcoma, malignant lymphoma, and colon cancer, on the one hand, and employment in agricultural occupations, on the other. The increased incidence of some of these types of cancers in some occupational categories could not be attributed to exposure to herbicides.

Thus, the results of epidemiological studies published during 1985 do little to resolve the issue of whether there is an association between exposure to phenoxy herbicides or their dioxin impurities and the incidence of certain types of cancer in humans. The few positive results either are inconsistent with the findings of similar studies or disappear when attempts are made to relate them more rigorously to exposure to phenoxy herbicides. Nevertheless, the absence of any findings of a pronounced carcinogenic response among individuals exposed to these compounds, either in the workplace or in Vietnam, does not mean that these types of studies should be abandoned. It is important to continue the surveillance of these individuals because of the potentially long latency period that may exist between exposure and manifestation of cancer.

4. Genetic toxicity

In one study, chromosomes of white blood cells were examined from 10 men who reported that they were exposed to Agent Orange in Vietnam and who had experienced reproductive problems. There was an apparent increase in the number of chromosome breaks among these men. The meaning of this finding is not clear, however, because the control group to which these men were compared was not appropriate, and other possible causative factors either were not investigated or were systematically excluded. In an experimental study, male mice were given doses of TCDD that damaged the liver, but the chemical did not adversely affect the chromosomes of blood cells taken at several time intervals after treatment. There is no strong evidence in the recent literature that either phenoxy herbicides or TCDD cause genetic damage in males.

5. Reproductive effects

No studies of adverse reproductive effects, including birth defects, among humans potentially exposed to phenoxy herbicides or TCDD were published during 1985. The studies in experimental animals were designed to elucidate the mechanism by which TCDD and related compounds cause birth defects in mice. Their relevance to human health effects is not yet clear.

6. Effects on the immune system

No studies of the effects of phenoxy herbicides or dioxins on the functioning of the human immune system were published during 1985, and there is still no substantial evidence that these compounds affect the immune system in humans. Animal studies published during 1985 provide additional evidence supporting previous findings that TCDD suppresses a variety of immune functions in mice. Some aspects of the mechanisms by which the immune system is suppressed are beginning to be understood. Like many of the effects of TCDD in experimental animals, suppression of immune function appears to be a consequence of the binding of TCDD to a specific receptor molecule within cells that regulate immune functions. The external manifestations of the immune suppression caused by TCDD have not been characterized. Nevertheless, TCDD is likely to impair an organism's abilities to resist infection and to identify and destroy cancer cells before they multiply.

7. Neurobehavioral effects

Among the studies published in 1985 were two separate case reports of neurological evaluations of men who complained of loss of feeling in their extremities, presumably as a result of exposure to Agent Orange in Vietnam. Nerve conduction velocities and latencies, which are the conventional parameters used to diagnose peripheral nerve damage in humans, were normal in 15 of the 16 individuals examined. However, further examination of one patient revealed abnormalities in specific nerve functions involving muscular control. These results are consistent with other findings, also published in 1985, of the effects of the phenoxy herbicide 2,4-D on rats. It was found that 2,4-D does not affect nerve conduction velocities in rats, but it does affect the junction of nerves with muscles, thereby interfering with normal muscle function.

8. Presence of the TCDD receptor in human tissues

As indicated above, studies in experimental animals have shown that for TCDD to cause many of its toxic effects, it must first bind to a special molecule, known as a receptor. These studies have also shown that the affinity of this receptor for TCDD varies from one animal species to another and even from strain to strain within a species. The susceptibility of experimental animals to some of the effects of TCDD depends on how well the receptor in that strain or species binds to TCDD. In other words, it takes a smaller amount of TCDD to produce an effect in a species with high affinity receptors than to cause the same effect in a species with lower affinity receptors. The affinity of the receptor is genetically controlled, so that the offspring of animals with high affinity receptors will have high affinity receptors, and the offspring of animals with low affinity receptors will have low affinity receptors.

Understanding more clearly how receptors affect the toxicity of TCDD in animals has raised the question of whether or not humans have such a receptor. If so, does it have a high or low affinity for TCDD? In the last year or two, several investigators have looked for this receptor in cultured human cells and in tissues from human surgical samples. Not surprisingly, given the wide genetic variation in the human population, these studies have shown great variability from one individual to the next. However, no receptor was detected in the majority of the

human tissue samples. For example, only 10 of 53 human lung tissue specimens had detectable receptors, and the highest concentration of receptors in these 10 humans was well below the normal range of concentrations in mice and rats.

These results are very preliminary and may have serious limitations. Nevertheless, it is reasonable to speculate that there may be wide variability among humans in their susceptibility to the receptor-controlled toxic effects of TCDD. In addition, most humans may be less susceptible to these effects than many experimental animals. A great deal more research is necessary, however, to test this hypothesis.

9. Summary and conclusions

Most of the scientific literature concerning the health effects of phenoxy herbicides and dioxins published during 1985, consisted either of reports of basic research on the mechanism of action of TCDD or review articles that described previously published studies. Relatively fewer significant new studies were published than in previous years. Noticeably lacking were studies on the health effects of the herbicidal active ingredients, 2,4,5-T, picloram, and cacodylic acid.

Taken together, the results of studies of cancer among people who may have been exposed to phenoxy herbicides and/or dioxins were inconclusive. A survey of cancer deaths among white males in Massachusetts indicated an excess of deaths due to soft-tissue sarcoma. Earlier studies had suggested that this cancer was associated with exposure to phenoxy herbicides during their application. Also, a study published in 1985 revealed an excess incidence of soft-tissue sarcomas among workers employed in phenoxy herbicide manufacturing in Denmark. In neither of these studies, however, could the excess cancer incidence be specifically attributed to exposure to phenoxy herbicides and/or their contaminating dioxin impurities. Several additional studies of cancer among farm workers who may have been exposed to phenoxy herbicides showed no excess incidence of any type of cancer that might be attributed to that exposure.

No other studies were published in 1985 that showed adverse health effects in humans as a result of exposure to either phenoxy herbicides or dioxins. Studies of the effects of these compounds in experimental animals revealed no significant new adverse effects. For the most part, these studies provided new information on the way in which these compounds, especially the chlorinated dibenzodioxins, cause their biological effects. A number of documents described studies of how TCDD and related compounds interact with specific molecules, known as receptors, in various bodily tissues and the role these interactions play in generating the ultimate biological responses to those compounds. These studies suggest that in experimental animals the interaction of TCDD with receptors in a necessary first step in causing a biological response. Preliminary results of studies in humans indicate that there may be great variability from person to person in the amount of this receptor that is present in the tissues. This variability in receptor level may result in variable susceptibility to the adverse effects of TCDD

and related compounds within the human population. Such variable susceptibility could contribute to the difficulty in detecting adverse health effects in studies of human populations exposed to chlorinated dibenzodioxins.

Much additional research will be necessary in order to determine the mechanism of action and the degree of toxicity of TCDD in humans. Also, population-based studies of people with more precise exposure information will be needed to establish a causal relationship between exposure to phenoxy herbicides and human diseases.