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Synopsis of Scientific Literature on Phenoxy Herbicides and Associated Dioxins

No. 1 - (Volumes I-IV)

Department of
Medicine and Surgery

VA CONTRACT NO: V101(93)P-953

SYNOPSIS OF SCIENTIFIC LITERATURE ON PHENOXY HERBICIDES AND ASSOCIATED DIOXINS

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PREFACE

In October 1981, the Veterans Administration published the first two volumes of a comprehensive report entitled *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. A continuation of this important effort resulted in the preparation and publication in April 1984 of volumes III and IV. At this point it was thought that a summary in layman's terms, with emphasis on health effects would be helpful to the general public's understanding of the complex and often controversial issue of Agent Orange. Consequently this summary has been prepared to fill that need. It should be noted that this synopsis includes only that body of scientific literature published through December 1983, and therefore does not include the results of more recent research such as the study of birth defects conducted by the Centers for Disease Control and published in August 1984. Also not included is the mortality study of Australian Vietnam-era veterans published in September 1984. The results of these and other more recent reports will be summarized in a similar synopsis currently being developed by the VA for publication in the near future. It is hoped that these lay-language summaries will serve as useful supplements for assisting non-technically oriented readers in understanding both the significance and impact of such literature and thereby assist in the ultimate resolution of the many and varied issues related to the phenoxy herbicides and associated dioxins.

Agent Orange Projects Office
Veterans Administration
Washington, D.C.
1985

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1. Introduction

For the past several years the Veterans Administration, in response to the concerns of veterans who served in the war in Vietnam, has been conducting or sponsoring research on the health effects of Agent Orange, the principal herbicide used by U.S. military forces in that country and to which some American military personnel were exposed.

In April 1984, under contract to the Veterans Administration, Clement Associates, Inc., a research firm in Arlington, Virginia, completed a two-volume survey of the extant scientific literature on the health effects of Agent Orange. The material that follows is a lay summary of that survey and is published because the Veterans Administration believes that it will be of interest to Vietnam veterans and others who have been following the Agent Orange issue.

2. What is Agent Orange?

"Agent Orange" is a name that has come to be used to describe a particular type of chemical herbicide that was used in military operations in Vietnam from 1965 to 1971. The name came from the orange stripe that identified the 55-gallon drums in which the herbicide was shipped and stored. Agent Orange was not a single chemical compound but rather a mixture of chemicals containing equal amounts of the two active ingredients, 2,4-D and 2,4,5-T. These weed-killing chemicals enjoyed extensive commercial and private use in the United States and in many countries around the world from the 1940s well into the 1970s. 2,4-D is still used extensively in this country and abroad.

Like many industrial chemical mixtures, the Agent Orange that was manufactured during the Vietnam era contained small quantities of impurities. These impurities included chemicals used in the production of 2,4-D and 2,4,5-T as well as by-products which developed during the manufacturing process. Some of the impurities were a family of closely related compounds known as polychlorinated dibenzodioxins which, as a group, have often been called "dioxins."

One of these dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or TCDD, has been extensively tested in experimental animals and is believed to be the most toxic member of the dioxin family. TCDD is one of the contaminating dioxins in 2,4,5-T. In the remainder of this report the term dioxin will be used to refer to any of a number of different polychlorinated dibenzodioxins, usually unidentified. The term TCDD will be used to designate the specific chemical 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Agent Orange was produced by several manufacturers in a number of chemical plants throughout the United States under contract to the Department of Defense, which specified the composition of the herbicide. Therefore the nature and amount of the active ingredients were the same regardless of the manufacturer. Although Defense Department specifications set an upper limit on the total amount of impurities that could be present in a batch of Agent Orange, it is certain that both the exact amount and the nature of these impurities varied from batch to batch, from year to year, and from manufacturer to manufacturer. Furthermore, since very little attention was paid to the importance of the impurities in Agent Orange until

late in the Vietnam experience, there is relatively little information available on the amount of the impurities contained in the herbicide shipped to Vietnam.

Agent Orange was somewhat different from commercial formulations of this class of herbicides made and marketed in the United States and in other countries around the world. In addition, we don't really know precisely all the types and amounts of the impurities that were present in Agent Orange, and furthermore we don't have any accurate way to find out. Because there is considerable evidence that the health effects of these herbicide mixtures depend heavily on the amounts and types of impurities such as dioxins which were present in the mixture, we can accept, only with reservations, information on health effects obtained from studies of people exposed to other herbicide preparations containing 2,4-D, 2,4,5-T, or both. If we hope to understand the health effects of Agent Orange with a high degree of certainty, it is essential to identify and study people who were exposed to Agent Orange.

3. Who was exposed?

The only individuals who are known to have been exposed to Agent Orange are those who were exposed during its manufacture and distribution or as a result of its use in Vietnam. Because Agent Orange was considered relatively safe at the time of its use, however, there were no systematic studies to determine how much Agent Orange might enter a person's system as a result of exposure in a manufacturing plant, during spraying operations or other applications, or from entering an area that had already been sprayed.

Another way of determining exposure is to depend on people's memory of when and how often they might have been exposed. Unfortunately, several different types of chemicals were manufactured in most of the plants that manufactured Agent Orange. In addition, several other herbicide mixtures as well as insecticides and other chemicals were used in Vietnam.

It would be very difficult for most individuals to know when they were exposed to Agent Orange specifically and how much exposure they received. The Air Force did keep records of most of the aerial herbicide spraying missions. By combining this information with data from records of the location of military units, the probability of exposure from aircraft spraying can be estimated. Those people who were actually involved in the handling and application of Agent Orange were undoubtedly among the most heavily exposed, but it is not possible to determine accurately the amount to which they were exposed.

4. What do we know about the health effects?

As one might guess from the information above, we don't have precise and direct information on the human health effects of Agent Orange itself. Scientists cannot identify people who were definitely exposed to known quantities of Agent Orange in order to compare such a group to people who were not exposed to Agent Orange or similar herbicides. Furthermore, Agent Orange as such was not tested in experimental animals at the time of its manufacture and use.

5. How do we determine the health effects?

Since we cannot study the human health effects of Agent Orange directly, we must use other techniques to learn what health effects might result from exposure to this material. Several methods are available and all of them have been used during the last 10 or 15 years. Each has limitations that make it difficult for scientists to reach definitive conclusions about the adverse human health effects of Agent Orange. Nevertheless, if scientists and health professionals review the entire body of information that has become available from all these approaches, certain patterns emerge.

It is now possible to begin reaching tentative conclusions about the health effects of Agent Orange. However, these conclusions are still somewhat uncertain. The results of studies which are currently in progress or planned will go a long way toward removing this uncertainty, but, for the general reasons described above and for specific reasons described below, it is quite likely that we may never be completely sure of what the health effects of Agent Orange are. This same uncertainty exists for many environmental health issues and is a result of the normal limitations of science.

One of the most promising approaches to studying the health effects of Agent Orange is to evaluate the health of people who may have been exposed to it as a result of the Vietnam experience and to compare their health with that of people who were not exposed to these herbicides. A few such studies have been conducted and several more are in progress. Some of the limitations of these studies have already been mentioned.

We don't have reliable records of everyone who was exposed, so assumptions are made such as "any veteran who served in Vietnam was exposed to Agent Orange" (Australian Veterans Health Study) or "any individual who was assigned to Operation Ranch Hand was heavily exposed to Agent Orange" (U.S. Air Force Epidemiology Study). These assumptions may lead to the inclusion in the "exposed" group of people who had very little exposure. If enough of these people are mis-classified as to exposure, scientists will not be able to detect any real health effects that might be present in those who were actually heavily exposed. In other words, the greater the mis-classification rate, the less reliable are conclusions regarding health effects of exposure.

Another serious limitation is that it is very difficult to select a group of "unexposed" people who can be closely matched with the people in the "exposed" group. Ideally, the two groups should be the same except for their potential exposure to Agent Orange. This means that individuals in both groups should not only be the same in age, weight, and sex, but they should also have similar smoking habits, diets, jobs, life styles, and places of residence. Another problem inherent in these studies relates to the widespread use in the United States of commercial herbicides that are similar to Agent Orange. In addition, dioxins are known to be present in other industrial chemicals in the environment. It is therefore very possible that some individuals in the "unexposed" group have actually been exposed to the ingredients of Agent Orange at other times and in other places.

Another problem with studies of people who were exposed to Agent Orange is that a relatively short period of time has elapsed since exposure took place. The phenoxy herbicides contained in Agent Orange were first used in Vietnam in 1962. Heavy use and potentially heavy exposure to Agent Orange did not begin until three years later, so the time that has elapsed since most veterans were exposed has been about 15 to 20 years. Certain adverse health effects such as cancer, heart disease, and respiratory problems that result from exposure to chemicals may take many years to develop. Increased cancer rates due to smoking or exposure to toxic chemicals have been shown to reach a peak 20 to 30 years after exposure. Thus, a lack of evidence of increased rates of cancer and heart disease in populations exposed to Agent Orange might suggest that exposure to Agent Orange does not increase the risk of developing these diseases. On the other hand, it might be that they haven't had time to appear in sufficient numbers to be detected.

The studies of populations who were probably exposed to Agent Orange as a result of the Vietnam experience have not yet provided clearcut answers to questions about its health effects. This is the result of some of the limitations described above. Furthermore, future studies of this type will not be capable of answering all these questions. It is therefore necessary to ask, "Where else can we look for these answers?" One potentially valuable source of information is the study of human populations with exposure to commercial herbicidal mixtures that were similar, but not identical, to Agent Orange. A number of such studies are available. Most are of workmen who sprayed herbicides on the job, but some are of populations who lived in areas where herbicides containing 2,4-D and 2,4,5-T were used. Most of these studies are subject to the same limitations as those of the people exposed to Agent Orange.

In all of these studies, the determination that a person is or is not exposed is based largely on that person's memory of past events or, in many cases, simply on where the person lived or worked. Also, people may be included in the exposed group who worked at a job or lived in an exposed area for only a few weeks. On the other hand, people may be included in the unexposed group if they are currently working in jobs or living in areas where they are not exposed to herbicides but who may have been exposed to herbicides in some previous job or place of residence, perhaps even without knowing it. Either type of error decreases the ability of scientists to detect possible effects of exposure to the chemical.

Other potential sources of information about the health effects of Agent Orange are studies of humans who were exposed to some of the components of Agent Orange. There are a number of groups of people throughout the world who were exposed to dioxins as a result of industrial accidents or unintentional release of dioxin into the environment. Several of these groups have been followed for a number of years and much information has been gathered. It is difficult, however, to judge how relevant these findings are to people exposed to Agent Orange. The specific dioxins to which these people were exposed were not always completely or accurately identified, and they may be somewhat different from those found in Agent Orange.

One of the most widely publicized incidents in which humans were exposed to dioxins was the explosion of a chemical reactor at the ICMESA plant near Milan, Italy, in July 1976. A cloud of chemicals containing relatively large quantities of dioxins blanketed a portion of the

small town of Seveso immediately downwind of the plant. In succeeding weeks many persons living in Seveso showed signs of dioxin exposure, the most prominent being chloracne, a form of acne which includes the appearance of blackheads around the eyes and ears and in some cases covers much of the body.

No direct measurements were made of the chemicals in the accidental gas cloud itself but it has been possible to estimate the dioxin exposure of people in different areas by three independent methods. The first was a calculation of the distribution of the dioxin based on the nature of the chemical reaction, the quantity of ingredients, and the wind direction and speed at the time of the accident. The second method recorded biomedical changes, such as the death of birds and other wild and domestic animals and the appearance of chloracne in people. These changes were then correlated with the geographic location of each person or animal affected. The third method, performed somewhat later, was the actual analysis of the soil for dioxin. This gave results which were judged to be in agreement with those of the other two methods. In addition, reports by the exposed individuals provided supplementary and confirmatory information.

In the areas with the most intense exposure, animals and birds died; humans did not. People experienced a variety of symptoms shortly after the explosion including weakness, headache, loss of appetite and weight, insomnia, impotence, nausea and abdominal pain. There was also a burning sensation and an eruption of the skin, but the role of dioxin, as opposed to other more caustic chemicals suspected of being present in the cloud, is unclear. The symptoms cleared up within a brief period but one characteristic skin change, chloracne, persisted. Chloracne was present, especially in children under the age of 14. In the most heavily contaminated areas about 20 per cent of the children developed the skin disorder. The changes gradually cleared over the ensuing months.

Early after the exposure there were laboratory results suggesting changes in liver function, but the test results did not differ a great deal from those obtained in an unexposed, control population. Within a year after the exposure careful examinations showed some problems with the nerves controlling muscle function. These changes apparently disappeared within the following two or three years.

It is not clear that the exposure to dioxin had any effect on the pregnancy rate, the miscarriage rate or the birth rate since there are no good statistics from nearby communities with which to compare the exposed populations. There is no convincing evidence that the dioxin caused birth defects, interfered with growth, disturbed resistance to disease or increased the death rate. Some details of these results may be questioned because of the difficulties encountered in collecting the data. It is reasonable, however, to say that the Seveso accident did not result in a very serious or life-threatening effect on the health of exposed persons, at least in the near-term. It is too soon to draw final conclusions regarding possible delayed effects.

A final potential source of information about the adverse health effects of Agent Orange includes studies using experimental animals. Care must be taken in interpreting the results of animal studies because animals may respond quite differently from humans in the way they absorb chemicals, in the distribution of these chemicals in the body, in the way the chemicals

are broken down or stored in the body, and in the way they are eliminated. Differences in body size, diet, lifespan, and the way individual organs function may also cause animals to respond differently from humans. For these reasons responsible scientists are reluctant to base predictions of human health effects on animal studies unless the chemical has been tested in several species of experimental animals and there is a good basis for believing that the test animals are similar to humans in the way they respond to the chemical.

For reasons noted earlier, Agent Orange when it was first used was not tested in experimental animals and, because the amount and identity of the impurities in Agent Orange varied, it cannot be exactly reproduced for studies in experimental animals now or in the future. It is therefore necessary to rely on the results of experimental studies of herbicide mixtures similar to Agent Orange as well as studies of individual components of Agent Orange such as 2,4-D, 2,4,5-T and TCDD to serve as a basis for predicting the human health effects of Agent Orange.

The remainder of this report on the health effects of Agent Orange summarizes the information available as of early 1984 from all the types of studies described above. The section that follows provides a discussion of each of the suspected or potential health effects and in each case the available evidence is evaluated as a whole. For more detailed information regarding specific studies the reader is urged to refer to the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins,* Volumes I, II, III and IV, published by the Veterans Administration.

6. Summary of the studies on health effects

Cancer

To date only one systematic study of cancer in military personnel exposed to Agent Orange in Vietnam has been published. In this study of Air Force personnel who were engaged in Operation Ranch Hand (the herbicide spraying operation in Vietnam), there was no increased occurrence of serious or life-threatening forms of cancer, but a greater incidence of a type of skin cancer was found in the exposed group compared to a control group of military personnel who were not exposed to Agent Orange. This type of skin cancer is a very common, localized form that is known to be associated with exposure to sunlight. Further studies need to be done to determine whether Ranch Hand personnel were more likely to have been exposed to sunlight than were the members of the comparison group. There was also a slightly increased incidence of cancer of the mouth and throat in the Ranch Hand group, but this excess is so small that it may be due to chance.

Two other reports are available on cancer in Vietnam veterans but in neither report was there any confirmation of exposure nor were matched control groups used. In one survey, based on Vietnam veterans who registered with the VA's Agent Orange Registry, a somewhat higher proportion of mouth and throat cancer and of lymphoma (cancer of the lymphatic system) was found compared to the same proportion of cancers among U.S. males aged 25 to 39. In the other report, a physician in Atlanta reported three cases of soft-tissue sarcoma (a rare

cancer) among his patients. All three of these patients had served in Vietnam but no other information was given about them.

Comparisons between groups exposed to the herbicides or to dioxins and unexposed groups have shown no overall increase in cancers. Attention has centered on certain types of cancers.

There have been 11 reports of studies of cancer in men who were employed in jobs that involved the spraying of herbicides similar to Agent Orange. Eight of these studies were limited to men who sprayed herbicides containing 2,4-D or 2,4,5-T. The other three studies were of workers exposed to agricultural chemicals in general, including herbicides. These three studies are not discussed here because of the uncertainty regarding exposure. The eight remaining reports are also based on groups of workers whose exposure was of doubtful duration and intensity. Two of the eight studies of 2,4-D or 2,4,5-T indicated that there was an association between exposure and the incidence of soft-tissue sarcoma. A third study showed an association between exposure and lymphoma, and one study showed an association between exposure and stomach cancer. Another of these eight reports described five cases of lymphoma with cutaneous (skin) lesions seen in an English hospital. Four of the five patients worked with 2,4-D or 2,4,5-T. A case-control study reported an association between herbicide exposure and cancer of the nose and throat. The remaining three reports showed no association between exposure and any form of cancer, although one suggested a slight association with soft-tissue sarcoma.

Of seven studies on populations exposed to dioxins either in the workplace or in the environment, two showed an increased incidence of cancers. A study of workers exposed to dioxin as a result of a reactor explosion in a 2,4,5-T manufacturing plant in Germany in 1953 showed an excess of stomach cancer. Another study of the residents of Midland County, Michigan, where Dow Chemical Company has a large plant, revealed an increased incidence of soft-tissue sarcoma in women between 1960 and 1980. This finding is unlikely to be related to dioxin exposure, however, because the excess cancer was seen only in women and several of the people with soft-tissue sarcoma had lived in Midland County only a short time before the diagnosis of cancer and had little or no connection with the company.

Three separate reports describe two cases of lymphoma and three cases of soft-tissue sarcoma in workers who may have been exposed to dioxin. These are isolated case reports, and they contained little evidence of dioxin exposure. Two studies of workers occupationally exposed to dioxin revealed no excess incidence of any form of cancer.

None of the studies of cancer in humans exposed to Agent Orange, related herbicides, or dioxins provides an answer to the question of whether Agent Orange might cause cancer in humans. When all the reports are taken together, however, certain patterns appear that provide suggestive evidence that exposure to dioxin-contaminated herbicides may be associated with an increased incidence of cancer. Thus, seven reports suggest a relationship between such exposure and soft-tissue sarcoma. Four reports point to a possible connection with lymphoma. Two studies show an association with stomach cancer and three reports suggest a possible association with cancer of the mouth, nose, or throat.

The results of animal studies lend support to the hypothesis that dioxins and dioxin-contaminated herbicides may cause cancer in humans. Six studies of the potential for TCDD to cause cancer in animals were positive when relatively large doses were given. TCDD painted on the skin of mice caused cancers related to soft-tissue sarcomas. Four studies in which rats were given TCDD by mouth showed that the rats developed cancer of the liver, mouth and nose, tongue, adrenals, and thyroid. In two studies in which TCDD was given to mice by mouth, liver and thyroid cancers resulted. Several studies suggest that when TCDD is given to mice with other cancer-causing chemicals, it increases the response to those cancer-causing chemicals.

As yet there have been no published studies which show that Agent Orange or similar commercial herbicides have a demonstrated potential for causing cancer in laboratory animals. A few studies designed to measure the effect of 2,4-D and 2,4,5-T on rats and mice have been negative for cancer, but these studies were not adequate to detect a small increase in cancer in the treated animals. The current evidence, though far from conclusive, justifies continued surveillance of people who have been exposed to dioxin and dioxin-contaminated herbicides in order to confirm or deny an increased incidence of cancer which can be attributed to that exposure.

Reproductive effects

The various possible causes of reproductive abnormalities are difficult to determine because there are fairly high rates of birth defects, stillbirths, miscarriages, and sterility in all populations. For example, between three and six percent of all children are born with some kind of defect. The percentage varies depending upon how serious a disturbance has to be before it is recorded as a defect. In addition, some defects are not noted at birth, but show up later in childhood or beyond.

Two systematic studies of reproductive performance and outcome among men who may have been exposed to Agent Orange in Vietnam have been published. In the first of these the Australian government sponsored a study to see whether birth defects were related to the father's service in Vietnam. No association was found, although there was a slightly increased risk of heart defects and Down syndrome among the children of Vietnam veterans.

In the study of Operation Ranch Hand personnel discussed in the cancer section above, a small increased incidence of miscarriages following Vietnam service was found among the wives of the Ranch Hand group when compared to wives of the control group. The same difference, however, was observed for pregnancies occurring prior to Vietnam service. There were also slight increases in deaths of newborn babies and minor birth defects. There may have been slight increases in learning disabilities and physical handicaps among children of Ranch Hand personnel. The significance of these findings is not clear because most of the increases are very small, and many of these differences disappear if the data are analyzed differently. In addition, these differences were based on self-reporting and at the time of the initial report had not been confirmed by a review of medical records.

Two studies have been reported of men who were exposed to herbicides similar to Agent Orange. A study of wives and children of herbicide sprayers in New Zealand showed no increases in birth defects, stillbirths, or miscarriages when compared to the population of New Zealand as a whole. There was a very small increase in the incidence of heart defects, but this may have been due to chance. Another study of children born to the wives of men who sprayed herbicides for the Long Island Railroad showed no increase in major birth defects but two relatively minor birth defects—minimally deformed feet and tear duct obstruction—were seen in excess.

Several studies have been conducted to ascertain whether there are increased incidences of spontaneous abortions, stillbirths, or birth defects in areas where herbicides similar to Agent Orange have been heavily used. In these situations there is the potential for exposure of both parents as opposed to exposure of only the father as in the four studies discussed above.

One of these general population studies gained a great deal of publicity in the late 1970s when it was asserted that women living in the vicinity of Alsea, Oregon, experienced a higher rate of miscarriage than did women living in other parts of Oregon where herbicides were not commonly used. Careful review of this study by expert scientists has resulted in a consensus that the results were misinterpreted and that the study did not show the claimed effect.

More recently, a study of people living in an area of New Zealand where herbicides containing 2,4,5-T were often used revealed an increase in the occurrence of clubfoot in children in the area. Other small and perhaps insignificant increases were found in heart defects and malformations of the penis. A study conducted in Hungary looked at the rate of five major birth defects in that country's general population over a five-year period in which the use of 2,4,5-T increased greatly. No changes in the rates of these birth defects were found.

Four studies have been conducted of men exposed to dioxin as a result of working in plants where 2,4,5-T was manufactured. None of these studies showed a clearcut effect on reproductive outcomes. Two of them did show a slight increase in spontaneous abortions in the wives of the workers. Two studies of the population exposed to dioxin as a result of the ICMESA accident at Seveso suggest that there may have been an increase in birth defects (particularly of the heart) and an increased incidence of spontaneous abortions in the year following the accident, but their validity is questionable because the reporting of birth defects and abortions was generally unreliable.

The studies of the reproductive effects of 2,4-D, 2,4,5-T, and TCDD in experimental animals are of limited usefulness in helping to predict the reproductive effects of Agent Orange in male Vietnam veterans. In almost all of the animal studies, the herbicide or dioxin was given to pregnant females rather than to male animals. In the one study in which the mixture found in Agent Orange was fed to male mice, it had no effect on reproductive performance or on the offspring. In two studies, relatively uncontaminated 2,4,5-T and TCDD were fed to both male and female rats and reproductive performance and outcome were recorded for three successive generations. These studies showed that both 2,4,5-T and TCDD decreased the number of live births and the weight of newborn animals, as well as causing an increase in birth defects of the kidneys. Numerous studies in which TCDD was given to pregnant females in relatively large

doses indicate that it can cause defects in the developing fetus. TCDD causes birth defects in pregnant rats, mice, rabbits, and monkeys when given by mouth or injection. It also causes an increase in the number of spontaneous abortions and a decrease in birth weight of newborn animals.

In summary, no study of reproduction in humans exposed to Agent Orange conclusively shows an adverse effect which has been caused by the herbicide. Scientists believe, however, that people with known exposure to TCDD-contaminated chemicals should be observed for possible adverse reproductive effects.

Enzyme effects

One of the best studied effects of dioxins in experimental animals is the ability of these compounds, especially TCDD, to alter the activity of certain enzymes. Enzymes are proteins that serve as catalysts in the formation or breakdown of various chemicals in the body. In some cases many enzymes are involved in the alteration of just one chemical, whereas other enzymes are capable of acting upon an entire class of chemicals.

It is very difficult to study the effects of chemicals on enzyme activities in humans. Most enzymes are located in tissues where metabolic activity is greatest, such as the liver, lungs, intestines, brain, and reproductive organs, and these tissues are the least accessible to study. Furthermore, there are large differences among people in their baseline metabolic activity. About the only approach available is to look at the levels of chemicals produced by enzyme reactions that appear in the blood or urine and determine whether they are different in people exposed to a specific compound when compared to people who are not exposed to that compound.

Only a few studies of enzyme activities have been conducted in animals which have been fed or otherwise dosed with 2,4-D and 2,4,5-T. These studies suggest that these compounds do not cause major alterations in enzyme activities, and some of the small effects seen may be the result of contamination of these chemicals with small amounts of dioxin. A number of studies of TCDD, on the other hand, have shown that it alters the activity of some enzymes in experimental animals.

The best studied effect is an increase in the activity of an enzyme known as aryl hydrocarbon hydroxylase (AHH). AHH is important because it makes certain chemicals more soluble in water and, thus, more likely to be excreted in the urine. Very small amounts of TCDD cause large increases in the activity of this enzyme in rabbits, mice, rats, guinea pigs, hamsters, birds, fish, and monkeys. In several studies in which living cells were taken from humans and allowed to grow in a culture medium, the addition of TCDD to the culture caused an increase in AHH activity in the cells.

It is interesting that in two studies of human populations exposed to dioxin as a result of industrial accidents (one at Seveso and the other at a 2,4,5-T manufacturing plant in England), scientists found elevated levels of d-glutaric acid in the urine of exposed people. This chemical

is believed to be formed by enzymes that are very closely associated with AHH. This finding adds support to the theory that TCDD may stimulate AHH activity in humans.

What are the health implications of stimulation of AHH activity? This is a difficult question to answer because the role of AHH is not yet fully understood. Evidence from animal experiments and some human evidence indicate that some of the aryl hydrocarbons that are altered by AHH are cancer-causing. Some experiments in which TCDD was given to animals several days before they were exposed to cancer-causing aryl hydrocarbons showed that it protected the animals against cancer. Thus, TCDD caused an overall health benefit.

Unfortunately, the picture is much more complicated than that because, if TCDD is given to animals at the same time as the aryl hydrocarbon rather than a few days earlier, the TCDD binds to the site of the AHH enzyme that is responsible for changing the aryl hydrocarbon and prevents the AHH enzyme from doing its job. Thus, administration of TCDD with aryl hydrocarbon causes more cancer than does the aryl hydrocarbon itself.

An additional complication is that there is evidence that AHH catalyzes other tranformations and that some of them may convert inactive chemicals into toxic ones. In the absence of complete information, the fact that TCDD stimulates AHH activity must be viewed as a potentially adverse effect.

Animal studies have also shown that TCDD alters some enzymes that are involved in the manufacture of heme, the portion of the hemoglobin molecule that binds oxygen in red blood cells. Animal studies indicate that TCDD *decreases* the activity of an enzyme known as uroporphyrinogen decarboxylase in the liver. This results in a decrease in the amount of heme synthesis and a build-up of the chemicals known as porphyrins from which heme is formed. As the porphyrin level builds up, more porphyrins are excreted in the urine.

A number of animal experiments have shown that the pattern and amount of porphyrins excreted in the urine changes after treatment with TCDD. Two studies of workmen exposed to dioxin have shown increased urinary excretion of porphyrins. The Air Force study of personnel involved in Operation Ranch Hand has also shown that there are more men with abnormally high porphyrin levels in the exposed group than in the comparison group, although this finding correlates more strongly with alcohol use than it does with potential exposure to Agent Orange.

Interference with porphyrin metabolism may result in a condition known as porphyria cutanea tarda (PCT) in which the skin blisters and later becomes dry and brittle, particularly on exposure to sunlight. Workers who were exposed to dioxins as a result of two industrial situations developed this condition but in both instances the men were also exposed to another chemical known to cause PCT.

The available medical evidence indicates that there are no lasting adverse human health effects that result from alterations in porphyrin metabolism due to exposure to TCDD. The body adjusts by producing sufficient heme to meet the oxygen-carrying needs of the body. PCT is a relatively rare manifestation of changed heme metabolism and may be caused by

other external factors, such as alcohol consumption. There is also a known genetic factor which influences the development of PCT. PCT resulting from exposure to such chemicals as dioxins and similar compounds is reversible and disappears after exposure.

Another enzyme activity for which there is indirect evidence of interference by dioxins is related to the conversion and storage of fats. Studies of workmen exposed to dioxins showed increased blood levels of fat molecules known as triglycerides. Although elevated levels of some triglycerides are known to be associated with heart disease, to date there is no conclusive evidence of an association between heart disease and dioxin exposure.

Although it appears that dioxins have the ability to alter the functions of a number of enzymes, at present none of these alterations has been shown to be associated with any serious or irreversible adverse health effects in humans. However, any influence that substantially alters the way the body handles internal and external chemicals must be viewed with concern. It should be remembered that as in the case of most of the effects of these chemicals, the active herbicide ingredients 2,4-D and 2,4,5-T by themselves are not known to affect the enzyme system in humans.

Effects on the immune system

Unlike such well-studied and relatively well-understood systems of the body as the cardiovascular and digestive systems, there is still much of the "immune system" which is not well understood. It is currently the subject of intensive research to better understand its chemistry, mechanisms, and functions. The immune system is involved in a large and complex array of processes that defend the body against foreign chemicals, disease-causing bacteria, viruses, foreign cells from outside the body, and abnormal cells from within the body. Virtually all of the body's organs and tissues participate in these processes to a greater or lesser extent.

Because of the lack of basic knowledge in some areas, it is difficult to assess the impact of chemicals on the immune system. One problem is that the system functions in many different ways. A chemical to which the body is exposed may activate only one or two of dozens of known defense mechanisms. Therefore, it may be necessary to run a large number of different tests to detect these changes. Since many of these tests are very complex and some require the examination of body tissues, it is especially difficult to study altered immune function in humans.

Two additional factors make it difficult to detect such changes in humans. First, there are tremendous differences among people in the manner in which their immune systems operate. For example, there is a wide variation in the way different people manifest an allergic reaction, which is one of the ways the immune system functions. Second, many activities of the immune system have no obvious or external manifestations. It is usually not possible to assess a person's immune function by a simple physical examination. These changes in immune function may only be reflected by subtle variations in indirect indicators, such as increased susceptibility to infections or increased sensitivity to materials that cause allergic reactions. One result of these problems is that the effect(s) of chemicals on the immune system of humans may

be very subtle and difficult to detect. Highly specialized and complex tests are often needed to detect these changes.

There is no evidence that 2,4-D or 2,4,5-T by themselves alter the immune function of animals. There have been no studies of humans exposed to Agent Orange or similar herbicides that show an adverse effect on the immune system, and there have been no reports of increased allergies or of increased susceptibility to infection, either of which might indicate altered immunity. On the other hand, there have been no studies reported that were designed specifically to look for such an effect in humans soon after exposure.

There is considerable evidence, on the other hand, that TCDD interferes with the functioning of the immune system in experimental animals. When TCDD is given to animals, a common effect is a decrease in the size of the thymus, an organ that is involved in the immune system. This effect occurs at doses lower than those that cause changes in other organs. At even lower doses, TCDD interferes with the ability of the animal to produce certain types of white blood cells in response to the presence of foreign materials in the blood stream. In some studies, this effect is paralleled by decreased resistance to bacterial and viral infections.

It appears that TCDD has the ability to suppress the immune system in unborn animals when the TCDD is given to pregnant females. Sensitivity decreases in newborns but significant effects can still be seen in adult animals treated with TCDD. In fact, immune suppression is the most sensitive indicator of TCDD exposure in mice, occurring at doses below those that cause changes in enzyme activity. Furthermore, although immune function improves after exposure ends, it remains relatively depressed for a very long time in experimental animals.

Most studies of humans who have been exposed to dioxins have not included tests of immune function. There has been a study of children who lived in the heavily contaminated area of Seveso, Italy. The results of this study showed that these children had higher levels of certain immunologically active blood components than did children from uncontaminated areas. The body also produced more white blood cells in response to certain foreign materials. These results suggest that exposure to dioxins *stimulated* immune function in these children rather than depressing it, as seen in the animal experiments. This finding is not inconsistent, however, with experimental findings that some chemicals which depress immune function at high doses may actually stimulate immune functions at low doses.

Another study of workers exposed to dioxin as the result of an industrial accident has been reported to have shown *decreased* immune function in the exposed workers 10 years after the accident, but this study has not been published and cannot be independently reviewed. These results, taken together, fall far short of providing convincing evidence that dioxin exposure can cause altered immune function in humans. Nevertheless, the evidence of such effects in experimental animals provides some basis for concern that exposure to dioxin may adversely affect immune function in humans.

Chloracne

Chloracne is a skin condition that is known to result from exposure to a group of structurally similar compounds in which chlorine atoms are bound to an aromatic hydrocarbon. One of

these compounds is TCDD. As its name suggests, chloracne, is similar in appearance to the common forms of acne that affect teenagers and usually appears within a few weeks after exposure to the chemical that causes it.

The first sign of chloracne may be excessive oiliness of the skin. This is accompanied or followed by the appearance of numerous blackheads. In mild cases the blackheads may be confined to the area around the eyes extending along the temples to the ears. In more severe cases blackheads may appear in many places on the body. The blackheads are usually accompanied by fluid-filled cysts and by an increased or darker growth of body hair. The skin may become thicker and flake or peel. In severe cases, the acne may result in opens sores and permanent scars. The condition fades slowly after exposure. Minor cases may disappear altogether, but more severe cases may persist for years after the exposure.

It is well known that chloracne can result from exposure to dioxins. In seven reported situations where workers were exposed to dioxins as a result of industrial accidents or poor housekeeping practices, many of the workers and, in a few cases, members of their families developed chloracne. Chloracne was also diagnosed in 187 people, mostly children, living in the section of Seveso that was most heavily contaminated with TCDD as a result of the ICMESA accident in 1976. Two laboratory workers who were exposed during the synthesis of TCDD developed serious cases of chloracne.

There are no authoritative reports in the literature that document an association between exposure to Agent Orange or similar herbicides and chloracne. The Air Force study of Ranch Hand personnel showed no excess of acne in those individuals when compared to unexposed controls and no cases of chloracne were found. Most of the epidemiologic studies of occupational groups involved in the spraying of herbicides like Agent Orange do not report the presence of chloracne among the workers who were studied. A research effort looking for cancer among herbicide sprayers in Finland turned up a few cases of possible chloracne, one of which was diagnosed by a dermatologist. It would appear, therefore, that chloracne is not a sensitive indicator of exposure to herbicides like Agent Orange.

Animal studies are of little use in measuring the potential of Agent Orange for causing chloracne in humans. The ingredients 2,4-D and 2,4,5-T have not been extensively tested, but it appears that they do not cause chloracne or similar skin conditions in experimental animals. Different kinds of animals react differently to TCDD, but it causes skin conditions very similar to chloracne when applied to the ears of rabbits and to the skin of certain kinds of mice. Scientists disagree, however, as to whether these skin effects are identical to human chloracne. Some types of experimental animals fail to show any acne-like condition when treated with TCDD. It seems that only monkeys exposed to TCDD develop a skin condition that appears identical to human chloracne.

One conclusion that is gaining support on the basis of both animal and human studies is that susceptibility to chloracne may be genetically controlled. Two individuals equally exposed to TCDD may respond differently because of variations in inherited susceptibility. This would explain why some of the workers exposed to dioxins in each of the seven industrial incidents did not develop chloracne, even though there is no reason to believe that they were less

exposed than workers who did develop chloracne. Thus, whereas chloracne may be a sensitive indicator of exposure to dioxins in some people, it may not be in others. Therefore, the absence of chloracne is not necessarily a reliable basis for concluding that a person has not been exposed to a chemical which is known to cause chloracne.

Neurobehavioral effects

It has been known for some time that exposure to relatively large amounts of 2,4-D, such as might occur when it is being mixed or sprayed, can cause adverse effects on the nervous system. Workmen who splashed 2,4-D on their skin or who stood for a long time in 2,4-D spray mist developed a variety of symptoms including tingling or decreased feeling in the hands and feet and tightening of muscles in the arms and legs. Examination of these workmen showed the loss of the knee-jerk reflex and an increase in the time for nerve impulses to travel from the hands or feet to the spinal cord and back. Studies in experimental animals give results similar to those seen in humans. These studies suggest that 2,4-D interferes with the transmission of nerve impulses to muscles. If the exposure is minimal the nervous system recovers. However, sustained exposure of experimental animals to relatively large quantities of 2,4-D may cause long-lasting changes in the brain and spinal cord itself.

A few studies of humans and experimental animals exposed to 2,4,5-T have failed to show any nervous system effects such as those caused by 2,4-D. There is some evidence, however, that humans exposed to dioxins as a result of industrial exposures or accidents may suffer impaired nervous system function. A wide range of signs and symptoms have been reported in these people including pain in the arms and legs, numbness in the hands and feet, muscular weakness particularly in the legs, headache, loss of memory and concentration, sleep disturbances, nervousness, and emotional and behavioral abnormalities. The speed of nerve impulses was slowed in two groups of workers who were probably exposed to dioxins.

There have been very few studies of the effects of TCDD or other dioxins on the nervous system in animals. It is not clear why this knowledge gap exists, but one possible explanation is that the doses of TCDD needed to cause detectable signs of nervous system damage in experimental animals are higher than those that cause other serious toxic effects. Scientists have therefore tended to concentrate on the other effects.

Whether nervous system and psychologic effects have occurred in individuals exposed to Agent Orange as a result of the Vietnam experience is unclear and controversial. It has been suggested that Vietnam veterans experience a high rate of psychologic problems, with certain symptoms appearing quite frequently. These symptoms include nervousness, disturbed sleep, irritability and short temper, depression, and suicidal thoughts. Many psychiatrists consider that some of these comprise a distinct collection of symptoms or a syndrome known as post-traumatic stress disorder and that this syndrome is unrelated to any chemical exposure. Evidence in support of this conclusion is that individuals such as prisoners of war and hostages who have undergone sustained stress display similar symptoms.

Unfortunately, there are almost no systematic studies of nervous system function or psychological problems among individuals exposed to Agent Orange. The recent Air Force

study of Ranch Hand personnel showed no difference between the exposed group and unexposed controls in several measurements of nervous system function including the speed of nerve impulse transmissions. On the other hand, when Ranch Hand personnel were evaluated by analyzing answers to questions on some of the tests designed to detect emotional disorders or personality disturbances, psychiatrists concluded that they were different from the comparison group and showed tendencies toward traits defined as "hypochondria, depression, hysteria, and schizophrenia." Ranch Hand personnel were also said to feel more isolated and to have a higher degree of nervousness and anxiety, to be more easily startled, and to experience more psychosomatic illness than did the comparison group. These differences were minor and are difficult to interpret. The methods used in this study would not show whether the differences between groups were due to post-traumatic stress, Agent Orange exposure, or both.

The fact that self-perception of psychologic problems is an important component of such an analysis was shown in a study of 100 veterans who were asked about their exposure to Agent Orange and their current mental and emotional well-being. Their potential exposure to Agent Orange was independently assessed by comparing their service records with records of the time and location of herbicide spraying missions in Vietnam. The frequency and seriousness of psychologic and emotional problems correlated very closely with how much herbicide the veterans *believed* they were exposed to, whereas the correlation was much weaker when the comparison was based on how much herbicide exposure the records showed.

The issue of the effects of Agent Orange on nervous system and psychologic performance is probably the most difficult health issue to resolve. There is a great deal of human and animal evidence that both 2,4-D and TCDD can adversely affect the nervous system. All of this evidence suggests that these effects are the result of short-term high level exposure rather than sustained exposure to lesser amounts.

Other toxic effects

Studies of people exposed to Agent Orange or similar herbicide mixtures have failed to reveal any significant toxic effects other than those discussed above. Other effects have been attributed to TCDD, however. As was mentioned briefly in the section on enzyme effects, there is suggestive evidence of a higher incidence of heart attacks among workmen exposed to dioxins in industrial accidents. This evidence is far from conclusive, but it is sufficient justification for continuing to observe the health of people exposed to dioxin, especially since it may take many years after exposure for adverse effects on the heart to show up.

The most dramatic sign of fatal dioxin poisoning in experimental animals is an apparent loss of appetite which leads to general body wasting. The animals eventually die of a condition very similar to starvation. This effect is observed following a large single dose of TCDD. No similar effect has been described in humans, so it may be of little relevance to human health. The mechanism by which TCDD causes this apparent loss of appetite is unknown and is the object of much current research. Some results suggest that TCDD may interfere with an appetite regulating system in the brain or thyroid.

Animal studies have suggested another aspect of the toxicity of TCDD which may have implications for human health. It has become increasingly clear that some animals are relatively resistant to some of the toxic effects of TCDD compared to others. Recent research has shown that this difference in susceptibility is genetically influenced and that mice with just one parent in common can show large differences in susceptibility to the toxic effects of TCDD. The effects for which susceptibility appears to be genetically controlled include the appearance of birth defects in the offspring of female mice exposed to TCDD, the increased activity of several enzymes including AHH and uroporphyrinogen decarboxylase, depression of immune function, chloracne, and the lethal effects of TCDD. This suggests the possibility that humans as a group who are known to be genetically very diverse, may have a wide variation in susceptibility.

7. Summary and Conclusions

What can we say about the health effects of Agent Orange? From the evidence now available we can arrive at almost no definitive conclusions. The limited evidence available suggests that 2,4-D and 2,4,5-T by themselves are not highly toxic to humans. 2,4-D appears to be capable of causing nervous system toxicity but only in situations where there is very high-level exposure. 2,4,5-T may contribute to birth defects when pregnant females are exposed. There is no evidence that purified 2,4-D or 2,4,5-T cause cancer, change the activity of enzymes, affect the immune system, or cause chloracne or porphyria cutanea tarda in humans.

There is very little direct evidence that Agent Orange causes adverse health effects in humans, but this may be the result of our limited ability or inability to identify different groups of people or large numbers of people with well-defined exposure and exposure to a known amount of the substances of concern. If adverse human health effects are found as a result of present or future research efforts, it is highly likely that these will be the result of the effects of toxic impurities such as dioxins, especially TCDD. The limited evidence of TCDD toxicity in humans comes from studies of humans exposed to dioxins, and indirectly from studies of dioxin toxicity in experimental animals. These studies provide some support for the possibility, but do not prove, that exposure to dioxin-contaminated herbicides may cause adverse health effects in humans.

These adverse effects may include chloracne, cancer at several different sites, spontaneous abortion and birth defects in the offspring of exposed females, altered enzyme activity, altered porphyrin metabolism, and altered immune function. Effects for which the available evidence is very inconclusive but which should be the subject of further study are neurobehavioral effects, including psychologic effects and heart disease. Chloracne does not seem to be of significant importance since it has not been commonly observed even among individuals heavily exposed to herbicides. Therefore chloracne does not appear to be a sensitive indicator of exposure to dioxin-contaminated herbicides.

What will future studies tell us about the health effects of exposure to Agent Orange? Studies that are planned or in progress have the potential to reduce much of the uncertainty about the health effects of exposure to Agent Orange. However, because of very serious problems in determining the exact amount and nature of exposure and in choosing appropriate

exposed and unexposed groups to examine, these studies will never be able to demonstrate conclusively the *absence* of a toxic effect. The areas in which future studies may be able to provide the most information are the delayed effects such as cancer.

Studies in experimental animals can still be helpful in suggesting possible adverse health effects of Agent Orange. Particularly helpful would be studies of the purified components of Agent Orange separately and in known combinations. Other important areas of investigation include effects on immune function and the genetic control of susceptibility to the toxic effects of dioxin.

In the meantime, exposed individuals can get some degree of reassurance from the fact that despite their inadequacies, the studies which have been completed to date have revealed no widespread or major adverse health effects among the people who were exposed. There is no evidence that the psychologic disturbances seen in Vietnam veterans are the result of exposure to Agent Orange.

For many of the potential health effects, there is little probability that they will first appear years after exposure. These include reproductive and enzyme effects, chloracne, and neurobehavioral problems. It is possible that cancer may first appear years after exposure. Persons exposed to Agent Orange should take no exceptional precautions beyond those that are prudent for everyone, i.e., consume a balanced diet, exercise regularly, have regular medical checkups, be alert for tell-tale signs of cancer, abstain from smoking, and use alcohol moderately, if at all.

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