Synopsis of Scientific Literature on Phenoxy Herbicides and Associated Dioxins No. 8—(Volumes XVII and XVIII)

Veterans Health Administration
SYNOPSIS OF SCIENTIFIC LITERATURE ON PHENOXY HERBICIDES AND ASSOCIATED DIOXINS NO. 8 – (Volumes XVII and XVIII)

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PREFACE

This synopsis is the eighth in a series of lay language summaries of the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. Synopsis No. 1 of Volumes I–IV was published in July 1985. Subsequent synopses were published as follows:

- October 1985 (Synopsis No. 2 – Volumes V and VI)
- October 1986 (Synopsis No. 3 – Volumes VII and VIII)
- July 1987 (Synopsis No. 4 – Volumes IX and X)
- September 1988 (Synopsis No. 5 – Volumes XI and XII)
- October 1989 (Synopsis No. 6 – Volumes XIII and XIV)
- May 1990 (Synopsis No. 7 – Volumes XV and XVI)

This current synopsis, a review of Volumes XVII and XVIII, continues the effort of the Department of Veterans Affairs (VA) to provide for the general public a summary in laymen’s terms, of the scientific literature published during 1990 related to the possible health effects of exposure to phenoxy herbicides and dioxins.

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1. Introduction

In April 1991, Clement International Corporation, a research firm in Fairfax, Virginia, completed a
review of the literature published during 1990 on the health effects of Agent Orange and related
compounds. A critical review and an annotated bibliography of this literature have been published as
Volumes XVII and XVIII of the ongoing Review of Literature on Herbicides, Including Phenoxy
Herbicides and Associated Dioxins. This synopsis summarizes the important new information that became
available during 1990.

Phenoxy herbicides are a group of structurally related chemicals that have been used in agriculture and
forestry to kill weeds in cultivated crops, to kill unwanted tree species in coniferous forests, and to clear
vegetation from road beds and fence lines. The phenoxy herbicides that have been most frequently used in
the United States are 2,4-D and 2,4,5-T. The latter has not been used in the United States for a number of
years, and its use has been banned in most countries around the world. Another phenoxy herbicide, MCPA,
has been used extensively in Scandinavian countries. Several herbicides were used by the U.S. Air Force in
Vietnam from 1963 to 1971. A major purpose of this operation (known as Operation Ranch Hand) was to
remove leaves from trees in heavily forested areas in order to be able to see enemy troop movements and
supply operations. While several herbicidal preparations were used in this operation, Agent Orange, a
mixture of 2,4-D and 2,4,5-T was, by far, the one used most frequently.

Commercial phenoxy herbicide preparations manufactured from the 1940s until the early 1970s
contained small quantities of contaminating impurities known as chlorinated dibenzo-p-dioxins. The
terms “dioxins” or “dioxin” have frequently been used as shorthand for this family of chemical compounds.
The exact dioxin compounds and the amounts of them that were present in phenoxy herbicide preparations
varied from preparation to preparation and perhaps even from batch to batch. Commercial preparations of
2,4,5-T were known to contain small amounts of one particular “dioxin”, 2,3,7,8-tetrachlorodibenzo-p
-dioxin, which is frequently abbreviated as 2,3,7,8-TCDD or just TCDD. TCDD was present in the Agent
Orange that was used in Vietnam. The effects of TCDD on experimental animals have been extensively
studied; it is believed to be the most toxic member of the dioxin family of compounds and one of the most
toxic chemical compounds known. While 2,4-D contained small quantities of dioxins, TCDD was not one
of them. When it was recognized that phenoxy herbicides were contaminated with dioxins, manufacturing
processes were changed to reduce or eliminate dioxin contamination. Some other herbicidal preparations
that were used in Vietnam contained cacodylic acid and/or picloram. These preparations were used in much
smaller quantities than Agent Orange, however, and they were not contaminated with dioxins.

2. Description of the literature published in 1990

The number of papers about the health effects of phenoxy herbicides and other herbicides used in
Vietnam that were published during 1990 was 333, which is slightly fewer than the year before but above
the average of the last five years. Thus, there has been no decrease in scientific interest in this area of
investigation. Consistent with preceding years, much of the literature described studies of the effects of
dioxins and related compounds in experimental animals because scientists are very interested in learning
the mechanism by which this family of compounds causes the wide variety of toxic effects that it does. At
the same time, the results of a number of studies of possible health effects in humans who may have been
exposed to phenoxy herbicides and/or dioxins were published in 1990. Furthermore, a number of papers were also published describing studies in which the concentration of dioxins in human blood, body fat, and breast milk were measured, and attempts were made to correlate these concentrations with information regarding past exposure to phenoxy herbicides or dioxins.

3. Studies of Vietnam veterans

Much research over the past 10–15 years has addressed the issue as to whether the health of Vietnam veterans has been adversely affected by their service in Vietnam, in general, and by exposure to phenoxy herbicides, in particular. The question of lasting effects of Vietnam service in general is easier to address than that of the effects of herbicide exposure, because it is much easier to determine whether a veteran served in Vietnam than to determine whether he or she was exposed to herbicides while there.

The question of whether there is an association between exposure to herbicides in Vietnam and adverse health effects, especially cancer, is difficult, if not impossible, to answer. One reason is the difficulty of accurately determining individual exposure to herbicides and especially to phenoxy herbicides many years after the war. Another reason is that exposure to herbicides is merely one aspect of military service in Vietnam that might have long lasting health consequences, and it is not possible to separate all the factors. For example, careful analysis of the data on herbicide application missions from Vietnam indicates that the ground troops that were most likely to have been exposed to herbicides during, or just after, their application were the same troops that were most likely to have been involved in combat. The stress of constant exposure to combat situations is thought to be associated with adverse physical health consequences.

How can herbicide exposure be assessed among Vietnam veterans? Three basic approaches have been attempted. The first is to ask Vietnam veterans whether they were sprayed with herbicides. This method is inaccurate for several reasons. First, a number of different chemicals were sprayed in Vietnam, including insecticides, and ground troops had no way of knowing what was being sprayed. Second, a number of independent studies have shown that a veteran’s recall of herbicide exposure is influenced by his/her belief regarding lasting health effects of that exposure, i.e., veterans who do not believe that they are in poor health as a result of herbicide exposure are likely not to remember being exposed even if other objective evidence indicates that they were. Third, significant herbicide exposure could have occurred when troops entered an area that had been sprayed several hours or a day or two earlier. In this case, troops would not have realized that they were exposed.

Another approach to assessing herbicide exposure is to combine records of herbicide application missions with individual service records in order to determine if an individual was in a specific area at the same time that a herbicide application mission took place. This method has been extensively evaluated and has been found to be less than totally reliable. First, service records identify only military units to which individuals were posted and may not reflect numerous details and temporary assignments. Furthermore, unit records are insufficiently detailed to identify the areas in which patrols and small units might have operated and the individuals who participated in such actions. Finally, the accuracy of data on herbicide spray missions are also in question since aircraft often jettisoned the herbicide when they came under enemy fire.
The development of sensitive and specific methodology for the analysis of TCDD and other dioxins in biological specimens such as blood and body fat has provided a new opportunity for assessing herbicide exposure in Vietnam. Since many of the phenoxy herbicides used in Vietnam were contaminated with TCDD, individuals who were exposed might have elevated levels of this compound in their blood. Over the past five years a number of studies have been conducted in which blood samples from Vietnam veterans, from workers who were exposed to dioxins in chemical manufacturing plants, from civilian populations exposed to dioxins as a result of environmental pollution, and from members of the population at large have been analyzed for TCDD. Taken together these studies have provided the basis for the following relatively firm conclusions.

1. A significant portion of the general population of industrialized countries has measurable concentrations of TCDD in their blood even in the absence of known occupational or accidental exposure.

2. A relatively small number of individuals who experienced relatively heavy exposures to phenoxy herbicides or dioxins and related compounds in the past currently have concentrations of TCDD in their blood that are clearly elevated above those found in the population at large.

3. Many individuals who were unquestionably exposed to phenoxy herbicides or dioxins in the past are indistinguishable from the general population in terms of present concentrations of TCDD in their blood. While TCDD can still be measured in their blood, it is not present at concentrations higher than those found in people with no known unusual exposure.

Because of the final conclusion stated above, attempts to identify veterans who were exposed to Agent Orange in Vietnam by measuring the concentration of TCDD in their blood have been disappointing. A number of individual veterans do have elevated levels of TCDD in their blood, but the vast majority of Vietnam veterans, including many who were unquestionably exposed to phenoxy herbicides, have blood TCDD concentrations that are indistinguishable from the general population. A good example is provided by the results of the analysis of blood samples taken from 888 Air Force veterans who participated in the herbicide application program (Operation Ranch Hand) in Vietnam. The concentrations of TCDD in the blood of these veterans were compared to those in blood samples from 856 Air Force veterans who did not participate in Operation Ranch Hand. While the average concentration of TCDD in the blood of Ranch Hand personnel was higher than in the blood of comparison subjects, there was considerable overlap between the groups and some Ranch Hand veterans who had no detectable TCDD in their blood. Since so few Vietnam veterans have clearly elevated concentrations of TCDD in their blood, it is not possible to use elevated blood levels of TCDD as the only criteria for identifying a cohort of herbicide-exposed Vietnam veterans for a health effects study.

Studies of mortality and health status among Vietnam veterans have fairly consistently indicated that there are differences between these individuals and military veterans of the same era who did not serve in Vietnam and between Vietnam veterans and the U.S. population at large. In general, Vietnam veterans believe that they have more health problems than do other veterans and the general population. While there is little evidence that Vietnam veterans are dying at a greater rate than other veterans or the population at large, there is consistent evidence that they are more likely to die from certain causes of death. These include a group of causes such as motor vehicle accidents and homicide that are lumped together as
There is no consistent evidence that Vietnam veterans in general experience more diseases or are more likely to die of any specific disease than other veterans of the U.S. population as a whole.

Most studies of cancer mortality among Vietnam veterans have shown little or no increased risk of cancer. On the other hand, some studies have shown increased risks of some types of cancer associated with military service in Vietnam. For example, an epidemiologic study that was published by scientists at the Veterans Administration in 1988 found significantly increased mortality from two types of cancer, non-Hodgkin's lymphoma and lung cancer, in U.S. Marine veterans of Vietnam but not in U.S. Army veterans. Another study conducted by investigators for the U.S. Centers for Disease Control found that Vietnam veterans were at 50% greater risk of developing non-Hodgkin's lymphoma than were veterans who did not serve in Vietnam. Risks for five other specific cancers, however, were not increased. In contrast to these studies are a number of other studies that have shown no differences between Vietnam veterans and other veterans or the U.S. population at large in terms of risks of cancer.

Three studies of the health status or mortality history of Vietnam veterans were published in 1990. One of these was the second update of an ongoing study of the health status of Operation Ranch Hand personnel who worked with Agent Orange daily. In 1987, 995 Air Force veterans who had been assigned to Operation Ranch Hand were interviewed and underwent a complete physical and medical examination. A comparison group of 1,113 Air Force veterans who served in Vietnam but were not involved in Operation Ranch Hand was studied in the same way. Only a few differences between these groups were seen in objective measures of health status. The only one of these that was of clinical importance was a significantly increased incidence of basal cell carcinoma (a type of cancer) of the skin among the Ranch Hand veterans. This difference had been observed in the two previous studies of the health status of these cohorts so it appears to be a real difference. Because this type of skin cancer is known to be related to exposure to the sun, the scientists conducting this study used two different methods to estimate the amount of exposure to the sun within the study groups. Their analysis indicated that the excess incidence of skin cancers among the Ranch Handers could not be accounted for by differences in exposure to the sun. While herbicide exposure cannot be ruled out as causing or contributing to the excess incidence of skin cancer among Ranch Hand personnel, it is only one of many possible factors that might account for this difference. With respect to other types of cancer, there were no differences between the Ranch Hand and comparison groups. There was one Ranch Hand veteran with non-Hodgkin’s lymphoma compared to none in the comparison group, but this is too few to represent a statistically meaningful difference.

One of the studies mentioned above was a study conducted by the Veterans Administration that showed elevated risks of non-Hodgkin's lymphoma and lung cancer in Marines who were in Vietnam but not in Army veterans. One possible explanation for a difference between Army and Marine veterans was that Marine ground troops in Vietnam were concentrated in only one of four military regions in Vietnam; the one known as I Corps (pronounced "eye core"); whereas Army personnel were evenly distributed throughout Vietnam. It is possible, therefore, that some aspect of military service that was unique to the I Corps region might be associated with an excess risk of cancer. In order to test this hypothesis, VA scientists conducted a new study in which they compared cancer mortality among only those Army veterans who served in I Corps to cancer mortality among Army veterans of the same era who did not serve in Vietnam. The results of this study did not support the hypothesis. Cancer mortality was lower in I Corps Army veterans than in non-Vietnam veterans, and the risks of non-Hodgkin’s lymphoma and lung cancer were not elevated. Furthermore, the authors reexamined the data from the earlier study. They reported that
the apparent elevation in the risk of these two types of cancer among Marines was not the result of an elevated mortality from these cancers among Marine Vietnam veterans; they concluded that it was the result of a lower than expected mortality from these two types of cancer among Marine veterans of the same era who did not serve in Vietnam. Thus, it is unlikely that there is any association between increased risks of non-Hodgkin’s lymphoma or lung cancer and exposure to herbicides in Vietnam.

There was another group of military personnel in Vietnam who may have experienced significant exposure to phenoxy herbicides. The U.S. Army Chemical Corps, while not involved in Operation Ranch Hand, did participate in missions in which herbicides, including Agent Orange, were applied by helicopter to kill vegetation around U.S. military installations. VA scientists published the results of a study of cancer incidence and mortality among 894 men who served in the Army Chemical Corps in Vietnam between 1965 and 1971. Cancer mortality in the Chemical Corps cohort was not different from what might be expected in the U.S. population at large; there were no deaths from types of cancer that had previously been suggested as being associated with herbicide exposure such as non-Hodgkin’s lymphoma or soft-tissue sarcoma. Two deaths each from brain cancer and leukemia were unusual, but these cancers have not previously been associated with herbicide exposure or the Vietnam experience in general. Of some note was the finding of two cases of Hodgkin’s disease among living members of the cohort when less than one would have been expected. The small size of the cohort in this study and the probability that Chemical Corps personnel were exposed to a number of different chemical agents do not allow one to reach any conclusions regarding a possible cause-and-effect relationship between cancer and herbicide exposure.

4. Cancer

The question of a possible association between cancer and exposure to phenoxy herbicides has been addressed over a number of years by studies of workers who may have been exposed to these compounds during their application in agriculture, forestry, and highway and railroad maintenance. Over the past 10 years, more than 50 publications in the scientific literature have described approximately 30 epidemiologic studies relevant to this question. These have included all types of epidemiologic approaches including proportionate mortality, historical cohort studies, and case-control studies. These studies have been conducted in the United States, the United Kingdom, Canada, Sweden, Finland, Italy, and New Zealand. When examined as a group these studies have been inconsistent in showing an association between herbicide exposure and the risk of cancer, in general, and the risk of any specific type of cancer, in particular. For example, several case-control studies conducted in Sweden have shown an association between exposure to phenoxy herbicides and an increased risk of soft-tissue sarcoma, but several large cohort studies in Sweden and several case-control studies in the United States and New Zealand have failed to find such an association. Likewise, case-control studies in the United States and Sweden have suggested an association between exposure to phenoxy herbicides and non-Hodgkin’s lymphoma, but studies in Sweden, the United States, and New Zealand have failed to provide any evidence of such an association. Attempts to explain the apparent inconsistencies among these studies have been largely unsuccessful, because no two studies are exactly the same and any number of minor methodological variants might account for the differences. One noteworthy aspect of literature published during 1990 was that several authors published in-depth review articles in which they compiled all of the epidemiologic evidence regarding these possible associations. It is not surprising that each of the authors reached slightly different conclusions regarding the interpretation of the accumulated evidence.
An additional complication in the assessment of potential associations between herbicide exposure and cancer in agricultural workers is the fairly consistent finding that, while farmers as a group are at lower risk of dying of cancer than is the general population, they appear to be at a higher risk of dying of specific types of cancer. Such specific cancers include cancer of the lymphatic system, in general, and non-Hodgkin's lymphoma, in particular. It is possible that this increased risk might be due to exposure to herbicides, but several studies that found an increased risk of non-Hodgkin's lymphoma in farmers did not find an association with herbicide used by those farmers. There are any number of unique exposures experienced by farmers including exposure to a wide range of agricultural chemicals and to a number of plant and animal pathogens. Thus, it is very difficult to design an epidemiologic study that could examine the possible association between herbicides and cancer and that would rule out the involvement of these other agricultural exposures.

A number of studies were published during 1990 in which possible associations between cancer and occupational exposure to phenoxy herbicides were examined. Three different studies of cancer in farmers in Nebraska, Saskatchewan, and Sweden were interpreted by their authors as demonstrating an association between non-Hodgkin's lymphoma and exposure to phenoxy herbicides. A fourth study conducted in Italy showed an association between non-Hodgkin's lymphoma and farming, but exposure to specific herbicides was not assessed in this study. Two more studies, both conducted in Sweden were interpreted by their authors as indicating an association between exposure to herbicides including phenoxy herbicide and soft-tissue sarcoma. A strong case can be made, however, that none of these studies shows what the authors claim. The determination of herbicide exposure was indirect and unreliable in all of them. Furthermore, other exposures associated with agricultural occupations could not be ruled out as playing a role. In fact, in several studies it appeared that other factors were more important in determining the risk of cancer than was exposure to herbicides. In one study the reported association did not even meet the criteria for statistical significance. Thus, while these studies provide some additional support for the hypothetical association between exposure to phenoxy herbicides and an increased risk for non-Hodgkin's lymphoma and, perhaps, soft-tissue sarcoma, that support is very weak.

Perhaps the two most significant papers published in 1990 and early 1991 presented the results of cohort mortality studies of workers in the United States and Germany who were exposed to dioxins in the workplace while employed at factories where chlorinated phenols and/or phenoxy herbicides were manufactured. The study of dioxin-exposed workers in the United States, conducted by the National Institute for Occupational Safety and Health (NIOSH), has been in progress for a number of years. The objective of this study when it was begun was to identify all workers in the United States with significant occupational exposure to dioxins and to determine mortality and health status within this cohort. The results published in January 1991 reflect the results of the mortality portion of that study.

The NIOSH investigators identified a cohort of 5,172 male workers at 12 facilities in 11 states. As of December 31, 1987, 1,052 of these workers had died; the cause of death was identified for 1,037. Death rates from specific causes within this group were compared to those that might be expected if the cohort was the same as the U.S. male population at large. The total number of deaths among these workers was almost exactly what would be expected for the general population. For causes of death other than cancer, there were significantly fewer deaths from diseases of the digestive system (specifically cirrhosis of the liver) and significantly more deaths from accidental causes than would be expected. The number of cancer deaths in the cohort was significantly larger than would be expected from data for the general population. This excess risk of cancer was even greater among workers who had been exposed to dioxins for more than a year and...
whose first exposure occurred at least 20 years before the study was conducted. Within the total cohort there did not seem to be any specific type of cancer that accounted for the excess mortality. Rather, mortality rates for a number of cancers were greater than expected, but only the rate for cancers of “other and unspecified” sites was significantly different from the expected rate. This category is simply a catch-all classification for a number of rare cancers that do not fit into other categories.

In the subcohort consisting of workers who had been exposed for more than a year beginning more than 20 years before the study, there was a significant excess in mortality from soft-tissue sarcomas, the same type of cancer that had been found to be associated with phenoxy herbicide and chlorinated phenol exposure in four studies in Sweden. Also, mortality due to Hodgkin’s disease and cancer of the stomach was higher in this group than in the total cohort, although these differences were not statistically significant.

The authors of this study concluded: “Although the study could not completely exclude the possible contribution of other occupational carcinogens or smoking, the increased mortality, especially in the subcohort with one year or more of exposure is consistent with the status of TCDD as a carcinogen.” The authors did qualify their conclusions slightly by suggesting that the excess risk of cancer was smaller than would have been predicted on the basis of other epidemiologic studies and studies in experimental animals. In support of this argument they cited data on the concentration of TCDD in blood samples taken from 119 workers in the cohort, which were clearly elevated compared to the general population. They concluded, therefore, that the cohort had experienced very heavy exposure. While there can be no question that some and perhaps many of the exposed workers were heavily exposed to dioxins, the median duration of exposure to dioxins in the cohort was less than one year, and a small but significant portion of the cohort had concentrations of TCDD in their blood that was comparable to the population at large.

In an editorial that accompanied the publication of the NIOSH study, John C. Bailar, III, M.D., Ph.D., a respected public health scientist, characterized the results of the NIOSH study as being entirely consistent with the results of other epidemiologic studies and studies in experimental animals that had indicated that TCDD causes cancer. Also, the fact that cancer was increased at a number of sites rather than at one or two specific sites was consistent with the role of TCDD as a promoter rather than as an initiator of the carcinogenic response. He also noted that the estimated quantitative relationship between degree of exposure and the increased risk of cancer was within the range that might be expected on the basis of animal studies.

In 1953 an accident at a chemical plant in Ludwigshaven, Germany resulted in the release of large quantities of dioxins and related compounds inside the plant. Many of the workers who were employed at the plant at the time developed chloracne. This development stimulated the research that led to the “discovery” of TCDD and the realization that it caused chloracne. Since the accident, a number of epidemiologic studies have been conducted among workers from the plant. In recent years conflicting approaches to the conduct and interpretation of the study have generated a great deal of controversy. At the heart of the controversy has been the question of how many workers were exposed to dioxins and to whom they should be compared.

The most recent study of workers from this plant was published in 1990. This study was sponsored and conducted by the company that owns the plant and was clearly designed to put to rest the various criticisms.
of earlier studies. Using a variety of sources, including extensive interviews with employees who worked at
the plant at the time of the accident and for several years after, the authors identified a total cohort of 247
persons who may have been exposed to dioxins. This is over 100 more workers than had been included in
any previous study of this cohort. The total cohort of 247 was divided into three subcohorts reflecting the
probably intensity of exposure. Blood samples were drawn and analyzed for TCDD. These results
correlated well both with the employment history and with the history of chloracne within the three
subcohorts. Mortality within the total cohort and in the three subcohorts was compared to that expected
within the population of Germany at large.

Mortality rates from all causes in the total cohort and in each of the three subcohorts were just what
would be expected for the population at large. Mortality from cancer, on the other hand, was higher than
expected in the two subcohorts with the greatest probability of exposure and was significantly elevated
among workers who had been exposed to dioxins at least 20 years before the time of the study. There was
also a significant excess of deaths of cancer among workers with a history of chloracne who were exposed to
dioxins more than 20 years earlier. These results clearly demonstrated a dose–response relationship, which
adds considerably to their validity. As in the NIOSH study, there was no specific type of cancer that
accounted for the overall increase in cancer. Rather, cancers at several sites were increased. One interesting
difference between this study and the NIOSH study was that no soft–tissue sarcomas have ever been found
in the German workers.

The German study is not directly comparable to the NIOSH study. The total cohort is less than 5% of the
NIOSH cohort. Only very dramatic differences in cause–specific mortality could be detected in such a
small group. Nevertheless, these two studies are quite consistent in showing increased risks of cancer
among dioxin–exposed workers especially among workers who were relatively heavily exposed (probably
as the result of industrial accidents) more than 20 years ago.

The lack of clear evidence that any single type of cancer is responsible for the overall increased risk has
two important implications. One is that TCDD is probably acting as a promoter rather than an initiator of
the carcinogenic process. Second, future studies that focus on the relationship between dioxin exposure and
cancer risk should look at overall cancer rates rather than at site–specific cancers.

5. Genetic effects

Extensive testing of TCDD and related compounds over the last 10–20 years in various strains of
bacteria, in animal and human cells in culture, and in whole experimental animals has indicated that these
compounds do not cause gene mutations or otherwise directly damage DNA. Less extensive testing
indicates that the same is true for phenoxy herbicides. There is no reliable evidence of genetic damage from
studies of humans exposed to phenoxy herbicides and/or their dioxin impurities. On the other hand, some
studies in experimental animals have suggested that TCDD can cause damage, other than mutations, in
chromosomes. No such effects have been observed in humans. Thus, the relevance of the results in animals
for human health is questionable.

No studies of the potential genetic effects of either phenoxy herbicides or dioxins in humans were
published in 1990. Only a few studies of the potential genetic effects of phenoxy herbicides or dioxins in
experimental animals were published. None of these produced evidence of a clear-cut relationship between the treatment and genetic damage that might result in clinically significant effects.

6. Reproductive effects

The question of whether exposure to phenoxy herbicides or their dioxin impurities cause adverse reproductive effects is complex. The cumulative weight of the evidence gathered over a number of years provides few definitive answers. What can be concluded with a fair degree of certainty is that exposure of female experimental animals to relatively small amounts of TCDD and related compounds during a critical period of pregnancy causes developmental deficits (decreased ability to learn) in newborn offspring. Exposure of pregnant females to slightly larger amounts can cause frank birth defects. Finally, exposure of female animals to even greater amounts of TCDD prior to mating and during pregnancy can prevent conception or cause spontaneous abortions and fetal death. Studies of women in Taiwan and Japan who were exposed to cooking oil that was contaminated with chlorinated dibenzofurans provides additional evidence that this class of compounds can cause delayed development and other adverse reproductive effects in humans. Thus, it can be safely concluded that TCDD and related compounds probably cause adverse reproductive effects when women are exposed to a sufficient amount before and/or during pregnancy.

Three questions remain for which the answers are not nearly so clear. Are women and fetuses who are exposed to phenoxy herbicides at risk of adverse reproductive effects? Do TCDD and related compounds cause adverse reproductive outcomes when males are exposed before mating with unexposed females? Are males who are exposed to phenoxy herbicides more likely to have reproductive problems or to father defective offspring than unexposed males?

With regard to the first question, a number of studies in experimental animals have indicated that exposure of female animals to the herbicidal active ingredients, 2,4-D or 2,4,5-T, does not interfere with the ability to get pregnant nor does it cause birth defects. Only a few studies have been conducted in which reproductive outcomes were assessed among females who may have been exposed to phenoxy herbicides. Because of methodological problems these studies neither confirm nor deny that such an association exists.

A number of studies have been published over the last ten years in which the authors conclude that there is a correlation between a large number of adverse reproductive consequences, including spontaneous abortions and birth defects, and exposure of civilian Vietnamese women to herbicides during the war in that country. One such study was published in 1990. Reproductive outcomes in three different villages (two sprayed and one not) were compared. The authors of this study, like the authors of earlier studies, concluded that there were more adverse reproductive outcomes in the sprayed villages than in the village that was not sprayed. Three deficiencies common to all of these studies cast serious doubt on the validity of the conclusions reached by the authors. First, there is no information on the historical incidences of birth defects and other adverse reproductive outcomes in Vietnam. It is, therefore, not possible to tell whether these effects occurred more frequently in the years since the war ended than they did before the war. Second, there is no objective means of confirming that a woman or group of women were exposed to Agent Orange or other herbicides during the war. Finally, a number of differences other than herbicide exposure exist between women of different geographical regions; any or many of these could account for differences
in reproductive outcomes. These studies, then, are not sufficient to support a conclusion that adverse reproductive outcomes in Vietnam are the result of exposure of the civilian population to herbicides during the war in that country.

The question of whether males who have been exposed to phenoxy herbicides or dioxins are at an increased risk of fathering defective offspring or are less fertile than unexposed males is very difficult to answer based on the available evidence. Only a few studies in humans have systematically examined this issue, and they have provided negative or equivocal results. A study summarized in last year’s volumes of this review found no evidence of an association between spontaneous abortions and a history of military service in Vietnam by the father. This study was extended, and the results were published in 1990. The authors found a slightly increased risk of congenital anomalies among children fathered by men who served in Vietnam, but the increase was not statistically significant. In contrast, the ongoing study of Ranch Hand personnel has revealed no consistent evidence of adverse reproductive effects.

Few experimental studies of the reproductive effects of phenoxy herbicides or dioxins in males have been published. Several studies have shown that relatively large doses of TCDD decrease testosterone levels, interfere with sperm formation, and cause testicular atrophy in male animals. However, studies in which males were treated with doses of TCDD that did not interfere with sperm production and subsequently were mated with untreated females have provided no consistent evidence of adverse effects. Thus, the limited experimental evidence available suggests that exposure of male animals to dioxin does not cause defects in their offspring.

7. Effects on the immune system

The available evidence from studies of exposed humans and of experimental animals indicates that the phenoxy herbicides do not affect the immune system, but many studies have indicated that dioxin can alter and interfere with the immune system in experimental animals. Studies of humans exposed to dioxins have not shown changed immune function. Some investigators, however, have observed changes in the relative numbers of different types of white blood cells in blood from humans who have been exposed to dioxins. These white blood cells play a major role in the immune system. Many investigators believe that a change in the proportions of these cells represents a change in immune status, although they have been unsuccessful in demonstrating a health effect due to alteration in immune function associated with these changes. It is important to recognize, in evaluating the possible immune effects of dioxins in humans, that scientific understanding of the functions of the immune system is primitive compared to our understanding of many other physiologic functions of the body. Furthermore, studies of immune status and function are generally not included in routine physical and medical examinations. Ordinarily, indicators of immune status are only investigated in humans when there is some clinical evidence of changed immune function. Thus, over the years, most of the studies of people exposed to dioxin in the workplace or from environmental contamination have not included specific tests for immune function.

Health studies of Air Force personnel who were involved in Operation Ranch Hand in Vietnam have included tests designed to detect effects on the immune system. These tests have consistently failed to show significant differences between the Ranch Hand cohort and their comparison group. In the most recent follow-up study published in 1990, the relative proportions of the different white blood cells were
measured in the cohort and in the comparison group, and no differences were noted between the two groups. During this follow-up no tests of immune function were conducted, but changes in the white blood cells’ proportions are considered to be more sensitive indicators of immune effects than tests of immune function. Furthermore, tests of immune function in the baseline study and the first follow-up of Ranch Hand personnel failed to reveal any effects.

In the only other study published in 1990 on potential immune effects of phenoxy herbicides or their dioxin impurities in exposed humans, 30 farmers who had developed allergies to pesticides were tested to identify the specific pesticides to which they were allergic. Three of the 30 tested positive for allergy to the phenoxy herbicide 2,4-D. Two of the three were allergic to other pesticides as well. The small fraction of farmers who reacted to 2,4-D is an indication that it is not a potent allergen. Furthermore, the allergic reactions seen in three farmers could have been generated by some inactive component of the formulation used, and not specifically by 2,4-D.

No experimental studies of the immune effects of phenoxy herbicides were published in 1990. A number of papers were published describing studies of the immune effects of dioxins in experimental animals.Taken together, these studies indicate that much more research is needed before we begin to have a clear understanding of how this class of compounds affects the immune system. The complexity of the issue is illustrated by the fact that dioxins affect many separate functions of the immune system. Different studies suggest that TCDD may both inhibit and stimulate immune function depending on the degree of exposure, the route of exposure, and the species tested. Fetal and newborn animals are much more sensitive to some of the immune effects of TCDD than are adult animals. While very low doses of TCDD appear to alter the relative proportions of immunologically active white blood cells in humans and monkeys, rats and mice seem much less sensitive to this effect. Thus, while it is clear that dioxins can cause numerous changes in the immune system, especially in experimental animals, the significance of these findings for human health is far from clear.

8. Other effects

While other potential toxic effects of phenoxy herbicides and their dioxin impurities have been identified and investigated, the literature published over the last several years clearly indicates that the potential human health effects of most concern are those discussed above, namely cancer, adverse reproductive effects, and alterations in the immune system. The literature published during 1990 contained very few studies of other potential toxic effects in humans. Two studies were published in which chloracne was the toxic effect of interest. One of these was a case report of a family in Spain that became ill after consuming cooking oil that had been contaminated with dioxins and furans. Both parents and all six children developed chloracne. In the other study, 47 cases of chloracne were diagnosed among employees of a factory where pentachlorophenol was manufactured. The significance of this finding is that these workers were unlikely to have been exposed to TCDD, per se. The dioxins in pentachlorophenol are what are referred to as more highly chlorinated dioxins. Thus, these dioxins are also capable of causing chloracne.

Several papers published during 1990 described cases in which humans deliberately drank phenoxy herbicides, primarily 2,4-D, in attempting suicide. In general these papers, supported earlier findings that
indicate that relatively large quantities of 2,4-D are required to cause death and that the primary target system for the toxic effects of 2,4-D is the central nervous system. Aggressive treatment of the cases described resulted in complete recovery without apparent lasting consequences for most of the victims.

9. Dioxins in human tissues

A topic of intense research interest over the past five years has been the relationship between concentrations of TCDD in blood, body fat, or breast milk and past exposure to dioxins and/or phenoxy herbicide preparations that contained dioxins. As has already been indicated in the discussion of human health studies above, a number of papers published during 1990 contained additional information on this topic. In general, these papers provided additional support for conclusions that had been reached on the basis of earlier studies. Air Force veterans who participated in Operation Ranch Hand in Vietnam, workers who were exposed to dioxins in 12 different chemical manufacturing plants in the United States, and workers who were exposed to dioxins as a result of a process accident in a German chemical company have higher levels of dioxins in their blood 20–30 years after exposure than do unexposed controls. Likewise, members of the general population living in areas where there is environmental contamination with dioxins, such as certain parts of Missouri, industrialized nations of Europe, and areas of South Vietnam that were sprayed with Agent Orange, have higher body burdens of dioxin in general than individuals living in more isolated areas of the world. At the same time, however, there is clearly a great deal of variability among individuals in how much dioxin they tend to absorb and how quickly it is eliminated from the body. Thus, some people who were unquestionably heavily exposed to dioxins in the past have blood concentrations in the "normal" range, whereas other individuals with little or no known exposure have elevated concentrations. While the determination of average concentrations of TCDD in the blood may be useful for identifying groups of people with unusually heavy exposure in the past, the measurement of the TCDD level in an individual's blood is not reliable for deciding whether or not that individual has been exposed.

10. Basic research on the mechanism of dioxin toxicity

As has been true for a number of years, a large proportion of the scientific literature published during 1990 described basic research on the mechanism by which TCDD and closely related compounds cause toxic effects in experimental animals. Individually, each of these studies has little relevance for identifying potential human health effects. Collectively, however, they have helped to provide a basis for better design and interpretation of human health studies. Two examples are the growing recognition that TCDD may act as a promoter, rather than an initiator, of the carcinogenic process, and the development of a better understanding of the effects of TCDD on the immune system.

One area of basic research that has received considerable attention during the last two years, and was the subject of numerous publications during 1990, is the growing awareness that TCDD possesses antiestrogenic activity in a number of experimental models. Thus, for example, treatment of cultures of estrogen-dependent human breast cancer cells with TCDD results in an inhibition or even a complete stoppage of growth of these cells. The mechanism by which TCDD alters estrogen responses in various tissues has been the subject of considerable research but has not yet been clearly identified.
Basic research over a period of years and continuing through the present has indicated that many of the
effects of TCDD and related compounds seen in experimental animals require the binding of these
compounds to a specific protein receptor in cells. The resulting combination of TCDD and the receptor then
interacts with genetic material (DNA) in the nucleus of the cell to “switch on” or “switch off” a series of
processes that control the function and regulation of the cell. Many researchers believe that TCDD
promotes cancer and induces birth defects in experimental animals by changing the way cells regulate their
growth. While there is general agreement among scientists that the general mechanism described here is
responsible for some of the effects of TCDD, there is growing controversy and disagreement about whether
this mechanism operates in all, most, or only a few of the effects. This debate has practical implications in
that the mechanism determines the choice of model that some scientists and regulatory officials use to
predict human health risks from experiments in animals. It appears, therefore, that basic research into the
mechanism by which dioxins exert their toxic effects will continue at its current level for the foreseeable
future.

11. Summary and conclusions

Clearly, the most important research results relevant to the potential human health effects of phenoxy
herbicides and dioxins to become available during 1990 was the finding of a significantly increased risk of
cancer among men who were occupationally exposed to relatively large amounts of dioxins more than 20
years ago. Two independent studies suggested that the degree of risk was related to the intensity of the
original exposure. That no specific type of cancer accounted for the increased risk of cancer overall is
consistent with the results of studies in experimental animals which indicate that dioxins promote cancer,
rather than initiate it.

In contrast to studies of dioxin–exposed workers, additional studies of cancer among Vietnam veterans
and among workers who were exposed to phenoxy herbicides during their application were either negative
or equivocal. Studies of Vietnam veterans found no increased risk of cancer except for sun–related skin
cancers among Air Force personnel who participated in Operation Ranch Hand. Some studies of farmers
and other occupational groups who may have been exposed to phenoxy herbicides during application were
interpreted by their authors as indicating associations between herbicide exposure and increased risks of
non–Hodgkin’s lymphoma and soft–tissue sarcoma. These conclusions are open to question on a number of
grounds, however, and the question regarding the cause of increased risks of non–Hodgkin’s lymphoma
among farmers remains unanswered.

Studies published during 1990 provided no convincing evidence for the existence of an association
between exposure of males to phenoxy herbicides or dioxins and adverse reproductive outcomes.
Furthermore, no studies of exposed humans were published that provided evidence of heretofore
unidentified toxic effects from exposure to these compounds.

Many questions remain regarding the potential human health effect of phenoxy herbicides and their
dioxin impurities. These include potential effects of these compounds on the immune system and on
hormone regulations. Also, questions regarding the mechanism by which dioxins cause many toxic effects
in experimental animals must be resolved in order to use animal models as a basis for predicting human
health risks from exposure to these compounds.