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**Author**

**Corporate Author** Veterans Administration, Department of Medicine and S

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# A SUMMARY OF THE AVAILABLE SCIENTIFIC INFORMATION ON THE HUMAN HEALTH EFFECTS OF AGENT ORANGE

Agent Orange Projects Office
Department of Medicine and Surgery
Veterans Administration
810 Vermont Avenue, N.W.
Washington, D.C. 20420

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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 were exposed.

Early this year, 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.

What is "Agent Orange"?

"Agent Orange" is a name that has come to be used to describe a particular type of chemical herbicide (a chemical that kills plants) that was used in military operations in Vietnam from 1962 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 like sodium chloride or sucrose. Instead, it was 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 were chemicals from which 2,4-D and 2,4,5-T had been made and chemicals that were produced as an unintentional contaminant in 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 (TCDD), has been extensively tested in experimental animals and is believed to be the most toxic member of the dioxin family. TCDD as one of the contaminating dioxins in 2,4,5-T. In the remainder of this report "dioxins" will be used to refer to mixtures of polychlorinated dibenzodioxins (usually unidentified). "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, and so 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 no one attached much significance to the presence of impurities in Agent Orange until late in the Vietnam experience, there is relatively little information availble on the amount of the impurities contained in the herbicide shipped to Vietnam.

Agent Orange was not identical to commercial formulations of similar herbicides that were and are currently made and marketed in

the United States, and these in turn may be slightly different from those made in other countries. In short, we don't really know precisely what impurities were present in Agent Orange, and we don't have any way to find out. Because there is quite a bit of evidence that the health effects of these herbicide mixtures depend heavily on the amounts and types of impurities 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.

Who was exposed to Agent Orange?

The only individuals who are known to have been exposed to Agent Orange are those who were exposed during its manufacture 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, from spraying or being sprayed with it, 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, and several herbicide mixtures other than Agent Orange, not to mention insecticides and perhaps 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 where herbicides were sprayed. By combining this information with information about where and when personnel were stationed in certain areas, the probability of exposure can be estimated. Also, those people who were actually involved in the handling and application of Agent Orange were undoubtedly among the most heavily exposed to it, but it is not possible to determine accurately the amount to which they were exposed.

What do we know about the health effects of Agent Orange?

As one might guess from the information above, we don't have specific information on the health effects of Agent Orange itself. Scientists cannot identify a group of people who were exposed to known quantities of Agent Orange and who can be compared to a group of 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.

How do we determine the health effects of Agent Orange?

If we cannot study the health effects of Agent Orange directly, how can we 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. Almost all of these conclusions are 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 100% sure of what the health effects of Agent Orange are.

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 herbicides like Agent Orange. 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 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 there are enough of these people, they tend to decrease the ability of scientists to detect any real health effects that might be present in those who were actually heavily exposed.

Another serious limitation is that it is very difficult to select a group of "unexposed" people to compare with 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 (fairly easy to do), but they should also have similar smoking habits, diets, jobs, life styles, and places of residence (difficult to do). A real problem in these studies is that because of the widespread use in the United States of commercial herbicides that are similar to Agent Orange and because of the presence of dioxins in other industrial chemicals in the environment, it is possible that some individuals in the "unexposed" group have actually been exposed to the ingredients of Agent Orange at other times 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. Agent Orange was first used in Vietnam in 1962. Heavy use and potentially heavy exposure did not occur until four to six years later, so the time that has elapsed since most veterans were exposed has been about 10 to 15 years.

Certain adverse health effects such as cancer, heart disease, and respiratory problems that result from exposure to chemicals often 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 these effects are not the result of exposure to Agent Orange. 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

studies of human populations who are or were exposed 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 2,4,5-T and 2,4-D 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 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 source 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.

This group of exposed people provides a potentially valuable resource for the study of the health effects of dioxin exposure in humans. Regrettably, much valuable health information that might have been gained from this incident has already been lost. The reasons illustrate why studies on human populations are seldom as informative as people would hope.

At the time of the ICMESA accident, few people understood what had actually occurred nor did they recognize the potential human health implications of the event. No measurements were taken to

ascertain the composition of the chemical cloud that moved over Seveso. It wasn't until nearly four weeks after the accident that the first systematic efforts were begun to determine the extent of exposure. In those four weeks much happened to alter the scene. Chemical residues in plants and soil had begun to decompose. Chemical deposits moved as a result of wind, rain, and human activity. Exposed humans moved out of the contaminated area and some unexposed individuals moved in. People living in relatively uncontaminated areas ate food grown in more contaminated areas, and children and pets roamed throughout the area, enhancing their chances of encountering "hot spots" of heavy chemical contamination.

When systematic health assessments began to be performed three months or more after the accident, many exposed individuals could not be located. Many more refused to participate in the studies and many of those who participated in early studies balked at returning several months later for time-consuming and sometimes painful examinations.

It was even more difficult to identify comparable "unexposed" people willing to undergo the same tests and examinations in order to provide data for comparison. Attempts to compare the health of Seveso residents after the accident to their health before were unsuccessful because health record-keeping was very poor and incomplete prior to the accident.

For these reasons all of the many studies of the Seveso

population that have been done in the eight years since the accident have been able to show only the most severe, widespread, and obvious effects. It is little wonder that so far these studies have generally been inconclusive. Future research designed to study such long-term effects of the accident as cancer and inherited genetic disease may not be sufficiently sensitive to detect small but important changes in the incidence of these diseases.

A final potential source of information about the adverse health effects of Agent Orange is contained in using studies in experimental animals. Care must be taken in interpreting the results of animal studies because animals may respond quite differently from humans. Experimental animals are often quite different from humans in the way they absorb chemicals, in where those chemicals are distributed 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 summarizes the information on Agent Orange's health effects available as of early 1984 from all the types of studies described above. This section is organized by effect and in each case the entire body of 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 III and IV, published by the Veterans Administration.

## Summary of health effects information

### Cancer

To date only one systematic study of cancer in individuals 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 cancers, but a greater incidence of a localized skin cancer was found in the exposed group compared to a control group of military personnel who were not exposed to Agent Orange. The type of skin cancer seen was a very common 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 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. 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 from the environment, two showed excess incidences 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.

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 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. TCDD painted on the skin of mice caused cancers related to soft-tissue sarcomas. Four studies in which rats were given TCDD by mouth were positive in 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. Another chlorinated dioxin, hexachlorodibenzo-p-dioxin, caused cancer of the liver in mice and rats when given by mouth. Several studies suggest that when TCDD is given to mice with other cancer-causing chemicals, it increases the response to those cancer-causing chemicals.

No studies of the carcinogenic potential in experimental animals of Agent Orange or of commercial herbicides similar to Agent Orange have been published. A few studies of the herbicidal ingredients 2,4-D and 2,4,5-T in 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 cancer incidence with that exposure.

Reproductive effects

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's syndrome among the children of Vietnam veterans.

In the study of Operation Ranch Hand personnel discussed in the cancer section above, an increased incidence of spontaneous abortion was found among the wives of officers in the Ranch Hand group when compared to wives of officers in the control group. The difference was not found for enlisted personnel. 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 spontaneous abortion 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 spontaneous abortion 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 club foot 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 reliability 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 Vietnam veterans who are, for the most part, male. 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 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 indicate that it is a potent teratogen (an agent that causes 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. When all of the studies of humans exposed to Agent Orange, similar herbicides, or dioxins are considered together, however, they suggest that there may be a small increase in the number of spontaneous abortions, heart defects, and "minor" birth defects. When this information is considered with the results of studies in female animals, especially studies of TCDD, scientists believe that people should be observed for adverse reproductive effects if exposed to Agent Orange and other mixtures that may be contaminated with TCDD.

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 destruction or formation of chemicals in the body. Many enzymes catalyze the formation or breakdown of just one chemical, whereas others 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 given the herbicidally active ingredients 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 to increase 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-glucaric 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 stimulates 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. Heme is the portion of hemoglobin that binds oxygen so that red blood cells can carry oxygen from the lung to the rest of body. Animal studies indicate that TCDD <u>decreases</u> 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 from which heme is formed (porphyrins) in the body. 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 health effects that result from alterations in porphyrin metabolism. 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 genetic or other external factors, such as alcohol consumption. PCT

is also reversible and disappears after exposure to dioxins ends.

Another enzyme activity for which there is indirect evidence of interference by dioxins is the conversion and storage of fats. In studies of workmen exposed to dioxins, increased levels of fat molecules known as triglycerides were found in the blood, and these increases were detectable for many years after exposure. High levels of triglycerides in the blood are known to be associated with heart disease. To date, however, there is no conclusive evidence of an association between heart disease and dioxin exposure.

Though not the active herbicide ingredients of 2,4-D and 2,4,5-T, it appears that dioxins have the ability to alter the functions of a number of enzymes. At present none of these alterations have been shown to be associated with any serious irreversible adverse health effects in humans, but any influence that substantially alters the way the body handles internal and external chemicals must be viewed with concern.

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 known. It is currently the subject of intensive research to better understand its mechanisms, chemistry, and functions. The immune system is a large 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.

The lymphatic system, consisting of the thymus, spleen, peripheral lymph nodes, lymph, blood, and cerebrospinal fluid, is the most important component of the immune system, but cells essential to certain immune functions are present in all of the body's active tissues.

Scientists have only recently begun to understand some of the functions of the immune system. Because of this lack of basic knowledge, it is difficult to assess the impact of chemicals on the immune system. One problem is the large number of ways in which the system functions. A chemical may alter only a few of a score of general defense processes. It may be necessary to run a dozen or so different tests to detect these changes. Only a few of these tests can be done outside the body, so it is especially difficult to study altered immune function in humans.

Two additional factors make it difficult to detect altered immune function in humans. First, there are tremendous variations among people in the manner in which their immune systems function. A simple example of this is how people differ in their allergies. Allergic reactions are simply one of the many manifestations of the immune system. Second, most activities of immune function have no

direct external manifestations. We usually cannot assess a person's immune function by simple physical examination. Altered immune function may only be reflected by subtle changes 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 alter the immune function of animals. There are no studies of humans exposed to Agent Orange or similar herbicides that show an adverse effect on the immune system. No systematic studies in which such effects were looked for have been reported. However, there have been no reports of increased allergies or of increased susceptibility to infection, either of which might indicate altered immunity.

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 the weight or appearance of other organs. At even lower doses, TCDD interferes with the capability 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 of animals to infection by bacteria and viruses.

It appears that the ability of TCDD to suppress the immune system is in unborn animals when the TCDD is given to pregnant mothers. 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 <u>stimulated</u> immune function in these children rather than depressing it, as 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 alter immune function in humans.

Chloracne

Chloracne is a skin condition that is known to result from exposure to a group of structurally similar compounds whose common feature is several atoms of chlorine bound to an aromatic hydrocarbon structure. One of these compounds is TCDD. Chloracne, as its name suggests, is a skin condition that, in most cases, appears to be very similar to the common acne that affects teenagers. It usually appears several 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 by confined to the area around the eyes extending along the temples to the ears. In

more severe cases blackheads may appear all over the body. In many cases the blackheads may be accompanied by pus-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; severe cases will persist years after the exposure.

It is well known that chloracne can result from exposure to dioxins. In seven situations where workers were exposed to dioxins as a result of industrial accidents or poor housekeeping practices, many of the workers 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 or other skin conditions 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 on whether chloracne was present among

the workers who were studied. A single report on cancer among herbicide sprayers in Finland indicated that a nationwide effort turned up "a few cases of possible chloracne." One of these cases was diagnosed as chloracne by a physician specializing in skin disorders. On the basis of this isolated report, it would appear that chloracne is not a sensitive indicator of exposure to herbicides like Agent Orange.

Animal studies are of little use in studying the potential of Agent Orange to cause 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. Only monkeys appear to develop a condition that is indistinguishable from human chloracne when they are exposed to TCDD.

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 get chloracne. Thus, whereas chloracne may be a sensitive indicator of exposure to dioxins and mixtures containing dioxins in some people, it may not be in others. The absence of chloracne is not a reliable basis for concluding that someone was not exposed.

Neurobehavioral effects

It has been known for some time that exposure to relatively large amounts of 2,4-D (one of the herbicides in Agent Orange), such as might occur when it is being mixed or sprayed, can cause adverse effects on the nervous systems. 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 loss of feeling or tingling 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 similar results to those seen in humans. These studies suggest that 2,4-D interferes with the transmission of messages from the nerves to the 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, loss of feeling in the hands and feet, muscular weakness particulary 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 posttraumatic 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 symptoms among individuals exposed to Agent Orange. A recent Air Force study of Operation Ranch Hand personnel showed no difference between them 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 tests designed to indicate personality traits, 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 posttraumatic stress, Agent Orange exposure, or both.

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 timing 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 <u>believed</u> 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.

<u>Other toxic effects</u>

Studies of people exposed to Agent Orange or similar herbicide

mixtures have failed to reveal any significant toxic effect 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 the result of large single doses 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. This "appetite regulating system" may have other less dramatic functions in controlling bodily processes and these may be of importance to human health.

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 controlled and that mice with 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 that among humans (who are genetically very diverse compared to experimental animals) there may be a range of susceptibility to the toxic effects of TCDD. This diversity of susceptibility is something of a good news/bad news situation. The good news is that many humans may be relatively resistant to the adverse effects of dioxins. The bad news is that the presence of resistant individuals in a group of people who are being studied for health effects of dioxins may mask the occurrence of severe health effects among a relatively few susceptible individuals within that group. This would increase the difficulty of discovering the adverse health effects of dioxins by studying exposed human populations.

## 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.

The presence of highly toxic dioxin impurities, especially TCDD, may determine the adverse human health effects of Agent Orange and similar herbicide mixtures. There is very little direct evidence that Agent Orange causes adverse health effects in humans, but this may be the result of our inability to identify groups of people with well-defined exposure and to study them properly. The limited evidence available comes from studies of humans exposed to Agent Orange and similar herbicides, from studies of humans exposed to dioxins, and from studies of dioxins in experimental animals. These studies provide some support for the possibility, but do not prove, that exposure to dioxin-contaminated herbicides causes adverse health effects.

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 except in situations where there has been considerable exposure to herbicides heavily contaminated with dioxins. The presence of chloracne does not seem to be a sensitive indicator of exposure to dioxin and 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. Because of insurmountable problems in determining the exact amount and nature of exposure and in choosing appropriate exposed and unexposed groups to examine, however, these studies will never be able to demonstrate conclusively the <u>absence</u> of a toxic effect. The areas in which future studies can provide the most information are the delayed effects of exposure such as cancer.

Studies in experimental animals can still be helpful in elucidating the possible adverse 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. It is unlikely that the adverse health risks associated with exposure to Agent Orange in Vietnam are nearly as widespread as the adverse effects from smoking or chronic alcohol use.

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.