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

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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 pure chemical compound like sodium chloride or sucrose. Instead, the herbicide was a mixture of chemicals, containing equal quantities of the two active ingredients: 2,4-D and 2,4,5-T. 2,4-D and 2,4,5-T are weed-killing chemicals that enjoyed extensive commercial and private use in the United States from the 1950s well into the 1970s. 2,4-D is still used extensively in this country.

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 inadvertantly 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. It is generally accepted that TCDD is one of the contaminating dioxins in 2,4,5-T. It is not known to be present in 2,4-D but other dioxins are.

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 at facilities throughout the United States under contract to the Department of Defense. The Department provided specifications as to the composition of the herbicide such that 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 very little information on how the nature and amount of these impurities varied.

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 around the world. 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 and/or 2,4,5-T.

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 individuals who were exposed during its manufacture or as a result of its use in Vietnam. However, because Agent Orange was considered to be relatively safe at the time of its use, 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 difficult, if not impossible, for individuals to know when they were exposed to Agent Orange specifically. 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 doubtlessly exposed to it, but it is not possible to determine 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 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 approaches are available and all of them have been followed during the last 10-15 years. Each of these approaches has limitations that prevent scientists from reaching 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 highly uncertain. The results of studies which are currently in progress or planned for the future will go a long way in removing this uncertainty, but, for the general reasons described above and for specific reasons described below, it is quite clear that we will 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 Agent Orange 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, lifestyle, and places of residence (difficult to do). A real problem attached to 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, there is a possibility that some individuals in the "unexposed" group have been exposed to the ingredients of Agent Orange.

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 several years later, so the amount of time that has elapsed since most veterans were exposed has been on the order of 10-15 years. Certain adverse health effects e.g., cancer, heart disease, and respiratory disease, that result from exposure to chemicals often take years to develop after exposure begins. Increased cancer rates due to smoking or exposure to toxic chemicals have been shown to reach a peak some 20 to 30 years after exposure. Thus, an absence of evidence

of elevated cancer and heart disease rates in populations exposed to Agent Orange could indicate that these effects are not caused by 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 provided clear-cut answers to questions about the health effects of Agent Orange. 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 necessary, therefore, to ask the question, "Where else do 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. There are a number of these studies 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 on 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 the basis of where the person lived or worked. Also people may be included in the exposed group who worked at a job for only a few weeks or who moved into an area recently.

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 without even knowing it. Either type of error decreases the ability of scientists to detect possible effects of exposure to the chemical.

Another potential source of information about the health effects of Agent Orange is 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 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 the small town of Seveso immediately downwind of the plant. In succeeding weeks many individuals living in Seveso showed signs of dioxin exposure, the most prominent

being chloracne, a severe form of acne which appears as blackheads around the eyes and ears and in some cases covers much of the body. This group of exposed people provides a potentially valuable, though unfortunate, resource for the study of the health effects of dioxin exposure in humans. Unfortunately 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 undergo chemical decomposition. 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 purposes. 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 incapable of showing all but the most severe and widespread effects. It is little wonder that these studies have generally been inconclusive. It is unlikely that future studies designed to study such long-term effects of the accident as cancer and heritable genetic disease will 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 studies in experimental animals. Extreme 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 the chemicals are eliminated. Also differences in body size, diet, lifespan, and the physiology of individual organs may cause animals to respond differently than humans. For these reasons 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 some basis for believing that the test animals are similar to humans in the way they respond to the chemical.

For reasons touched on earlier, Agent Orange was not tested in experimental animals and, because the quantity and identity of the impurities in Agent Orange varied, it cannot be exactly reproduced for studies in experimental animals now or in the future. Therefore, it is 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 the basis for the prediction of human health effects of Agent Orange.

The remainder of this report summarizes the information on 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 VA.

Summary of health effects information

Cancer

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 an increased incidence of skin cancer in the exposed group compared to a comparison 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 study was there any confirmation of exposure nor were matched control groups used for comparison. In one study based on Vietnam veterans who registered with the VA's Agent Orange Registry, there were excess incidences of cancer of the mouth and throat and of lymphoma (cancer of the lymphatic system) when compared to the U.S. white male population as a whole. In the other report, a physician in Atlanta, Georgia 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.

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 2,4-D- or 2,4,5-T-containing herbicides. In the others, the workers were exposed to agricultural chemicals in general, including herbicides. These three studies are not discussed here because of the uncertainty regarding exposure. 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 5 cases of lymphoma with cutaneous (skin) lesions seen in an English hospital. Four of the five cases 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 in one of these there was a slight association with soft-tissue sarcoma.

Of seven studies on populations that were 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 prior to 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 with no control groups. The evidence for dioxin exposure is very weak in the three soft-tissue sarcoma cases.

None of the studies of cancer in humans exposed to Agent Orange, related herbicides, or dioxins provides an answer to the question as to whether Agent Orange might cause cancer in humans. However, when all the reports are taken together certain patterns appear that provide suggestive evidence that exposure to dioxin-contaminated herbicides may lead to an increased incidence of cancer. Thus, seven reports show or suggest a relationship between such exposure and soft-tissue sarcoma. Four reports provide such evidence for 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 strong 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 resulting in 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 (no 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, is sufficiently suggestive to justify continued surveillance of people who have been exposed to dioxin and dioxin-contaminated herbicides in order to confirm or refute the association of increased cancer incidence with that exposure. Such surveillance ought to include cancer of many types, not only soft-tissue sarcoma. This limited evidence is also sufficient to justify limiting future exposure of humans to dioxins (especially TCDD) and dioxin-contaminated mixtures.

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 service by the father in Vietnam. No association was seen, although there was a slightly increased risk of heart defects and Down's syndrome among the children of Vietnam veterans. It should also be recognized that most of the Australian troops who were stationed in Vietnam were assigned to areas in which there was little, if any, herbicide spraying and no Australian troops were directly involved in spraying herbicides.

In the study of Operation Ranch Hand personnel discussed in the cancer section above, there was an increased incidence of spontaneous abortion among the wives of officers in the Ranch Hand group when compared to wives of officers in the control group. There were also increases in deaths of newborn babies and unspecified (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.

Two studies have been reported of men who had been exposed to herbicides similar to Agent Orange. A study of wives and children of herbicide sprayers in New Zealand found 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 minor birth defects, i.e., misshapen 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 there has been heavy use of herbicides similar to Agent Orange. 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 reported that women living in the vicinity of Alsea, Oregon experienced a higher rate of spontaneous abortions than did women living in other regions 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 there was frequent use of herbicides containing 2,4,5-T revealed an increase in the occurrence of club foot in children in the region. Other small and perhaps insignificant increases were

seen in heart defects and malformations of the penis. A study conducted in Hungary looked at the rate of five major birth defects in the general population of the country over a five year period when the use of 2,4,5-T increased greatly in that country. No changes in the rates of these birth defects were seen. This study is not very reassuring when it is considered that most people in the general population were probably not exposed to the herbicide.

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 clear-cut effect on reproductive outcomes. Two of these studies did show a slight increase in spontaneous abortions. Two studies of the population exposed to dioxin as a result of 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 the reliability of these studies is questionable for reasons discussed above.

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. Nevertheless, in two studies, relatively uncontaminated 2,4,5-T and TCDD were fed to both male and female rats and reproductive perfor-

mance 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. Furthermore, numerous studies in which TCDD was given to pregnant females indicate that it is a potent teratogen (an agent that causes birth defects). TCDD causes birth defects in rats, mice, rabbits and monkeys when given by mouth or injection. It also causes an increase in the number of spontaneous abortions and smaller newborn animals.

In summary, no single study of reproduction in humans exposed to Agent Orange conclusively shows an adverse effect. However, when all of the human studies of populations exposed to Agent Orange, similar herbicides, or dioxins are considered together, several of them show or suggest an increase in the number of spontaneous abortions, heart defects, and "minor" birth defects. When this information is considered with the results of studies in experimental animals, especially studies of TCDD, it provides a basis for concern among scientists that adverse reproductive effects may result from exposure 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 other enzymes are capable of acting upon an entire class of chemicals.

It is next to impossible to study the effects of chemicals on enzyme activities in humans. Most enzymes are located in tissues where metabolic activity is greatest, e.g., 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 and/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 herbicidal 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 a number of enzymes in experimental animals. The most well-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 where 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 one 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 indicates that some of the aryl hydrocarbons that are altered by AHH are cancer-causing. Some experiments in animals where TCDD was given to animals several days before the animals were exposed to cancer-causing aryl hydrocarbons 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 these 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 manufacturer 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 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 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 upon exposure to sunlight. Workers who were exposed to dioxins as a result of two industrial accidents developed this condition and an unconfirmed report described a number of these cases among residents of the Seveso area.

The available medical evidence indicates that there are no lasting adverse health effects that result from alterations in porphyrin metabolism. The body adjusts to manufacture sufficient heme to adequately supply the oxygen-carrying needs of the body. PCT is a relatively rare manifestation of changed heme metabolism and may be caused by genetic factors and other external factors, such as alcohol consumption, as well as by dioxin exposure. Also PCT is 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 many of the studies of workmen exposed to dioxins, there were increased levels of fat molecules known as triglycerides in the blood, and these increases were detectable for many years after exposure. High levels of triglycerides in the blood are thought to be associated with heart disease. To date, there is no conclusive evidence of an association

between heart disease and dioxin exposure but heart disease would not be expected to appear until many years after exposure.

It appears that dioxins, though not the active herbicide ingredients 2,4-D and 2,4,5-T, 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 easily defined systems of the body as the cardiovascular system and the digestive system, the "immune system" is not easily defined and is currently the subject of intensive research to better understand its structure and function. The immune system is a large array of processes and mechanisms that serve to defend the body against foreign chemicals, disease-causing bacteria, viruses, foreign cells from outside the body, and abnormal cells from within the body. Various organs and tissues of the body participate in these processes. 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 functions of the immune system, are present in all the active tissues of the body.

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 immune 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 types of 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 capability of their immune systems. A simple example of this is the difference among people in their allergies. Allergic reactions are simply one of the many functions of the immune systems. 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 in humans 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 it is unlikely that effects of chemicals on the immune system will be detected in humans exposed to those chemicals unless they are looked for very carefully.

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. However, no systematic studies in which such effects were looked for have been reported.

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 experimental animals, one of the most common effects 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 sensitivity to the immunosuppressive effects of TCDD is greatest when the animals are still unborn and the TCDD is given to pregnant mothers. Sensitivity decreases in newborns but sig nificant 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. A study has been

described of children who lived in the heavily contaminated area of Seveso. The results of this study showed that these children had higher levels of certain immunologically active components of the blood than did children from uncontaminated areas. Also the body 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 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 ten years after the accident, but this study has not been published and cannot be independently reviewed. Two other studies of workers exposed to dioxins in industrial settings have shown decreased resistance to infection among the exposed workers. These results, taken together, fall far short of providing convincing evidence that dioxin exposure can cause impaired immune function in humans. Nevertheless, the overwhelmingly positive 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 most teenagers. It commonly 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 these blackheads may by confined to the area around the eyes extending along the temples to the ears. In more severe cases blackheads may break out all over the body. In many cases the blackheads may be accompanied by pus-filled cysts and by an increased and/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.

There can be little doubt that chloracne results 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. Most of the epidemiologic studies of occupational groups involved in the spraying of herbicides like Agent Orange are silent on whether or not 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 chloacne 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. TCDD causes skin conditions very similar to chloracne when applied to the ears of rabbits and to the skin of certain types of mice. Scientists disagree, however, as to whether these skin effects are identical to human chlor-

acne. 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 differences in inherited susceptibility. This would explain why some of the workers exposed to dioxins in each of the seven industrial incidents did not have 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 a reflex leg jerk when tapped below the knee and an increase in the amount of time that it takes for nerve impulses to travel from the hands or feet to the spinal column 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 not too great 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 the other herbicide in Agent Orange, i.e. 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 psychiatric abnormalities. Measurement of the speed that nerve messages are transmitted showed that this speed was slowed down 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 notable signs of nervous system damage in experimental animals are higher than those that cause other serious toxic effects. Therefore, scientists have tended to concentrate on the other effects.

The issue as to whether nervous system and psychological effects have been seen in individuals exposed to Agent Orange as a result of the Vietnam experience is unclear and controversial. There is little question that Vietnam veterans experience a high rate of psychological problems with certain symptoms appearing with great frequency. 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. The only evidence in support of this conclusion is that individuals such as prisoners of war and hostages who have undergone sustained stress display similar symptoms. This does not rule out the possibility that Agent Orange or dioxin exposure might cause or exacerbate the condition. 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 Ranch Hand personnel and unexposed controls in terms of several measurements of nervous system function including the speed

of transmission of messages along nerves. 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 these individuals 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 because the diagnoses were subjective. 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.

That self-perception of psychological 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 psychological and emotional problems correlated very closely to how much herbicide the veterans <u>believed</u> they were exposed to whereas the correlation was much weaker when the comparison was to how much herbicide exposure the records showed.

The issue of the effects of Agent Orange on nervous system and psychological 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 the sustained exposure to lesser amounts. Clearly more studies are needed, but, because of the uncertainty regarding the validity of testing methods and the determination of the extent of exposure, it is unlikely that future studies will provide definitive results.

Other Toxic Effects

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 that there is 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 to continue 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 a general wasting of the body. The animals eventually die

of a condition that is very similar to starvation. This effect is the result of large single doses of TCDD and 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 objective 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 great importance to human health. There is much to be learned in this area.

Animal studies have suggested another aspect of the toxicity of TCDD which may have important 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 other animals. 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 whole range of suscepti-

bility to the toxic effects of TCDD. This may explain why many workmen who were exposed to dioxin in industrial accidents never developed chloracne. 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 exposed to dioxins who are being studied for health effects may mask the occurrence of severe health effects among a relatively few susceptible individuals within that group. This will 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? Based on the evidence that is available at the present time 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 PCT in humans. The evidence is quite good that 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 include cancer at several different sites (not limited to soft-tissue sarcoma), spontaneous abortion, certain birth defects, altered enzyme activity, altered porphyrin metabolism, and altered (probably depressed) immune function. Effects for which the available evidence is very inconclusive but which should be the object of further study are neurobehavioral effects (including psychological effects) and heart disease. Chloracne does not seem to be of significant importance except in situations where there has been heavy exposure to herbicides heavily contaminated with dioxins. Scientists should abandon the position that the presence of chloracne is 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 a lot of the uncertainty regarding the health effects of exposure to Agent Orange.

Because of insurmountable problems in determining the exact amount and nature of exposure and in selecting appropriate exposed and unexposed groups to study, however, these studies will never be able to conclusively demonstrate the absence of a toxic effect. The areas in which future studies can provide the most information are in the study of delayed effects of exposure such as cancer and heart disease.

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 achieve 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 except for possible psychological effects. There is no evidence that the psychological 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 effects, enzyme effects, chloracne, and neurobehavioral effects. It is possible that cancer, immune deficiencies, and heart disease may first appear years after exposure. Heart disease can be detected early, and changes in life style can dramatically alter the risks of this disease. Furthermore, factors such as smoking, stress, and lack of exercise are much more likely to play a major role in heart disease, and possibly cancer, than is exposure to dioxin. 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 check-ups, be alert for tell-tale signs of cancer, abstain from smoking, and use alcohol moderately.