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Synopsis of Scientific Literature on Phenoxy Herbicides and Associated Dioxins

No. 2 - (Volumes V and VI)

Department of
Medicine and Surgery

VA CONTRACT NO: V101(93)P-953

SYNOPSIS OF SCIENTIFIC LITERATURE ON PHENOXY HERBICIDES AND ASSOCIATED DIOXINS

No. 2 - (Volumes V and VI)

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PREFACE

This synopsis is the second in a series of lay language summaries of the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. The synopsis of Volumes I-IV was published in July 1985.

This current synopsis, a review of Volumes V and VI, continues the efforts of the Veterans Administration to provide for the general public a summary in laymen's terms, of the scientific literature published during 1984 related to the possible health effects of exposure to phenoxy herbicides and dioxins.

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

ACKNOWLEDGEMENTS

Publication of Synopsis No. 2, which provides a lay-language summary of Volumes V and VI of the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins,* is largely a reflection of the efforts of those individuals within the Department of Medicine and Surgery's Agent Orange Projects Office (AOPO) who were involved in its development. Preparation and distribution of Synopsis No. 1 and of the six-volume series upon which these two synopses are based, is due largely to the professionalism and perseverance of the following VA (AOPO) staff: Dr. Lawrence B. Hobson, Deputy Director; Mr. Layne A. Drash, Chief, Administrative Section; and Mr. Donald J. Rosenblum, Staff Assistant. Without the high caliber clerical support provided by Mrs. Paula Piersall and Mrs. Laverne Cooper, it would not have been possible to prepare the manuscripts for publication.

Special recognition is given to Mrs. Elaine Morrow, Budget Analyst, Administrative Section, for her unique contribution as "in-house editor," proof-reader and publications control officer responsible for the myriad and complex tasks associated with the final preparation of this publication and of the entire literature update series.

The VA also gratefully recognizes the efforts of the staff of Clement Associates, Inc., the contractor responsible for the preparation of the manuscripts of these synopses as well as Volumes III - VI of the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins.* Mr. Wayne D. Reichardt, Vice President, Life Sciences, and Dr. Carl O. Schulz, Senior Toxicology Advisor and principal scientist for this effort, are deserving of special mention.

BARCLAY M. SHEPARD, M.D.

CONTENTS

1. Introduction

In May of 1985, Clement Associates, Inc., a research firm in Arlington, Virginia, completed a review of the literature published during 1984 relevant to the health effects of Agent Orange and related compounds. A critical review and an annotated bibliography of this literature have been published as Volumes V and VI of the ongoing *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins.* The present synopsis summarizes for nonscientists the key new information that became available during 1984.

Phenoxy herbicides are a group of structurally related chemicals that have been used as herbicides to kill plants and trees. Historically, the most frequently used of these have been 2,4-D and 2,4,5-T. Several herbicidal preparations were used during the military action in Vietnam from 1963 to 1971 primarily to defoliate jungle areas. The herbicide spraying operation conducted by the U.S. Air Force was known as Operation Ranch Hand. Agent Orange, a 50:50 mixture of 2,4-D and 2,4,5-T, was the herbicide that was used most frequently during this period. Commercial phenoxy herbicides manufactured in the past contained small and variable quantities of contaminating impurities known as chlorinated dibenzodioxins. The term "dioxins" has frequently been used as a shorthand term for these compounds. One of these dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), is known to have been present in very small amounts in the 2,4,5-T portion of the Agent Orange used in Vietnam. It was not present in 2,4-D. The effects of TCDD have been extensively studied in experimental animals. Some other herbicides that were used in Vietnam but in much smaller quantities were cacodylic acid and picloram. These were not contaminated with dioxins.

2. How much information was published during 1984?

Approximately 250 new documents relevant to the health effects of phenoxy herbicides and their impurities became available during 1984. Of these documents about a third describe results that have already been published elsewhere (secondary references). The rest are reports of new studies of the effects of phenoxy herbicides and/or their dioxin impurities in humans or experimental animals. More than half of these reports of original research describe studies of the way in which TCDD causes specific effects in experimental animals. These studies are very helpful to scientists in the development of an understanding of how TCDD may affect human health but, because there are still major gaps in our knowledge of how to transfer information from animals to humans, these studies are of limited use in adding to our present knowledge of the human health effects of exposure to dioxins including TCDD.

Thus, about 50 new documents that became available in 1984 contain the results of studies that are directly relevant to the human health effects of exposure to phenoxy herbicides and their associated dioxin impurities or to cacodylic acid or picloram. A majority of these reports describe studies of humans who were exposed either to phenoxy herbicides or to mixtures of dioxins including TCDD. The results of these studies are discussed in the remainder of this report.

3. Cohort epidemiology studies

Many of the studies of humans who were probably exposed to phenoxy herbicides or dioxins are designed to reveal a single or very few health effects. These studies are discussed below under the specific health effects. One type of epidemiology study, however, involves the identification of a group of exposed people and a comparison group of unexposed people and compares the incidence of numerous diseases or conditions between the groups to determine if there are any differences. Several studies of this type were published during 1984. One was a study of causes of death among Australian servicemen who had served in Vietnam. There were three studies of workers who had probably been exposed to dioxins including TCDD during the manufacture of 2,4,5-T and/or trichlorophenol. One was a study of people who lived in an area that had been contaminated with TCDD.

The Australian Vietnam Veterans Mortality Study identified all 46,166 Australian servicemen who enlisted between 1965 and 1971 and who served for more than 90 days. These servicemen were then divided into two groups, 19,206 men who had served in Vietnam and 26,960 who had not served in Vietnam. For each of the men who had died up to the time of the study the cause of death was determined. Overall death rates and the proportion of deaths attributed to specific causes were compared between the two groups and between each group and the overall male population of Australia as determined from national health statistics. Further analyses were conducted by comparing Vietnam veterans to non-Vietnam veterans within specific service corps, e.g., engineers.

The proportion of deaths among Vietnam veterans was significantly higher than that among non-Vietnam veterans. However, most of these excess deaths were due to external causes, such as accidents. When analyzed by service corps, almost all of the excess deaths among Vietnam veterans were found in the Royal Australian Engineers, a group who were less likely to have been exposed to Agent Orange than other groups such as the infantry. The numbers of deaths among the Vietnam veterans as well as the non-Vietnam veterans were significantly lower than would be predicted from statistics for the Australian male population at large, confirming the observation in several countries that veterans are healthier, on average, than their non-veteran counterparts.

When analyzed by specific causes of death, there were only a few differences between Vietnam veterans and non-Vietnam veterans. The percentages of deaths due to all forms of cancer were the same in Vietnam veterans and non-Vietnam veterans and were similar to those predicted on the basis of national statistics. There were two deaths due to soft-tissue sarcomas among Vietnam veterans versus none in non-Vietnam veterans. There were three deaths due to non-Hodgkin's lymphoma among Vietnam veterans versus four in non-Vietnam veterans. These numbers are too small to permit any meaningful statistical analysis.

The proportion of deaths from circulatory diseases, digestive diseases, and external causes, e.g., accidents, were higher in Vietnam veterans than in non-Vietnam veterans. However, for all three of these causes, the rates in Vietnam veterans were similar to those predicted from

national health statistics whereas the rates in non-Vietnam veterans were unusually low.

Overall, the results of this study indicated that there was no meaningful difference in mortality between Vietnam and non-Vietnam veterans in Australia. The implications of this finding, however, are limited by several factors. First, this group of veterans is still relatively young, and the small number of deaths preclude detection of all but the most dramatic alterations in cause-specific mortality. Second, the maximal length of time between service in Vietnam and death was 16 years. A rise in death rates due to cancer is generally not detected until at least 15 years after exposure to cancer-causing chemicals. Finally, Australian servicemen did not participate in the use of dioxin-contaminated herbicides in Vietnam. Australian ground troops were, on average, less likely to be in areas where Agent Orange was used than were U.S. troops.

One of the three studies of people exposed to dioxins in the workplace was a survey of the health status of workers from the Dow Chemical plant in Midland, Michigan. The cohort consisted of 204 men who worked in the manufacture of 2,4,5-T for at least one month between 1950 and 1971 and 61 men who were employed in trichlorophenol production in 1964 when there was an accidental release of chlorinated dioxins including TCDD at the facility. The health of these individuals, as determined by a questionnaire and a physical examination, was compared to that of another group of workers from the same company who had not been exposed to TCDD or other chemicals known to cause cancer in humans.

Analysis of the questionnaires indicated a significantly higher incidence of ulcers among the exposed workers compared to nonexposed workers. The data from the physical examinations revealed that exposed workers were more likely to have a disease of the digestive system than workers in the control group. There was no difference between the two groups in the occurrence of cancer or in any other measures of health status. The results of this study, however, may not represent accurately the health status of workers at the plant because only 114 of the 265 exposed workers completed the questionnaire, and only 183 underwent physical examinations.

Two more studies of people who may have been exposed to dioxins in the workplace were surveys of health effects among workers from a Monsanto plant in Nitro, West Virginia. 2,4,5-T was one of a number of chemicals manufactured at this plant from 1948 to 1969. Many of the workers who had worked in 2,4,5-T manufacturing had developed chloracne, a skin condition similar to adolescent acne known to result from exposure to certain chlorinated hydrocarbons.

In one of these studies, interviews and physical examinations were administered to assess and compare the health of workers with chloracne or a past history of chloracne to that of workers who had never had chloracne. Of the 226 participants in the study, 70 had chloracne and another 47 had a history of chloracne. Thirty-five workers with chloracne had developed actinic elastosis, a condition in which the skin becomes thickened and leathery. Workers with chloracne or a history of chloracne were more likely than workers without chloracne to report

muscle pain, insomnia, decreased libido, sexual dysfunction, and eyelid cysts. In the chloracne group, 11 workers had an abnormally low sensitivity to pain when pricked with a pin, and one had a severe loss of sensory nerve function in his arms and legs. No workers without chloracne displayed abnormal nerve function. Workers in the chloracne group had higher blood levels of a specific type of fat and of a certain enzyme than did workers without chloracne. These differences may reflect changes in liver function, but it is not clear whether they actually represent adverse health effects. In this study, there was no difference in the incidence of ulcers between the two groups nor were there differences in reproductive outcomes. The authors of this study reported that there were 12 cases of non-melanoma skin cancer among the workers, but they did not indicate which of these were in the chloracne group. Some forms of skin cancer are very common and it is difficult to obtain accurate incidence rates in the general population.

In the second study of workers from this plant, which probably included many of the same workers as the study above, company employment records were used to divide the men into a group who worked in 2,4,5-T manufacturing and a group who never worked in 2,4,5-T manufacturing. Interviews and clinical exams were conducted. Over half the exposed workers were found to have chloracne at the time of the examinations and on interview 86% of them reported having had chloracne at some time in the past. Exposed workers also reported a greater frequency of ulcers, decreased libido, and impotence than did the nonexposed workers. Physical examinations of the exposed workers revealed a higher incidence of actinic elastosis and abnormal respiratory function values than were found in the nonexposed group. Workers with chloracne had more changes in blood cholesterol levels as compared to workers without chloracne. No differences were found in nervous system function and reproductive history between exposed and nonexposed workers.

Both of the studies of the workers at the Monsanto plant have some limitations that interfere with their interpretation. Both studies had low participation rates so that the workers studied may not have been representative of the entire population of workers at the plant. Classification of workers as exposed or nonexposed was not clearcut and the potential for misclassification was large, particularly in the first study. In the second study, the nonexposed cohort was significantly different from the exposed cohort in terms of age, years of employment, and smoking history. Thus, differences between the groups of workers may have been caused by these factors instead of by different exposure.

A health effects screening study was conducted in Times Beach, Missouri among people who may have been exposed to TCDD as a result of ground application of waste oils to control dust. These waste oils were found to contain relatively high levels of TCDD.

A "high risk" group consisting of 68 people and a "low risk" group consisting of 36 people were identified on the basis on the answers to questions about their possible exposure to contaminated soil. When the "high risk" cohort was compared to the "low risk" cohort, there was no evidence of chloracne, abnormal urinary porphyrin excretion, excess cancer, or impaired

liver function. Other minor differences in kidney function and in immune system function were reported by the authors but these were not statistically significant. Because of the relatively small number of people in this study, small but potentially important differences between the two groups may not have been detected. Furthermore, the classification into high and low risk groups was based on subjective recall of possible exposure. People in the low risk group may have been exposed to TCDD but to a lesser degree than the people in the high risk group. Therefore, the study cannot be considered to be definitively negative.

Cancer

None of the five studies described above found a statistically significant association between any form of cancer and exposure to phenoxy herbicides and/or TCDD. In addition to these studies, several reports dealing specifically with cancer in humans were published in 1984.

In one study, all cases of soft-tissue sarcoma that had been diagnosed among New York State males who were of draft age (18-29) during the Vietnam war were identified from the New York State Cancer Registry. For comparison purposes a control group consisting of an equal number of men of the same age and place of residence but who did not have soft-tissue sarcoma was identified. The men with soft-tissue sarcomas, or if they were deceased, a close living relative as well as those in the control group were interviewed about their military service, occupation, exposure to specific chemicals, past illnesses, family history, and smoking and drinking habits.

Analysis of the results of this study showed that there were fewer veterans in the soft-tissue sarcoma group than in the comparison group. Analysis of the data also indicated that there was no significant association between soft-tissue sarcoma and service in Vietnam or exposure to herbicides or chemicals that might contain TCDD.

In another study conducted in New York State, all deaths that occurred among men who were of draft age during the Vietnam war were identified and classified according to cause of death. Using military service records, all of the men who died were divided into three groups, Vietnam veterans, veterans who never served in Vietnam, and nonveterans. The proportion of the deaths due to each of 26 different causes were compared among the three groups. There were no significant differences between Vietnam veterans and non-Vietnam veterans in terms of cause of death.

The final report of a study of soft-tissue sarcomas in New Zealand was published in 1984. A comparison based on exposure to phenoxy herbicides was made between individuals with soft-tissue sarcoma and a matched group of individuals with other forms of cancer. There was no difference between soft-tissue sarcoma patients and other cancer patients with respect to their exposure to phenoxy herbicides. This study was designed to be as similar as possible to a study conducted in Sweden in the late 1970s that showed a positive association between soft-tissue sarcoma and exposure to phenoxy herbicides. The authors of the New Zealand study were unable to identify methodological differences between their study and the Swedish study

that fully explained the difference in results between the studies. However, uncertainties regarding such factors as the frequency, intensity and duration of exposure and the chemical composition of the herbicides used in both countries may obscure important differences that might explain why the Swedish and New Zealand studies arrived at different conclusions.

A case of sarcoma was reported in a man who worked in a trucking terminal in St. Louis where TCDD-contaminated waste oil was spread to control dust. It was not possible to determine whether this sarcoma was a soft-tissue sarcoma or a bone sarcoma. Also, very little information was given in the report regarding other factors which might influence the development of cancer in this patient.

A study conducted in Italy revealed that women who developed a specific type of cancer of the ovary were more likely to have been exposed to herbicides than women who did not have that form of cancer. The authors of this report indicated that this form of cancer is related to soft-tissue sarcoma and that these results are consistent with the results of the soft-tissue sarcoma studies in Sweden. The authors did not describe the type of herbicides to which the women may have been exposed.

In summary, all but one of the studies of cancer in humans published during 1984 showed no association between any type of cancer and exposure to phenoxy herbicides or TCDD. All of these studies, however, show the common flaws of inadequately characterized exposure and insufficient latent period and thus do not provide complete assurance of a lack of association. In three of the studies, military service in Vietnam was the single criterion for exposure. The two positive reports consisting of a single case-report of sarcoma and a case-control study of ovarian tumors lack the detail necessary for critical evaluation and provide little support for a cause-and-effect relationship between exposure to phenoxy herbicides and/or TCDD and cancer.

Reproductive effects

The Centers for Disease Control published the results of a large study of birth defects occurring in a five-county area surrounding Atlanta, Georgia. One of the objectives of this study was to determine whether men who had been exposed to Agent Orange or had served in Vietnam were more likely to father babies with serious birth defects than men who had not been exposed and who had not served in Vietnam. All children who had been born with serious birth defects between 1968 and 1980 in the Atlanta area were identified and, so far as possible, both parents were interviewed. A large control group consisting of children without birth defects were also identified and their parents were interviewed for comparison purposes. The results of this study indicated that Vietnam veterans were no more likely to father babies with birth defects than were men who had not served in Vietnam. When broken down by specific defects, however, there were a few statistically significant findings. The occurrence of spina bifida (a congenital defect of the spine), cleft lip, and a group of conditions labeled "other neoplasms" were proportionally increased among the children of veterans with potential exposure to Agent Orange. Certain heart defects were associated with Vietnam veteran status of

the father and with potential exposure to Agent Orange during the period from January 1968 to April 1972. These significant findings may be chance occurrences resulting from the large number of comparisons undertaken. This possibility is strengthened by the finding of significantly *decreased* occurrences of some defects among infants whose fathers were potentially exposed. Overall, this study provides considerable assurance that military service in Vietnam does not increase the risk in males of having child with a serious birth defects. As in most of these studies, however, estimated exposure to Agent Orange was based in part on recall and may not accurately reflect actual exposure. A minor problem with this study is that many of the fathers of babies with birth defects could not be located and/or interviewed.

An isolated case report described a child born with multiple physical abnormalities and severe mental retardation. Both of her parents had been exposed to the phenoxy herbicide 2-4-D, before and after conception. Like all case reports, this report cannot be considered as evidence of a cause-and-effect relationship. The association may be concidental. No other studies of an association between reproductive effects in humans and exposure to phenoxy herbicides were published in 1984.

Several reports in the 1984 literature described results of studies of populations potentially exposed to TCDD. The Michigan Department of Public Health conducted an exploratory study to determine whether any of 37 types of birth defects occurred in Midland County, Michigan at elevated rates between 1970 and 1980. Only one defect, hip dislocation in the absence of central nervous system defects, occurred at a rate significantly in excess of the national average, but this defect also occurred at elevated rates in five other Michigan counties that were not "downwind" of the Dow Chemical plant. A few other defects were elevated but not significantly so.

In a separate study, the Michigan Department of Public Health looked at rates of birth defects in 29 counties throughout the United States where trichlorophenols (usually contaminated with TCDD) were produced. The rate of hip dislocations and heart defects were significantly elevated in 6 of these 29 counties. Because these studies do not relate exposure and effects in individuals, they do not support definitive conclusions. They do suggest that possible associations between certain defects such as hip dislocations, heart defects, and perhaps cleft lip, and exposure to TCDD should be examined further.

Several reports expanding and refining the examination of reproductive effects among people who may have been exposed to TCDD as a result of the Seveso accident were published in 1984. These studies continue to indicate that there may have been an increase in the rates of spontaneous abortions and certain birth defects including hip dislocations in the 2 years following the accident. The lack of precise information regarding exposure and background rates of spontaneous abortions and birth defects in the area continues to interfere with the interpretation of these findings.

In general, the information published in 1984 provides no new evidence linking exposure to

phenoxy herbicides or TCDD with impaired reproductive performance or the occurrence of birth defects. The relatively powerful CDC study of birth defects revealed no conclusive evidence for increased birth defects in children born to men who were likely to have been exposed to Agent Orange in Vietnam. The findings that TCDD causes reproductive impairment and birth defects in experimental animals when administered to pregnant females, and the independent suggestive findings of certain types of birth defects in Midland County, Michigan and the Seveso region in Italy supports continued research into potential adverse reproductive effects in humans who may have been exposed to TCDD.

Enzyme effects

Earlier studies have shown that one of the most sensitive effects of TCDD in experimental animals is an increase in the activity of certain enzymes that transform internal and external chemicals. It is not possible to study directly the activity of these enzymes in humans. However, the levels of an enzyme known as gamma-glutamyl transpeptidase (GGTP) in the blood and of a metabolic product, d-glucaric acid, in the urine are thought to be indirect indicators of increased enzyme activity in the human liver. In a series of studies of children from the Seveso region of Italy, it has been found that GGTP levels are increased in children who were most likely to have been exposed to dioxins as a result of the ICMESA accident. Also children with chloracne had higher levels than children without it.

In the study of workers at the Monsanto plant at Nitro, West Virginia, workers with chloracne or a history of chloracne had higher levels of GGTP than workers without chloracne. In the other Monsanto study, where exposed workers were compared to nonexposed workers, no such difference was found.

Levels of d-glucaric acid in urine were significantly higher in a group of workers who were exposed to TCDD as the result of a reactor accident in a factory in England when compared to a group of workers from a nearby factory who were not exposed to TCDD. Blood levels of GGTP were also higher in TCDD-exposed workers, but this difference was not significant.

Measurement of d-glucaric acid in the urine of 117 adults living in the area of Seveso contaminated by TCDD revealed that the average level was higher than that in a group of adults living in a remote mountain village. A separate study of children living in the vicinity of the ICMESA plant indicated that the higher the probable exposure to TCDD, the higher the mean urinary d-glucaric acid levels.

The fact that several independent studies of people exposed to TCDD show increased levels of GGTP in the blood and of d-glucaric acid in the urine suggests that these are effects of exposure to TCDD. It should be pointed out that these people were all exposed to TCDD as a result of accidents or contaminated workplaces and not as a result of exposure to phenoxy herbicides. The results of studies of GGTP levels in Ranch Hand personnel were inconclusive, but indicated the possibility of increased levels in exposed men. At this point, it is not clear whether small changes in either GGTP or d-glucaric acid levels are indicative of any adverse

health effect. If, as postulated, they do reflect alterations in the activity of a group of enzymes in the liver, then they may be indirect indicators of alterations in the way the body transforms and stores fats, steroid hormones, and environmental chemicals. Such alterations may or may not constitute an adverse health effect.

Effects on the immune system

Scientific reports published before 1984 indicated that TCDD interfered with a number of different functions of the immune system in experimental animals, but the results of studies of immune function in humans who may have been exposed to TCDD were inconclusive. 2,4-D and 2,4,5-T have not been extensively tested for effects on the immune system. Most of the studies of humans exposed to phenoxy herbicides or TCDD that were published in 1984 did not include evaluation of immune function. In both studies where immune function was assessed, no difference between the exposed group and the unexposed group was found.

In a study of Ranch Hand personnel who were known to have been heavily exposed to Agent Orange during its application in Vietnam, tests were performed to count the various types of immunologically active cells in the blood and to assess the response of these cells to the presence of foreign materials that stimulate immune responses. There were no differences between the Ranch Hand personnel and unexposed controls. The authors of this study indicated, however, that both the small number of men examined in this study and laboratory difficulties precluded the detection of small but possibly important differences.

In a study of immune function in residents of a TCDD-contaminated neighborhood in Missouri, no significant differences were found when people who may have had contact with contaminated soil were compared to people with little or no direct contact with contaminated soil. The author did indicate that there were "trends" that might indicate altered immune function. This study can only be considered to be preliminary in nature because there were only a small number of people tested and determination of exposure was based on interviews with the potential study subjects, whose recall may have been inaccurate.

Chloracne and other skin effects

Chloracne has been recognized as a consequence of human exposure to TCDD for some time. Studies published during 1984 indicated that relatively heavy exposure to TCDD in industrial settings can cause persistent chloracne and other skin changes such as actinic elastosis and abnormal growth of body hair. All of these changes were seen in the studies described above of workers at the Dow and Monsanto plants. It is interesting to note that in the two studies of workers at the Monsanto plant somewhere between 14% and 24% of the workers who were probably exposed to TCDD never developed chloracne. These findings along with the results of studies of children exposed to TCDD at Seveso and studies in experimental animals add weight to the evidence that some individuals are more susceptible to TCDD-induced chloracne than others.

In contrast to the studies of occupationally exposed workers, two studies of people potentially exposed to TCDD in other settings revealed no indication of chloracne or other skin conditions. One of these studies was the study of Ranch Hand personnel and the other was of residents of an area of Missouri where TCDD-contaminated waste oil was used to control dust. In each of these studies, the amount of TCDD to which people were exposed is unknown, but it is reasonable to assume that exposure was much less than among the workers in 2,4,5-T manufacturing plants.

Neurobehavioral effects

Studies of humans exposed to phenoxy herbicides or TCDD have been inconclusive with regard to potential effects of these compounds on behavior or nervous system function. Some studies of workers who may have been heavily exposed to TCDD during the manufacture of 2,4,5-T or trichlorophenols have suggested that nerve impulses travel more slowly, and there is a loss of sensation in the extremities of exposed workers, but this has not been a consistent finding.

In one of the studies of workers from the Monsanto plant discussed above, the authors found that 11 of 60 subjects with chloracne had decreased sensation to pain when pricked with a pin compared to none of 34 subjects without chloracne. However, the authors of another study of workers from this same plant reported no differences between exposed and nonexposed workers in tests of nerve function. Both of these studies revealed that workers with chloracne or exposed workers had decreased libido compared to workers without chloracne or unexposed workers. This finding could be an indirect result of other effects of the exposure.

Gastrointestinal effects

Statistically significant increases in the history of stomach ulcers were found in studies of the workers who were probably exposed to TCDD at both the Dow and the Monsanto 2,4,5-T manufacturing facilities. These findings are unique, but not all of the earlier studies of exposed humans included the gastrointestinal system among the potential target organs considered. The findings of these two studies are important when considered along with the findings of earlier studies that showed that oral administration of TCDD to monkeys caused injury to the stomach lining.

Changes in fat metabolism

Studies published during 1984 have served to focus scientific attention on another potential effect of TCDD exposure, namely changes in the way the body absorbs, transforms, and stores fat. Several studies of workers who were probably exposed to TCDD in industrial settings have suggested a potential association between increased levels of two kinds of fat (triglycerides and cholesterol) in the blood of exposed workers. Three studies of workers potentially exposed to TCDD showed differences in the concentrations of various types of fats in the blood when workers with chloracne were compared to workers without chloracne. In

addition, two studies of children, who were probably exposed to TCDD as a result of the ICMESA accident at Seveso, indicated that blood levels of triglycerides and cholesterol were higher in children with chloracne than in children without this condition. In another study, liver tissue taken from humans who inhaled soot containing dioxins and other similar compounds during and after a fire in New York State was examined using an electron microscope. The liver tissue was found to contain abnormal accumulations of fat suggesting a change in fat metabolism.

A number of studies of the effects of TCDD on fat metabolism in experimental animals have been published recently. Taken together, these studies suggest that TCDD may interfere with the ability of liver and fat cells to move fat molecules in and out of the cell. TCDD may also interfere with the transformation of fats into other biologically useful forms once they are inside the cell. As a result of these interferences, certain forms of fat tend to accumulate in the blood.

The ultimate health significance of slight alterations in fat metabolism are not clear. There is a great deal of normal variation among humans in the levels of various forms of fat in the bloodstream. However, some human health studies have suggested that increased levels of cholesterol and triglycerides in the blood may be associated with an increased risk of heart disease. No studies of humans exposed to phenoxy herbicides and/or TCDD have shown an increased risk of heart disease.

Other effects

In one study of workers exposed to TCDD during the manufacture of 2,4,5-T at the Monsanto plant in Nitro, West Virginia, the authors measured lung function in exposed and nonexposed workers. A significantly higher number of exposed workers had impaired lung function than unexposed workers even when smoking behavior was taken into account. This finding represents a single report of a potential adverse effect of TCDD on lung function. However, lung function has seldom been measured in individuals exposed to phenoxy herbicides and/or TCDD since obvious respiratory disease has not been observed in these individuals.

The authors of a study of residents of an area in Missouri, where TCDD-contaminated oil was disposed of, reported that people who may have been exposed had more kidney and urinary problems than did people who were not as likely to have been exposed. No objective measures of kidney function were reported in this study. Although animal studies have indicated that relatively high exposures to TCDD can impair kidney function, both human and animal studies have suggested that the kidneys are not among the more sensitive target organs for TCDD toxicity.

4. Summary and conclusions

Only a small proportion of the literature on the health effects of phenoxy herbicides and associated dioxins published during 1984 consisted of studies of potential health effects in humans

who were exposed to these compounds. A major proportion of the literature described studies in experimental animals that were designed to test hypotheses regarding the mechanism of action of TCDD. Although these studies are invaluable in the establishment of a scientific basis for extrapolating from animal studies to humans at some future time, they are of limited use in increasing our present understanding of the human health effects of exposure to phenoxy herbicides and their contaminating impurities.

Relatively few of the studies published during the past year were designed to measure the effects of the active herbicidal chemicals 2,4-D, 2,4,5-T, picloram, or cacodylic acid in humans or animals. These studies revealed no newly discovered health effects. Recent reports on 2,4-D and 2,4,5-T serve to support earlier conclusions that based on the limited evidence available, these compounds are not highly toxic to humans. The available information on cacodylic acid and, especially, picloram is inadequate to support definitive conclusions regarding the human health effects of long-term, low-level exposure to these herbicides.

Several studies were published in 1984, where potential health effects were investigated in veterans who had served in Vietnam and who may have been exposed to the phenoxy herbicides contained in Agent Orange and associated dioxins. None of these studies revealed an adverse health consequence that could be conclusively attributed to service in Vietnam and/or exposure to Agent Orange. A study of Australian servicemen indicated a somewhat higher mortality rate among those who served in Vietnam as compared to those who did not. This difference however, was unrelated to Agent Orange exposure and was attributable to external causes such as motor vehicle accidents. No specific form of cancer was seen in excess among Vietnam veterans nor could any other specific cause of death be related to potential herbicide exposure. A study of birth defects in the Atlanta, Georgia metropolitan area showed no overall increased likelihood of major birth defects among children whose fathers served in Vietnam although three specific defects were proportionately increased among the children of veterans with potential exposure to Agent Orange. On the other hand, a few defects were found less frequently among infants whose fathers were possibly exposed. A study of soft-tissue sarcoma in New York State indicated that men who served in Vietnam were no more likely to develop soft-tissue sarcoma than males who served elsewhere and that males with military service during the Vietnam era were less likely to develop this form of cancer than were non-veterans. Finally, a study of mortality among Vietnam veterans in New York State revealed no excess mortality due to cancer or any other disease among veterans who served in Vietnam when compared to either veterans who did not serve in Vietnam or the general population. These studies together with earlier studies of veterans potentially exposed to Agent Orange in Vietnam provide additional evidence that this potential exposure has not resulted in major adverse health consequences for the exposed population. However, both the inability to identify accurately highly exposed individuals and the lack of adequate time for some potential long-term health effects to develop preclude a definitive conclusion that such exposures were completely without effect.

A number of other studies of humans exposed to phenoxy herbicides or dioxins during application, manufacturing, or as a result of the ICMESA accident at Seveso provided no

conclusive evidence of previously undiscovered adverse health effects due to dioxin. These studies provided additional confirmation that chloracne and related skin conditions such as excessive hair growth and leathery skin texture are caused by relatively heavy exposure to dioxins. Significant new findings, suggesting the need for further investigation, included an apparent excess of stomach ulcers, other gastrointestinal disease, decreased lung function, increased GGTP and urinary d-glucaric acid levels in TCDD-exposed people, increased blood levels of triglycerides and cholesterol in workers and children with chloracne, and a possible association between ovarian cancer in women and exposure to phenoxy herbicides.

Recent studies of immune system function and neurobehavioral effects in humans exposed to TCDD have failed to reveal clearcut evidence of adverse effects, and several studies of cancer have not revealed statistically significant increases in specific forms of cancer in exposed groups. These studies however do not conclusively prove the absence of such effects because of limitations inherent to most studies of this type.