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Veterans Administration

Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins

Volume IX
Analysis of Recent Literature on Health Effects
and
Volume X
Annotated Bibliography of Recent Literature on Health Effects

Department of Medicine and Surgery

VA Contract Number: V101(93)P-1136

REVIEW OF LITERATURE ON HERBICIDES, INCLUDING PHENOXY HERBICIDES AND ASSOCIATED DIOXINS

Volume IX: Analysis of Literature on Health Effects Published in 1986

Prepared for:

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May 26, 1987

FOREWORD

Public Law 96-151 enacted December 20, 1979, mandated the Veterans Administration to conduct "a comprehensive review and scientific analysis" of the worldwide literature on Agent Orange and other phenoxy herbicides. This mandate was in response to an increasing awareness among veterans, the Congress, and the public of the potential long-term health consequences of exposure to these herbicides and the contaminant dioxin. In October 1981, the Veterans Administration published a two-volume "Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins." Because of continued active research, a two-volume update covering the literature through December 1983 was published in 1984. Each year since that time the review has been updated. The present two-volume update covers literature that became available during 1986.

This report was prepared by Clement Associates, Inc. It is an independent assessment of the current state of knowledge about the health effects of phenoxy herbicides, their contaminating polychlorinated dibenzo-p-dioxin impurities, and two other herbicides (picloram and cacodylic acid) that were used in Vietnam. The publication of this document does not signify that the contents necessarily reflect the views and policies of the Veterans Administration.

The project director for Clement Associates, Inc., was Carl O. Schulz, Ph.D. Other contributing authors were Peter K. LaGoy, B.S., Mary B. Paxton, Sc.M., and William H. Phillips, M.S. Ian C.T. Nisbet, Ph.D., provided technical advice and senior level review.

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I. INTRODUCTION

This report consists of a bibliography and critical review of scientific literature that became available during 1986 on the health effects of the herbicides (including impurities) used as defoliants in the Vietnam conflict. This update comprises Volumes IX and X of an ongoing series of publications entitled, "Review of Literature on Herbicides, and Associated Dioxins." Volumes I and II were prepared by JRB Associates and published by the Veterans Administration in October 1981. Volumes III and IV, covering literature published from 1981 through 1983, were prepared by Clement Associates, Inc., and published by the Veterans Administration in June 1984. Volumes V and VI, covering literature that became available during 1984, were published by the Veterans Administration in 1985, and Volumes VII and VIII, covering literature that became available in 1985, were published in 1986. In this report, Clement Associates, Inc., has identified and reviewed information that became available during 1986 in order to update the available data base on the potential adverse health effects of exposure to these herbicides and their contaminating impurities.

An attempt has been made to identify all scientific literature (including unpublished reports) relevant to the potential human health effects of the herbicidal preparation commonly referred to as Agent Orange, the herbicidal active ingredients 2,4-dichlorophenoxyacetic acid and 2,4,5-trichloro-acetic acid and their esters, polychlorinated dibenzo-p-dioxins (primarily 2,3,7,8-tetrachlorodibenzo-p-dioxin, henceforth referred to as TCDD) known to be contaminating impurities of some phenoxy herbicide preparations, and the herbicides, picloram and cacodylic acid. The scope of this review does not include literature dealing exclusively with the chemistry, analysis, or environmental fate and effects of these compounds.

In order to identify relevant literature, Clement searched on-line data bases for literature published since late 1985. These searches covered the MEDLINE, TOXLINE, and CANCERLINE data bases of the MEDLARS on-line information system of the National Library of Medicine. Print-outs of these searches were manually screened to identify relevant resources not already included in the earlier reviews.

Searching of on-line data bases is of limited usefulness because of a lag time of approximately 6 months between publication of scientific reports and their entry into on-line data bases. Therefore, Clement personnel manually screened weekly issues of Current Contents, Life Sciences published by the Institute for Scientific Information, Philadelphia, Pennsylvania, and biweekly issues of CA Selects: Carcinogens, Mutagens, and Teratogens published by Chemical Abstracts Service, Columbus, Ohio. Clement personnel also screened approximately 20 scientific journals and current awareness publications available in the Clement library.

Clement personnel obtained additional information at scientific meetings, including the 1986 Annual Meeting of the Society of Toxicology in New Orleans, Louisiana, and at the regular meetings of the Veterans Administration Advisory Committee on Health-Related Effects of Herbicides. Also, in order to identify unpublished documents or documents published in unconventional resources, Clement personnel contacted scientists who have been active in research on the health effects of phenoxy herbicides and dioxins. A list of these scientists and their affiliations is presented in Table I.

TABLE I

NAMES AND AFFILIATIONS OF RESEARCHERS CONTACTED FOR INFORMATION ON THE HEALTH EFFECTS OF HERBICIDES AND ASSOCIATED DIOXINS

Charles F. Conroy, Jr.	Agent Orange Assistance Program West Virginia State Department of Health
Ralph R. Cook, M.D. Corporate Director of Epidemiology	Dow Chemical Company
Marilyn A. Fingerhut, Ph.D. Chief, Epidemiology Section I	Industrywide Studies Branch National Institute for Occupational Safety and Health
Daniel O. Hryhorczuk, M.D. Director, W.G. Krummrich Study	Department of Medicine Northwestern University Medical School
Peter C. Kahn, Ph.D. Associate Professor of Biochemistry	Department of Biochemistry and Microbiology Rutgers University
Sir Robert Kilpatrick, M.D. Dean, School of Medicine	University of Leicester
Ellen K. Silbergeld, Ph.D. Director of Toxicology	Environmental Defense Fund
Col. William H. Wolfe Chief, Epidemiology Division	USAF School of Aerospace Medicine
James S. Woods, Ph.D. Senior Research Scientist	Battelle Seattle Research Center

II. SUMMARY AND CONCLUSIONS

The annotated bibliography that accompanies this critical review contains 314 citations representing literature that became available in 1986 relevant to the health effects of phenoxy herbicides, their chlorinated dibenzo-p-dioxin impurities, and the herbicides picloram and cacodylic acid. This represents a slight increase in the rate of publication compared to the previous three years although the increase is primarily due to an increased number of abstracts rather than full length papers. A significant portion of the literature cited in the bibliography consists of papers presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds held in Bayreuth, West Germany, in September 1985 and published in a special volume of Chemosphere in 1986. A similar number of citations are abstracts of papers presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds held in Fukuoka in September 1986. A smaller but still significant portion of the 1986 literature consists of papers that were presented at an International Symposium on the Use of Herbicides and Defoliants in Warfare, held in Ho Chi Minh City, Vietnam, in January 1983. These papers had been referred to in secondary sources prior to 1986 but were published as a full proceedings in 1986. It is interesting to note that many of these papers were presented again at the 6th International Symposium on Chlorinated Dioxins and Related Compounds in Fukuoka.

Of the 314 documents retrieved in 1986, 130 (41%) were full-length primary articles. The remainder consisted of review articles, letters to the editor, and abstracts. Slightly less than half of the primary articles were on the effects of these compounds in humans, although a number of these were studies of tissue residues of chlorinated dibenzo-p-dioxins, a research area that is receiving a great deal of attention at the present time. The percentage of primary resources that described studies in humans was higher than in past years. This is due in

part to the desire within the scientific community to provide epidemiologic evidence that confirms or refutes the health effects information available from studies in experimental animals.

The remaining primary literature consists mostly of studies relevant to the mechanism of action of chlorinated dibenzo-p-dioxins in experimental animals. This continues a trend of increasing interest in this type of research over the past several years. Only 15 primary articles describe studies of 2,4-D and 2,4,5-T, active ingredients in phenoxy herbicide formulations. Another four primary sources describe studies of picloram or cacodylic acid. These two herbicides continue to attract scant research interest. It is worth noting that the Veterans Administration published a comprehensive monograph on cacodylic acid in 1986 (Hood 1986).

It is safe to say that there were no major breakthroughs in research into the potential human health effects of phenoxy herbicides and their associated dioxins during 1986. The most noteworthy findings were a positive association between non-Hodgkin's lymphoma and exposure to 2,4-D in Kansas farmers (Hoar et al. 1986), possible alterations in indicators of immune function among residents of a mobile home park that was contaminated with chlorinated dibenzo-p-dioxins (Hoffman et al. 1986b), a possible association of multiple myeloma with phenoxy herbicide exposure (Morris et al. 1986), a possibly increased risk of soft-tissue sarcoma in Vietnam veterans in West Virginia (West Virginia Health Department 1986), and possible cytogenetic alterations, reproductive effects, and cancer in Vietnamese who may have been exposed to phenoxy herbicides as a result of their use as defoliants during military action in Vietnam (numerous authors). All of these "positive" studies have shortcomings that limit their usefulness as evidence of a cause-and-effect relationship between the health effects seen and exposure to phenoxy herbicides and/or their contaminating dioxin impurities. These shortcomings are discussed in the individual chapters of this report. Furthermore, the findings of possible

associations between phenoxy herbicide exposure and cancer, cytogenetic effects, and adverse reproductive outcomes are counter-balanced by an equal or greater number of apparently negative studies published in 1986 or earlier years. Thus, for example, the finding of an association between non-Hogkins's lymphoma and 2,4-D exposure in Kansas was not replicated in a similar study of farmers in western Washington state, and there was no increased incidence of soft-tissue sarcoma in the Kansas study in contrast to the findings of Swedish studies of similar design.

These apparent contradictions in scientific evidence may be indicative of three equally probable explanations. First, limitations inherent in epidemiological methodology, including inability to determine individual doses, may preclude observation of statistically significant increases in risks of adverse health effects that have a relatively high background incidence in the general population. Second, the vast majority of human exposures to phenoxy herbicides and/or chlorinated dibenzo-p-dioxins may have been of sufficiently short duration and/or low intensity that they do not result in sufficient incidence or severity of disease to be observable within the population as a whole. In either case, scientists are unable to provide definitive resolution of the question. Finally, the positive associations seen in some studies may be caused by an unidentified confounder or several confounders that are associated with, but are not attributable to, exposure to phenoxy herbicides and/or TCDD.

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III. HEALTH EFFECTS OF PHENOXY HERBICIDES AND THEIR IMPURITIES

A. MORBIDITY STUDIES IN POPULATIONS EXPOSED TO CHLORINATED DIBENZO-P-DIOXINS THROUGH ENVIRONMENTAL CONTAMINATION

No studies were published during 1986 that assessed the general health status or the incidence of disease (morbidity) among populations or occupational cohorts exposed to phenoxy herbicides. One study was published that assessed the health status of individuals who may have been exposed to polychlorinated dibenzo-p-dioxins as the result of environmental contamination. Hoffman et al. (1986b) assessed the health status of residents of a mobile home park in Missouri where TCDD-contaminated waste oil had been used to control dust in 1971 and where soil analyses conducted in 1983 revealed TCDD contamination. The health status of these individuals was compared with that of residents of mobile home parks where there was no evidence of TCDD contamination.

In order to be eligible for the study, an individual needed to have lived in the Quail Run Mobile Home Park for at least 6 months between April 1971 and May 1983. Eligible individuals and controls were asked to undergo physical and medical examination and to be interviewed. Examinations were conducted from November 1984 through January 1985. Physicians, technicians, and interviewers involved in the study were not aware of the exposure status of the individual subjects.

The physical examination included measurement of height, weight, pulse rate, and blood pressure and examination of skin, peripheral pulses, lymph nodes, abdomen, and peripheral nervous system. Routine urinalysis and urine cultures were performed. Urinary porphyrin and D-glucaric acid levels were also measured. Blood samples were taken for cell counting and routine clinical chemistries. Blood samples were also used to measure the percentage of peripheral T-cells with specific markers (T3, T4, T8, and T11) and to measure proliferative responses of lymphocytes to mitogens and tetanus toxoid and allogenic T-cell cytotoxicity.

All subjects older than 7 years of age were tested for delayed-type hypersensitivity to seven standardized recall antigens using skin tests. They were alsp tested for tactile and thermal sensory thresholds. Subjects older than 7 years of age were also given a battery of neurobehavioral tests. Subjects were also interviewed regarding medical history (including use of pharmaceuticals), socioeconomic status, educational level, smoking history, alcohol use, and potential confounding occupational and environmental exposures.

An estimated 207 households comprising approximately 450 individuals were identified as being eligible for the study. Of these, 95 households comprising 207 individuals were located, and 154 individuals agreed to participate in the study. Controls were selected from the residents of three similar mobile home parks containing 515 households (approximately 990 individuals); 105 participants were recruited from 109 of these households. The control and exposed subjects were comparable in terms of age, sex, race, tobacco and alcohol use, and other sources of exposure. However, the exposed cohort had significantly less education and was of lower socioeconomic status than the control group. The mean duration of residence in the Quail Run Mobile Home Park was 2.8 years, and the median year of first residence in the park was 1978. Only 13 of the cohort lived in the park when the initial contamination occurred.

The prevalence of physician-diagnosed medical conditions was similar in the two groups, with the exception of "other skin diseases" and "other miscellaneous diseases," both of which were significantly more prevalent in the exposed group. Of the conditions that previous studies have suggested as being associated with exposure to TCDD, i.e., chloracne, porphyria cutanea tarda, lymphoma, soft-tissue sarcoma, and liver cancer, there were no cases in either the exposed or control groups. There were no differences in the frequency of reproductive disorders or adverse outcomes of pregnancy. Among self-reported symptoms, the prevalence of numbness or tingling sensations in the extremities and the prevalence of persistent severe

headaches were significantly greater in the exposed group than in controls. These differences could not be accounted for by stress, age, sex, or socioeconomic status.

Physical examination revealed a significantly higher incidence of nonspecific dermatitis in the exposed group than in the controls. The exposed group also had a statistically significant increase in the number of individuals with abnormally elevated white blood cell counts. There was a significant elevation in mean urinary uroporphyrin levels and an increased number of individuals with elevated urinary uroporphyrin levels in the exposed group, but no individuals had urinary porphyrin patterns or levels that were indicative of porphyria cutanea tarda. Serum cholesterol and bilirubin levels were significantly lower in the exposed group than in the control group. A multivariate regression analysis in which years of residence in the Quail Run Mobile Home Park was used as a surrogate for dose showed a statistically significant positive relationship of this parameter with serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alanine aminopeptidase, and alkaline phosphatase levels. There were no meaningful differences between the exposed and control populations with regard to tests of neurological and neurobehavioral functions.

The results of skin tests for dermal sensitivity were read by trained readers. Because of a high incidence of anergy (diminished reactivity to antigens) among the subjects that were read by two of the four readers, the results of subjects examined by these readers were not included in the results of the study. There was significantly more anergy among exposed subjects than among unexposed controls. There were also decreased percentages of T3, T4, and T11 cells in the exposed group. Exposed and nonexposed subjects had similar lymphoproliferative responses to phytohemagglutinin, conconavalin A, and tetanus toxoid, but exposed subjects had an increased response to pokeweed mitogen. Cytotoxic T lymphocyte activity was not different between the two groups. Based on these results, the

authors concluded that long-term exposure to TCDD was associated with depressed cell-mediated immunity. They noted, however, that there was no excess of clinically diagnosed immune suppression among the exposed population nor was there a history of prolonged or repeated infections. Therefore, the immunologic effects were considered to be subclinical.

The conclusions of the authors of the Quail Run study were challenged in a letter (Allison and Lewis 1986) to the editor of the journal in which the study was published. The authors of the letter contended that the subjectivity of scoring of the skin tests for delayed hypersensitivity reactions made the results of these tests unreliable because of the possibility of bias. They also contended that animal studies had indicated that the most sensitive indicator of TCDD-mediated immunotoxicity was decreased cytotoxic T-cell activity, and because this activity was not different between the two groups, the study did not provide evidence of immune suppression.

The Quail Run study is difficult to interpret. The participation rates in both the exposed and control populations were low, introducing the possibility of selection bias in the makeup of the cohorts. The exposed cohort was less educated and of lower socioeconomic status than the control population. These differences raise the possibility of important lifestyle differences, such as differences in nutrition and overall health, between the two groups. No attempt was made to characterize actual exposure in the exposed group. Because of the very large number of parameters measured and the variety of statistical comparisons that were made, it is probable that a number of "statistically significant" associations would occur by chance. A majority of the significant differences were in end points that were subjectively evaluated. The results of the immune function tests are quite uninformative because there are very minor differences, they are not consistent with findings in animal studies, and they are not internally consistent, i.e., suppressed delayed hypersensitivity reactions and stimulated lymphoproliferative responses to pokeweed mitogen. Perhaps the

more meaningful results of this study are the findings of increased urinary excretion of D-glucaric acid and uroporphyrins. These findings are consistent with findings among individuals who were exposed to chlorinated dibenzo-p-dioxins as a result of environmental contamination in the ICMESA accident in Seveso, Italy.

Although not an original report, a review of health studies among people exposed to chlorinated dibenzo-p-dioxins as a result of the accident at the ICMESA plant in Seveso, Italy, published in late 1985, deserves special mention (Merlo 1985). This book chapter provides the reader with a concise but critical review of the studies done through 1984 among the general population and among workers at the ICMESA plant. The author emphasizes the problems of study interpretation that are caused by the inability to determine exposure. He also indicates, perhaps for the first time, that there may have been earlier releases from the ICMESA plant that may have resulted in chloracne in the human population and deaths among domestic animals. This allegation may explain the less-than-precise correlation of density of chloracne cases with soil levels of TCDD in the Seveso area. Such confounding may also interfere with future studies of long-term health effects in the Seveso population. With the exception of the well-documented chloracne outbreak and a suggestive transient increase in spontaneous abortions following the accident, there is little evidence of clinical illness in the general population, although the author suggests that there is a trend to increased mortality from cancer of the larynx, trachea, bronchus, and lung, and a significant excess of soft-tissue sarcoma in the population living in the area around the plant. This finding is discussed in detail in the following section on cancer.

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B. CANCER

Over the years, the question of whether or not phenoxy herbicides and/or their contaminating chlorinated dibenzo-p-dioxins cause cancer in humans has defied resolution. The ability of TCDD, one of the chlorinated dibenzo-p-dioxins, to cause cancer in rodents has been established, as has the ability of TCDD to promote the action of carcinogenic initiators in mouse skin and liver. The human evidence for a causal association between exposure to these compounds and any form of cancer is largely negative, the exceptions being case-control studies in Sweden showing an association between occupational exposure to phenoxy herbicides (not necessarily contaminated with TCDD) and soft tissue sarcoma and non-Hodgkin's lymphoma; studies of occupational cohorts exposed to chlorinated dibenzo-p-dioxins suggesting a possible association with stomach and skin cancer; and a number of isolated case reports. The apparently negative results of the majority of studies of exposed human populations may be interpreted as evidence that the positive findings in the few studies above are artifacts. However, the negative results are equally likely to be the result of methodological limitations. The most common of these inadequacies are lack of adequate statistical power, inability to characterize exposure and therefore select an appropriate "exposed" cohort, and insufficient latency between exposure and ascertainment of health status. The uncertainty surrounding this issue has resulted in continuing scientific attempts to resolve it. The results of several major epidemiologic studies were made public in 1986. These are summarized, along with other relevant information, in this chapter.

1. Studies of Cancer among Vietnam Veterans

The West Virginia Health Department (1986) conducted a proportionate mortality study among veterans of the Vietnam era for the purpose of generating hypotheses regarding the possible association of specific causes of death with service in Vietnam. The methods used for this study were similar to those

for proportionate mortality studies conducted in Massachusetts (see Kogan and Clapp 1985 in Volumes VII and VIII of this review) and in New York (see Lawrence et al. 1985 in Volume VIII of this review). The West Virginia Health Department compiled a record of all deaths by cause, as listed on death certificates, among residents of the state from 1968 through 1983. This record was matched with a list of all individuals who had qualified for a bonus under the West Virginia state bonus program. To be eligible for a bonus, a person must have been on active military service between August 1, 1964, and March 28, 1973; have been a resident of West Virginia for at least 6 months immediately prior to entry on active duty; have served on active duty for at least 90 days; and have been honorably discharged upon completion of military service. Bonuses of $400 were awarded to eligible veterans who had served in Vietnam, and bonuses of $300 were awarded to those who did not serve in Vietnam. The bonus record was matched with the mortality record by name for the years 1968-1978 because Social Security numbers were not entered into the mortality record during that period. For deaths from 1979-1983, matching was done using Social Security numbers.

The matching of the bonus to the mortality records was used to generate four groups for the purpose of comparing causes of death. These were all deceased male veterans who had served in Vietnam (Vietnam veterans); all deceased male veterans who had served during the Vietnam era but had not served in Vietnam (Vietnam-era veterans); all male veterans who died during the study period; and all non-veteran male West Virginians who died during the study period. The analyses conducted were proportionate mortality analyses stratified on age at death (by 5-year period) and on year of death (by 2-year interval).

A total of 1,225 deaths among all veterans was identified by the record matching. Of these, 610 were Vietnam-era veterans and 615 were Vietnam veterans. A comparison of mortality patterns between all veterans and the non-veteran male population of West Virginia showed numerous differences.

Veterans were more likely to die from accidents, poisoning, and violence than were non-veterans. Veterans were less likely to die from allergic, metabolic, and endocrine diseases and from "all other causes" than were non-veterans. Mortality from cancer was similar in veterans and non-veterans. The authors attributed the differences in mortality between veterans and non-veterans to the "healthy veteran effect," in that individuals with preexisting disease (many of which are in the category of allergic, metabolic, and endocrine disease) are excluded from military service. Veterans, being less likely to die of disease, are more likely to die of non-disease causes, i.e., accidents, poisoning, and violence.

When cancers of specific sites were analyzed, veterans were more likely than non-veterans to have died of cancer of the respiratory system and melanoma of the skin and were less likely to have died of leukemia and cancer of the nervous system. The authors speculated that the difference in respiratory cancer may be attributable to increased smoking among veterans compared to non-veterans.

Of potentially more interest for future study is the comparison of the Vietnam veterans with veterans who did not serve in Vietnam. These groups were not different from each other in deaths due to accidents, poisoning, and violence, or in any other major categories of cause of death including all cancers combined. With regard to specific types of cancer, these groups differed only for soft-tissue sarcoma (STS), Hodgkin's disease, and testicular cancer. There were three deaths caused by soft-tissue sarcoma among Vietnam veterans while there were none among Vietnam-era veterans. There were five deaths caused by Hodgkin's disease among Vietnam veterans compared with one among Vietnam-era veterans. Interestingly, non-Hodgkin's lymphoma accounted for two deaths in each group.

The authors of this study were very conscientious in describing the limitations of the study and the uncertainties associated with the findings. There is no way to determine the number of eligible veterans who did not apply for the bonus and

were, therefore, excluded from the study or misclassified as non-veterans. The State of West Virginia did undertake two nationwide publicity campaigns to advertise the availability of the bonus. Veterans who died outside of West Virginia were also excluded. The inclusion of deaths from as early as 1968 raises the possibility that the study may have been biased against finding an excess occurrence of cancers with long latency periods. Finally, as in similar proportionate mortality studies, there was no attempt to determine actual exposure to herbicides or even to ascertain combat status among the Vietnam veterans. It is likely that the Vietnam veteran subgroup includes a significant number of individuals with no exposure to herbicides in Vietnam. Conversely, all groups may contain individuals who were exposed to phenoxy herbicides and/or polychlorinated dibenzo-p-dioxins in other occupational or environmental settings. The authors concluded that their study "only suggests the possibility that the risks of death from soft-tissue sarcomas, Hodgkin's disease, and testicular cancer are elevated among veterans who served in Vietnam." The authors are attempting to obtain service records for the Vietnam veterans who died of these cancers in order to determine exposure histories. They also hope to design new studies that incorporate exposure data and allow for a longer latency.

Kang et al. (1986) published a case comparison group analysis of STS among patients of 172 Veterans Administration medical centers. The authors reviewed the Veterans Administration Patient Treatment Files in order to identify all cases of STS that were diagnosed between 1968 and 1984 in individuals who had been on active military service between August 5, 1964, and May 7, 1975. A control group was identified by randomly selecting individuals from the patient treatment files who served on active duty during the same time period and who had a diagnosis other than STS. Military personnel records were located for cases and controls and were abstracted.

Pathology reports were obtained for 394 of the 418 cases diagnosed as STS during the study period. Upon review of these

records by a pathologist specializing in STS, 151 cases were excluded as being unlikely to have been STS, and another nine cases were excluded because the diagnosis of STS was "doubtful," leaving a total of 234 cases. The control group consisted of 13,496 veterans for whom military personnel records could be located.

The age distribution of the case group was similar to that of the control group. The rate of diagnosis of STS was constant over the study period. Of the cases, 86 (36.8%) had served in Vietnam compared to 5,544 (41%) of the controls. The odds ratio was 0.83 with confidence limits of 0.63 and 1.09. When analyzed by branch of service, there were no differences between cases and controls. There was no disproportionate number of ground troops among the cases. The authors concluded that the study did not reveal a positive association between STS and military service in Vietnam.

The interpretation of this study is complicated by several factors. First, to be included in the study, only those cases of STS diagnosed in inpatients of Veterans Administration hospitals were eligible. An unknown, but possibly large, number of cases were probably diagnosed in Vietnam-era veterans in other medical facilities. Second, although there was some breakdown by branch of service, the only criterion of exposure was military service in Vietnam. No attempt was made to characterize exposure to herbicides. As in all such studies, it is likely that the "exposed" category includes a significant number of individuals with little or no exposure to Agent Orange. Conversely, the group of Vietnam-era veterans who did not serve in Vietnam may have included individuals with significant exposure to phenoxy herbicides and/or chlorinated dibenzo-p-dioxins. Finally, by including cases of STS diagnosed as early as 1969 the study is biased against detecting an association for cancers of long latency. For all of these reasons this study may not have been able to detect a weak but biologically significant association between STS and exposure to phenoxy herbicides.

The Air Force released a brief update on the mortality portion of the Air Force Health Study, which is better known as the Ranch Hand Study (Wolfe et al. 1986). This study is designed to monitor mortality and morbidity among a cohort of individuals who participated in herbicide application by the United States Air Force in Vietnam (Project Ranch Hand) during the period 1962-1971. The baseline mortality study was published in 1983 and was discussed in Volume III of this review (Clement 1984). The morbidity study results were published in 1984 and were reviewed in Volume V of this review (Clement 1985).

The current update is a brief report summarizing cumulative deaths occurring in the cohort and the comparison groups through December 31, 1985. During 1985, there were 4 deaths in the cohort and 27 deaths in the comparison group. Because of the small number of deaths and the lack of any remarkable cluster associated with any cause, no statistical analyses of mortality data were conducted for this update. The authors concluded that the essentially negative findings of the earlier mortality study are still valid. The authors did indicate that a full statistical analysis of cumulative mortality data will be included in the 1987 update. In the meantime, the authors are also continuing the statistical analysis and interpretation of data collected during the second physical and medical examination under the ongoing morbidity portion of the overall study. An updated report containing these data is expected to be available in the second half of 1987.

2. Studies of Cancer among Populations with Occupational Exposure to Phenoxy Herbicides

Several epidemiologic studies of possible associations between cancer and exposure to phenoxy herbicides through their use in agriculture were published in 1986. Two of these were conducted in the United States, one in Sweden, and one in the United Kingdom. The methodology and objectives of all the studies were different, and precise comparison is difficult. Taken together, the results of the studies are equivocal with

one showing a clear positive association between exposure to the phenoxy herbicide 2,4-D and non-Hodgkin's lymphoma (NHL), and the others being either negative or weakly positive.

Hoar et al. (1986) published the results of a case-control study of STS and lymphoma in Kansas. The case group consisted of all newly diagnosed cases of STS, Hodgkin's disease (HD), and non-Hodgkin's lymphoma among white males, 21 years of age or older, between 1976 and 1982. Cases were identified from the University of Kansas Cancer Data Service. Cases were not included in the study unless the diagnosis was histologically confirmed. Controls were selected from the adult white male population of Kansas by random digit dialing. Deceased controls were selected from the Kansas mortality files. Controls were matched to cases in a ratio of 3 to 1 by age (±2 years) and vital status. Deceased controls were matched by year of death as well. Individuals who had died of STS, HD, or NHL, of cancer at an ill-defined site, or by homicide or suicide were excluded from the control groups.

Telephone interviews of cases and controls or of next-of-kin of deceased cases and controls were conducted by trained interviewers. Subjects were questioned about their farming history, pesticide usage, and other potential occupational exposures. Detailed questions regarding brand names of pesticides, number of acres treated, and use of protective clothing and equipment were included in the interview. For a random sample of cases and controls, suppliers of pesticide formulations were questioned about the quantity and types of pesticides purchased by the subjects in order to provide independent confirmation of the accuracy of the subjects' recall of pesticide use.

Of 200 cases of STS selected, 139 were histologically confirmed, and interviews were conducted for 133 (67%). Comparable numbers were 173, 132, and 121 (70%) for HD and 200, 172, and 170 (85%) for NHL. Complete interviews were obtained for 948 controls. Information provided by pesticide suppliers

correlated well with the recall of the cases and controls or their next of kin regarding types and amounts of pesticides used.

The relative risks for STS and HD were similar for farmers and non-farmers. The risk of NHL was slightly elevated for farmers but this elevation was not statistically significant. The relative risks of STS and HD were not increased for any agricultural exposure. For NHL there was a statistically significant trend to increasing risk with years of herbicide use. Among individuals with 20 days per year or more of exposure to herbicides, the relative risk of NHL was 6.0. Risk of NHL was also higher among farmers who mixed and applied herbicides themselves than among those who had others do the application. When broken down by specific type of herbicide use, all of the excess risk for NHL was associated with the phenoxy herbicides. In Kansas, 2,4-D accounts for almost all of the phenoxy herbicide used. Only three cases and 18 controls reported exposure to 2,4,5-T, and all but two of these had also used 2,4-D.

The authors of this study examined the possible association of NHL with several potentially confounding variables. They found no association between risk of NHL and use of insecticides, non-farming use of pesticides, smoking behavior, consumption of coffee, consumption of raw unpasteurized milk products, or previous radiation treatment. The risk of NHL was significantly elevated among individuals with a family history of cancer and among individuals who had a relative with lymphoma. The risk of NHL was also significantly elevated among farmers who treated seeds with fungicides.

The authors concluded that their findings were consistent with the findings of Hardell et al. (1981 and 1983) (see Clement 1985) in Sweden of an excess risk of NHL among individuals exposed to phenoxy herbicides not likely to be contaminated with tetrachlorodibenzo-p-dioxins. They did not discuss possible reasons for the difference between their results and those of Pearce et al. (1985) (see Clement 1986) who showed no statistically significant association between NHL and phenoxy herbicide exposure among agricultural workers in New Zealand.

Neither did they address the lack of association between STS and phenoxy herbicide exposure.

Compared to many other case-control studies, the present study appears to have been well-designed and carefully conducted. Although ascertainment was greater for NHL cases than for STS and HD, this was primarily due to greater histological confirmation and would not be expected to result in a spurious positive association. As in all retrospective epidemiologic studies, the question of inaccurate recall of exposure is unanswered. The interviewing of pesticide suppliers for a sample of cases and controls in this study provides some assurance that recall was not inaccurate. Furthermore, it is highly unlikely that recall bias would be present only among NHL cases and not STS and HD cases. Although the authors looked at some sources of potential confounding and ruled them out, it is not possible in a study of this nature to identify all potential sources of confounding. It is primarily for this reason that scientists do not accept evidence of an association as equivalent to demonstration of a causal relationship in single studies of this type. Of particular interest in assessing potential confounding in this study is the significant association between NHL and treatment of seeds with fungicides.

In a somewhat similar study, Woods et al. (1986) identified all cases of STS and NHL among white males, ages 20-79, diagnosed between 1981 and 1985 in 13 counties of western Washington. Living controls were identified by random digit dialing (ages 20-64 years) or from Health Care Financing Administration records (ages 65-79 years). Deceased controls were selected from death certificates where the cause of death was not cancer, suicide, or homicide. Controls were matched to cases by vital status and age (±15 years). Cases of STS were confirmed by review of histological specimens.

Potential exposures were identified using interviews with living subjects or with close relatives of deceased subjects. Each interview lasted approximately an hour and covered residential, military, medical, and occupational histories. For

a random sample of subjects, recall of occupational history was checked by contacting a supervisor or a close co-worker. Specific questions were asked regarding exposure to herbicides, chlorinated phenols, several industrial chemicals, immunosuppressant medication, and a family history of cancer or autoimmune disease.

Of 206 cases of STS identified, 128 (62%) were histologically confirmed, and complete interviews were conducted. For NHL cases the comparable numbers were 746 and 576 (77%). Among 910 controls, interviews were conducted for 695 (76%). Cases of STS were slightly younger than NHL cases. There were slightly more Asians among STS cases. Otherwise the cases and controls were demographically similar.

Thirty-four specific job titles and 17 specific job activities were identified as involving potential exposure to either phenoxy herbicides or chlorinated phenols. Each of these was classified into low, medium, or high potential exposure categories by experienced industrial hygienists.

There was no increased risk of either NHL or STS associated with increasing potential exposure to either phenoxy herbicides or chlorinated phenols. There was a significantly increased risk of NHL among farmers. However, the risk of NHL was not increased among farmers who had farmed for 20 years or more, nor was there any difference between farmers who were "regularly exposed" to phenoxy herbicides and farmers who were not exposed. Individuals who worked in forestry and sprayed herbicides had a significantly increased risk of NHL, but there was no such increased risk in other job categories that also involved spraying of phenoxy herbicides. There was a statistically significant increase in the relative risk of NHL among individuals who were exposed to herbicides for a duration of 15 years or more in a period ending at least 15 years before diagnosis of cancer.

The authors concluded that their study provided no evidence of an association between STS and exposure to phenoxy herbicides or chlorinated phenols. With respect to NHL, there was no

general association with exposure to phenoxy herbicides or chlorinated phenols, but an increased risk of NHL did appear to be associated with prolonged exposure to phenoxy herbicides among those who were initially exposed at least 30 years ago. There was an increased risk of NHL among farmers but this did not appear to be associated with phenoxy herbicide use. The authors emphasized that the findings of their study were not consistent with those of the studies conducted in Sweden (Hardell et al. 1981, 1983) showing an association between NHL and exposure to phenoxy herbicides or chlorinated phenols even though the studies were methodologically similar.

In an extensive discussion section, the authors advanced and addressed a number of possible reasons for the apparent inconsistency between their study and the Swedish studies. These include possible differences in the intensity or duration of exposure in comparable occupational categories, different non-occupational exposure to chemicals, and differences between study populations with respect to unidentified confounding variables. The authors discussed the similarity of their study to that of Hoar et al. (1986) only in passing and considered the results of the two studies to be consistent. However, the increased risk of NHL among farmers not exposed to phenoxy herbicides is not consistent with the Hoar et al. study.

Like the Hoar study, the Woods study was carefully designed and conducted, and there are no obvious sources of bias or confounding. There are certain key differences between the studies. Woods et al. included no cancer cases among controls, whereas Hoar et al. excluded only individuals with a diagnosis of STS, NHL, and HD from their control group. This difference might be expected to bias the Woods study toward finding a positive association, however, because individuals with cancer may be more likely to recall a chemical or occupational exposure that they feel may be causally related to their disease than would individuals without cancer. The phenoxy herbicide exposure in the Hoar study was confined to farmers who used phenoxy herbicides in farming, by and large in wheat farming.

Exposure to phenoxy herbicides in the Woods study comprised 34 different job classifications. The Woods study did not go as far as the Hoar study in identifying specific formulations and quantities of herbicides used. It should also be noted that the few statistically significant associations found in the Woods study may be due to chance as a result of the large number of statistical comparisons made in analyzing the data.

Wiklund (1986) conducted a cohort epidemiologic study of soft-tissue sarcoma (STS) among agricultural and forestry workers in Sweden. This was a record-linkage study that used the 1960 Swedish census to identify a cohort of 354,620 Swedish males born between 1891 and 1940 whose occupations were listed as agriculture or forestry at the time of the census. A comparison cohort of 1,725,845 males working in "other activities" was also identified from the 1960 census. Cases of STS diagnosed from 1961 through 1979 in both cohorts were identified from the Swedish cancer-environment register. Data were stratified on year of birth by 5-year age classes and on county or city of residence in 1960.

In addition to comparison of cancer incidence in the entire cohort, the "exposed" cohort was subdivided into six subcohorts, and cancer incidence within these subcohorts was also compared to the comparison cohort. The subcohorts were farm workers, truck farm owners and employees, other agricultural workers, forest management workers, timber cutters, and other forestry workers. Of these subcohorts, the farm workers accounted for 72% of the total cohort. The other five subcohorts ranged in size from 6,083 to 61,153.

There were 331 cases of STS in the "exposed" cohort versus 1,508 cases in the comparison cohort resulting in a relative risk for STS of 0.9 (95% C.L. = 0.8, 1.0). The relative risk for STS in each of the subcohorts was 1.0 or lower and was not significantly different from 1.0. Further analysis revealed no time-related trends of relative risk in the entire cohort or the subcohorts.

The types of herbicides and the patterns of their use varied among the subcohorts. Farm workers were exposed primarily to methylchlorophenoxyacetic acid (MCPA) with much less exposure to 2,4-D and 2,4,5-T. Truck farmers were exposed to other herbicides than phenoxy herbicides. Forestry workers were exposed primarily to 2,4-D and 2,4,5-T, but exposure among timber cutters was likely to be passive and to occur some time after application. Other agricultural workers and other forestry workers had heterogeneous herbicide exposure.

Although this study yielded negative results it provides little additional assurance that there is no association between STS and exposure to phenoxy herbicides. Eligibility for inclusion in the "exposed" category was based on self-reported occupation at the time of the 1960 census. Thus, the "exposed" cohort could contain individuals who had been employed in agricultural or forestry occupations for only a short time in 1960. Of greater importance is the probability that the comparison cohort may have contained a number of individuals who were employed in agriculture or forestry before or after the 1960 census. Within the "exposed" cohort there was no attempt to determine the intensity or duration of herbicide exposure. It is probable that a significant portion of the "exposed" cohort had negligible exposure to phenoxy herbicides. No attempt was made to confirm the diagnoses of STS even though numerous studies have shown that this class of cancers is frequently misdiagnosed or misclassified in health records. Despite the large number of subjects and the relatively great statistical power of this study, the lack of characterization of herbicide exposure in either cohort and the possible misclassification of a relatively rare form of cancer allow little confidence to be placed in the apparently negative outcome. It is also unfortunate that the relative risks for other forms of cancer, e.g., NHL and stomach cancer, were not evaluated.

At the 6th International Symposium on Chlorinated Dioxins and Related Compounds held during September 1986 in Fukuoka,

Japan, Kilpatrick et al. (1986) described the results of a study similar to that of Wiklund. Unfortunately, a full report of this study is not yet available. According to the abstract of this report, the authors used death certificates to identify 3,600 deaths in England and Wales from 1972 through 1981 where the cause of death was malignant disease of connective and other soft tissue (STS). Using 1971 and 1981 census data the authors established the population of agricultural workers in England and Wales for each year in the 10-year period. Age-specific death rates due to STS among agricultural workers were compared to the rates for the total male population.

A total of 23 deaths attributed to STS were observed in agricultural workers compared to an expected number of 28.5. Among farmers only, the comparable figures were 19 and 22.3. For females married to agricultural workers, the number of deaths due to STS was 13 compared to 10.3 expected. The authors concluded that the study provides no evidence indicative of increased mortality due to STS among agricultural workers.

Based on the limited information available, this study appears to be very similar in design to the study by Wiklund (see above), and is subject to the same criticism. The use of death certificates to identify deaths from STS adds additional uncertainty to the outcome in that misclassification is more likely on death certificates than in a national cancer registry. On the other hand, Kilpatrick et al. used census data from two different censuses to establish whether or not the cases of STS occurred among the "exposed" cohort. Unfortunately, the censuses used were concurrent with the period of the study whereas the critical period for determining potential exposure would be 20-30 years earlier. This study does little to support a hypothesis that there is no causal relationship between herbicide exposure and STS.

Morris et al. (1986) published the results of a case-control study of multiple myeloma (MM) conducted in four separate locations in the United States. The objective of this study was to determine whether MM might be associated with any of a number

of occupational exposures, including pesticides. This study was not specifically designed to investigate an association between MM and exposure to phenoxy herbicides or their dioxin contaminants and, therefore, is of limited relevance to this review. There was a statistically significant increase in the risk of MM among individuals occupationally exposed to "pesticides." When individuals with potential exposure to phenoxy herbicides were considered, the relative risk for MM was 6.0, but the small number of cases (4 exposed, and 2 not exposed) prevented statistical analysis. Multiple myeloma is not a cancer that has been linked to phenoxy herbicide exposure by earlier epidemiologic studies or case reports, although the risk of MM has been found to be increased among farmers. At most, this study can be considered to be hypothesis-generating but it cannot be relied upon as substantial evidence of an association between MM and exposure to phenoxy herbicides.

Coggin et al. (1986) published the results of a mortality study among the employees of a company that manufactured methylchlorophenoxyacetic acid (MCPA) from 1947-1982. The process by which MCPA was manufactured did not involve chlorophenol as an intermediate, so the potential for formation of chlorinated dibenzo-p-dioxin impurities was low. Some, if not all, employees of the factory were also potentially exposed to 2,4-D, 2,4,5-T, and their chlorinated dibenzo-p-dioxin impurities. The company was involved in the formulation and application of these herbicides throughout Britain, and employees were rotated freely among the field stations and the manufacturing facility.

The exposed cohort included all men who had been employed by the company during the period from January 1, 1947, through December 31, 1975. Using the most recent job title each employee was placed in a "high," "low," or "background" exposure category. Vital status of each member of the cohort was determined as of December 31, 1983. For those that had died, the cause of death was determined from death certificates. For those for whom the cause of death was some form of cancer, the

authors "obtained details" of the disease, but it is not stated how this was done. For comparison purposes the expected numbers of deaths were calculated from death rates for the white male population of Great Britain. A second comparison was made based on death rates in the male population of aggregate rural areas of England and Wales in the period 1968-1975.

Of 5,784 eligible individuals, vital status and birth dates were ascertained for 5,400 (93%). Of these, 4,078 were considered to have had greater than "background" exposure to herbicides. Overall mortality in the cohort was less than expected as was mortality due to cancer. When the cohort was compared to the rural population of England and Wales, there was a slight excess of deaths from cancer, but this was not statistically significant. For no cancer of a specific site was there a statistically significantly elevated mortality in the cohort compared to either the nation as a whole or to the rural population. Higher than expected mortality was seen for cancer of the nose, prostate, and brain, and for leukemia. Of the cancers that previous studies had suggested might be associated with exposure to phenoxy herbicides, there was 1 death from STS compared with 0.94 expected, 2 deaths from NHL compared with 5.53 expected, 26 cancers of the stomach compared with 33.34 expected, 3 skin cancers (other than melanoma) compared with 0.97 expected, and 5 multiple myelomas compared with 3.09 expected. Analysis of cancer mortality by intensity and duration of exposure, allowing for 5- and 10-year latencies, did not reveal any significant trends or associations. The one case of STS was histologically confirmed and occurred in an individual who worked as an herbicide sprayer for 6 months, 18 years before his death. Histologic specimens of two cancers classified as retroperitoneal cancer were also examined to ensure that they were not soft-tissue sarcomas.

The results of this study are difficult to interpret. Compared with most other cohort studies, it appears to have been well designed and conducted. A number of factors, however, argue against its use as evidence that there is no association

between exposure to phenoxy herbicides and cancer. The predominant exposure was to MCPA, a phenoxy herbicide not previously linked to human cancer and one that is unlikely to be contaminated with polychlorinated dibenzo-p-dioxins. Mortality in the cohort was compared with mortality in the general population of England and Wales and is expected to be lower because of the "healthy worker effect." Finally, the number of cancers of special interest in the cohort, i.e., STS and NHL, is small, making for low statistical power of the study.

3. Studies of Cancer among Populations with Occupational Exposure to Chlorinated Dibenzo-p-dioxins

At the two most recent symposia on chlorinated dioxins and related compounds, R.R. Cook and co-workers (1986a,b) have reported on the methods and results from an ongoing mortality study among workers with potential exposure to chlorinated dibenzo-p-dioxins at the Dow Chemical Company plant in Midland, Michigan. As of 1986, the cohort consisted of 2,192 men who had worked in one of over 500 job classifications at Dow where there was potential exposure to "higher chlorinated dioxins." Causes of death were ascertained from death certificates.

A cumulative exposure index was developed for each deceased individual by combining an exposure intensity score, based on job assignment, with the duration of the job assignment in months. The exposure intensity scores ranged from 0 to 4 and were developed by industrial hygienists using process information, analytical measurements, industrial hygiene records, and the results of rabbit ear bioassays to assess potential chlorinated dioxin exposures.

Mortality within the cohort was compared with age-specific death rates among the white male population of the United States using data from the U.S. National Center for Health Statistics. In addition, mortality was also analyzed in relation to intensity and duration of exposure within the cohort.

Of the 2,192 eligible male employees in the cohort, 25 were lost to follow-up. In the remaining cohort there were 370

deaths during the period 1940-1982. Death certificates were located, and the cause of death was coded for 369 of these. The expected number of deaths in a cohort this size, based on the U.S. white male population as a whole, was 396. There were 81 deaths from cancer compared with 79.3 expected. When cancers were broken down by site and type, the only category of cancer that yielded a statistically significant excess of deaths in the cohort was the catch-all category designated as "other and unspecified neoplasms."

For those cancers that have previously been potentially linked to exposure to chlorinated dibenzo-p-dioxins, there was no statistically significant elevation in mortality. However, several of these were more common than expected. Specifically, there were 6 deaths from stomach cancer versus 3.8 expected, 12 cancers of the lymphatic and hematopoietic tissues versus 8 expected, and 1 soft-tissue sarcoma versus 0.4 expected. The histological specimens for the soft-tissue sarcoma case were reviewed, and the diagnosis was found to be incorrect. Of the cancers of the lymphatic and hematopoietic tissues, 5 were non-Hodgkin's lymphoma compared with 2.6 expected.

When causes of death other than cancer were looked at, there was no statistically significant excess for any cause within the cohort. There were 5 deaths from diseases of the stomach and the duodenum in the cohort versus 2.7 expected. Interestingly, cirrhosis of the liver as a cause of death increased with increased duration of employment and appeared to be associated with jobs where there was potential exposure to heptachloro- and octachloro-dibenzo-p-dioxins. There were no trends or associations for any other causes of death, including cancers, with intensity and duration of exposure.

The standardized mortality ratio for deaths from all malignant neoplasms increased from 102 to 127 when only those individuals who were first exposed 20 years or more prior to death were considered. The authors chose to explore this finding by conducting a type of case-control study within the larger cohort study. In this study, cases with the cancer of

interest were matched by age to controls from the cohort who died of a cause other than the cause of interest. These were analyzed to determine whether, on average, cases were more likely than controls to have a greater intensity and/or duration of exposure to chlorinated dibenzo-p-dioxins than were controls. This analysis was performed for all cancers combined, for stomach cancers, and for cancers of lymphatic and hematopoietic tissues. None of these analyses showed a clear-cut increase in risk with increased exposure, although there were slight excesses near the 20-year point in duration since first exposure. The authors concluded that their study did not support a causal association between any chronic disease and occupational exposure to chlorinated dibenzo-p-dioxins.

Compared with occupational cohort studies in general, this study has evolved into a relatively good study. The cohort is relatively large, and ascertainment is high. A significant portion of the cohort was first exposed at least 20 years ago, thus allowing for adequate latency. Estimated exposure is based on better-than-average information. The reports do lack information on the exact nature of the exposures, except that most individuals who were assigned to the highest intensity-of-exposure index had demonstrated a chloracnegenic response. One aspect of the interpretation of this ongoing study is problematic. In the earlier of the two recent reports (R.R. Cook et al. 1986a), the authors presented the internal comparisons on the basis of the cumulative exposure index, which, as described above, combines the intensity and duration of exposure. In the more recent report (R.R. Cook et al. 1986b), however, the authors analyzed mortality only in relation to the duration of exposure. These two analyses give slightly different results, and the two are not directly comparable. In the earlier analysis where cumulative exposure index was used, only slightly more than 10% of the deaths occurred in the highest exposure group, and the two highest exposure groups accounted for only 30% of the total deaths. However, within these two exposure categories, deaths from all causes, from all

malignant neoplasms, from cancer of the stomach, from STS, and from non-Hodgkin's lymphoma were higher than expected, although none of these differences was statistically significant. In the more recent report, a much higher percentage of the total deaths is accounted for by the two longest duration-of-exposure categories, and observed mortalities are much closer to expected. It is likely that these categories include workers with long duration but little opportunity for significant exposure to chlorinated dibenzo-p-dioxins. This change in method of analysis raises significant questions.

Despite the large size of the cohort, the study is still relatively insensitive. Risks of STS or NHL that are twice those of the average U.S. male population could not be detected. If the cohort contains a number of individuals with little or no exposure and if average latency is not sufficient for the development of these cancers, then a much greater relative risk would not be detected. For these reasons, these studies cannot be considered to be definitive negative studies.

Another epidemiologic study among workers at the Dow Chemical Company facility in Midland, Michigan, was presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds (Sobel et al. 1986). Beginning with records for 37,000 people who had been employed at Dow's Midland facility for at least 1 year between 1940 and 1979, the authors identified all deaths where the probable cause according to the death certificate was STS. For these cases, medical records and histopathology reports were obtained and reviewed in order to confirm the diagnosis. Each confirmed case was matched with 9 controls selected from deceased members of the cohort and matched on sex, race, year of birth, and year of hire. An industrial hygienist who reviewed the employment records determined potential exposure to chlorinated dibenzo-p-dioxins for all cases and controls. The reviewer was not informed as to whether the individuals were cases or controls.

In all, 14 cases of STS were confirmed, and these were compared with 126 controls. In the judgment of the industrial

hygienist, none of the cases had ever been occupationally exposed to chlorinated dibenzo-p-dioxins, whereas seven of the controls had been exposed. The authors concluded that the study does not support a causal association between STS and exposure to chlorinated dioxins.

It is of interest to note that both R.R. Cook et al. (1986b) and Sobel et al. (1986) reported the death, in 1983, of an individual from STS. This person had been exposed to chlorinated dibenzo-p-dioxins but was not included in either study because he died after the cutoff. If one case like this had been included in the Sobel case-control study and no additional cases of STS were seen during the extended follow-up period, the odds ratio for STS among exposed individuals would have changed from zero to 1.2.

A mortality study among workers who were presumed to have been exposed to high levels of chlorinated dibenzo-p-dioxins as the result of an industrial accident at the BASF plant in Ludwigshaven, Germany, in 1953, was reviewed in Volume III of this review (see Thiess et al. 1982 in Clement 1984). The cohort consisted of 74 workers of whom 21 had died at the time of the study. Of particular note to the authors was the fact that three of these deaths were due to cancer of the stomach. In response to this finding, the chemical industry trade association of West Germany commissioned an expert analysis to address the issue of whether or not there was sufficient evidence of a causal association between the accident and the occurrence of cancer to support a legal claim by the workers at the plant or their surviving relatives for disability insurance benefits. The results of the expert analysis were published in late 1985 (Lehnert and Szadowski 1985).

Lehnert and Szadowski (1985) evaluated the worker population of the plant and identified a total cohort of 133 workers whom they considered to have been exposed to chlorinated dibenzo-p-dioxins as a result of the accident. Of these, 43 had died at the time of the study. There were 17 deaths due to cancer in the cohort. The relative risk for cancer was 1.7 but this

increase was not statistically significant. Cancer of the stomach accounted for three deaths and bronchial carcinoma for six. There were two deaths due to cancer of the colon or rectum. None of these were statistically significantly greater than expected. From a review of the scientific literature and on the results of their analysis of the cohort, the authors concluded that it was not possible to support a conclusion that 2,3,7,8-TCDD is a human carcinogen and that the accident at the BASF plant did not cause cancer in the exposed cohort.

The publication of the report by Lehnert and Szadowski generated a large number of letters and comments. The editorial board of the journal in which the report was published constructed a "readers' forum" which was published in 1986 (Anonymous 1986). Among others, comments were included from one of the co-authors of the earlier study of this cohort, Dr. R. Frentzel-Beyme, and from the West German Medical Association. Several commentators provided detailed reviews and critiques of the methods and interpretations of all the earlier studies of the cohort and took issue with the conclusions of Lehnert and Szadowski. It was pointed out that the lack of statistical significance of the increased mortality rate for all cancers and for specific cancers was a result of the small size of the exposed cohort and that statistical criteria should not determine liability alone, especially if the sensitivity and methodology of such studies cannot be improved.

Taken together, the original paper of Lehnert and Szadowski and the commentaries of the various participants in the "readers' forum," aptly illustrate the limitations of epidemiologic investigation as a means of resolving the issue of whether or not occupational exposure to chlorinated dibenzo-p-dioxins is causally associated with increased incidences of cancer among workers. None of the studies performed to date can be considered to be definitive evidence for or against such an association. The generic limitations of these studies include the inability to characterize exposure adequately and, therefore, to make an appropriate selection of an exposed

cohort; the very small size of the cohorts involved, and therefore, the lack of statistical sensitivity of the studies; and the inability to select appropriate comparison cohorts.

4. Studies of Cancer Among Populations Exposed to Chlorinated Dibenzo-p-dioxins as a Result of Environmental Contamination

In a brief letter to the editor of Lancet, Puntoni et al. (1986) published data on the incidence of soft-tissue sarcoma (STS) among residents of 11 municipalities in the vicinity of the ICMESA plant near Seveso, Italy. A Seveso Cancer Registry was established in 1981 to record all cases of cancer occurring in the population of the 11 municipalities. Cancer cases were identified from hospital admission or discharge records, and diagnoses were histologically confirmed. Cases were identified as being exposed if the patient lived in a "polluted area" at the time of and/or after the accident of the ICMESA plant. The authors did not indicate the criteria for defining the "polluted area," although it was probably zones A, B, and R (see Merlo 1985). All other cases were classified as unexposed. There were 15 cases of STS in the polluted area during 1975-1981 compared with 44 in the unpolluted area. The incidence rate of STS was consistently higher in the polluted area during the study period than in the unpolluted area. There was also an increased incidence rate of STS in the years 1980 and 1981 in the unpolluted area. Over the entire 7-year period, incidence rates of STS in both the polluted and unpolluted areas of the study area were higher than in another province of Italy or in results of studies conducted elsewhere.

Evaluation of the results of this study is complicated by the lack of detail in the very brief report. Several factors argue against an interpretation that would suggest that an increased incidence of STS occurred as a result of the ICMESA accident. First, the incidence rate of STS was higher in the "polluted area" than in the "unpolluted area" during 1975 and 1976, even though the accident occurred in July of 1976.

Second, the maximum length of time between the accident and diagnosis of STS is 5 years, which is exceptionally short, based on the current estimates for latency of chemically induced human cancer. The authors raised the possibility that the Seveso area may have been contaminated with chlorinated dibenzo-p-dioxins before the well-publicized accident in 1976, and that the increased rates of STS may be due, in part, to that prior contamination. Far more study is required to begin to understand this apparent high incidence of a specific cancer in the region.

5. Studies of Cancer Among Vietnamese Citizens

In 1983 an international symposium was held in Ho Chi Minh City, Vietnam in which scientists from all over the world presented scientific papers relevant to the health effects of chemicals, especially phenoxy herbicides, that were used in the war in that country. A number of studies by Vietnamese investigators were described at that symposium. Many of these studies have been summarized in secondary sources since that time but it was not until 1986 that a three-volume published proceeding of the original papers translated into either French or English was published.

Five studies of cancer among Vietnamese who may have been exposed to phenoxy herbicides were included in the proceedings and merit review. Two of these were morbidity studies, and three focused on primary liver cancer as the end point of interest. The two morbidity studies (Doan et al. 1983, Do et al. 1983) were conducted at unspecified dates. They suggest that certain aspects of the health of residents of areas sprayed during the war may have been worse than that of residents of unsprayed areas or Ho Chi Minh City. However, the methods used were not rigorous, and no attempt was made to separate possible effects of exposure to herbicides from other direct or indirect effects of the war.

The three studies of primary liver cancer (PLC) include two case-control studies of reasonably sound design (D.V. Do 1983,

Pham et al. 1983) and a histopathological comparison of tissues from "exposed" and "unexposed" patients (Jerusalem and Kubat 1983). None of these studies provided substantial evidence of an association between PLC and prior exposure to components of Agent Orange. However, both the case-control studies inappropriately used controls with conditions (gastrointestinal ulcers and stomach cancers) that have been associated in studies elsewhere with exposure to chlorinated dibenzo-p-dioxins. Thus, any association that may have existed could well have been obscured. The study by Jerusalem and Kubat (1983) revealed a strong association between PLC in Vietnam and infection with hepatitis B virus. These authors cited evidence that hepatitis B and aflatoxins may act jointly to increase risks of PLC, and that both were prevalent in South Vietnam during the war. This may account, at least in part, for earlier reports of an upsurge in PLC in Vietnam during that period. However, Jerusalem and Kubat (1983) proposed the hypothesis that TCDD could have promoted PLCs inhaled by aflatoxins and/or hepatitis B.

A common defect in all these studies is the inadequate characterization of exposure. Individuals were characterized as "exposed" if they reported having direct contact with sprays or living in sprayed areas. None of these studies mentioned any attempt to verify or document either of these indicators of "exposure," or the nature of the chemicals used in any of the areas in question. When broad categorizations of sprayed areas are used (as, for example, in the study by D.V. Do 1983), "exposure" becomes effectively synonymous with residence in rural areas of South Vietnam; the studies are then subject to major confounding with other adverse factors prevalent in these areas, including aflatoxins, hepatitis B, food deprivation, and stresses and other direct and indirect effects of the war.

6. Summary and Conclusions

The epidemiologic investigations of possible associations between human cancer and exposure to phenoxy herbicides and/or

their associated chlorinated dibenzo-p-dioxin impurities are summarized in Table III-1. The results of these studies are summarized in Table III-2. Simply on the basis of numbers, the apparently negative studies outweigh the positive findings with six studies being clearly negative, four studies being positive, and two studies (Woods et al. 1986, Lehnert and Szadowski 1985) being equivocal. Of the positive studies, those by Puntoni et al. and Morris et al., provide little evidence of cause and effect and must be interpreted with caution. The West Virginia study is methodologically very similar to an earlier study conducted in Massachusetts (Kogan and Clapp 1985), which also showed a statistically significant increase in mortality due to soft-tissue sarcoma. A third study of similar design (Laurence et al. 1985) in New York state was apparently negative. The interpretation of these studies is complicated by the fact that they were record-linkage studies and military service in Vietnam was the sole criterion for classification in the exposed cohorts.

The positive study of greatest interest is that by Hoar et al. (1986). This study is consistent with studies by Hardell et al. in Sweden showing an increased risk of non-Hodgkin's lymphoma in people occupationally exposed to phenoxy herbicides, regardless of whether or not those herbicides were likely to have been contaminated with higher chlorinated dibenzo-p-dioxins. Of equal importance, however, is the finding that there was no such association for soft-tissue sarcoma. This is <u>not</u> consistent with the Swedish studies. Furthermore, Woods et al. (1986) and other investigators have shown positive associations between farming and increased risk of non-Hodgkin's lymphoma. It may be that the etiologic agent for this cancer in a farm setting is not the herbicide but some other factor, which in Kansas farmers correlated with use of phenoxy herbicides.

The negative studies, as mentioned earlier, cannot be interpreted as ruling out associations between cancer and exposure to these compounds. All of these have limitations that would tend to hide a true causal association. The most

TABLE III-1

DESCRIPTION OF STUDIES OF CANCER IN HUMANS EXPOSED TO PHENOXY HERBICIDES OR ASSOCIATED DIOXINS

Reference	Type of Study	Exposed Group	Methods of Identification of Cases	Possible Latency (years)	Size of Study
		A. STUDIES OF CANCER AMONG VIETNAM VETERANS			
West Virginia Health Department 1986	Ecological mortality	Veterans who served in Vietnam	West Virginia Health Dept. records from death certificates	4-19	615 Vietnam veterans 610 Vietnam-era Veterans
Kang et al. 1986a,b	Case-control	Veterans who served in Vietnam	VA patient treatment files (histologically confirmed)	4-20	234 Cases 13,496 Controls
		B. STUDIES OF CANCER AMONG POPULATIONS WITH OCCUPATIONAL EXPOSURE TO PHENOXY HERBICIDES			
Hoar et al. 1986	Case-control	Kansas farmers who used phenoxy herbicides	University of Kansas Cancer Data Service	?	133 Cases STS 121 Cases HD 170 Cases NHL 948 Controls
Woods et al. 1986	Case-control	Men in western Washington state who were employed in any of 34 jobs with potential exposure to phenoxy herbicides or chlorinated phenols	Western University regional cancer registry	?	128 Cases STS 576 Cases NHL 695 Controls
Wiklund 1986	Ecological	Swedish males working in agriculture or forestry at the time of the 1960 census	Swedish cancer-environment registry	1->19	354,620 "Exposed" 1,725,845 Controls
Kirkpatrick et al. 1986	Ecological mortality	Males working in agriculture in England and Wales from 1971-1981	Death certificates	1->10	3,600 Cases STS
Morris et al. 1986	Case-control	Individuals exposed to pesticides including phenoxy herbicides	SEER Program of NCI for 4 areas of the U.S.	?	609 Cases of multiple myeloma 1,683 Controls
Coggin et al. 1986	Cohort mortality	All male employees of a firm that manufactured and applied phenoxy herbicides	Death certificates and medical records	8-36	4,078 exposed

TABLE III-1 (Continued)

Reference	Type of Study	Exposed Group	Methods of Identification of Cases	Possible Latency (years)	Size of Study
C. STUDIES OF CANCER AMONG POPULATIONS WITH OCCUPATIONAL EXPOSURE TO CHLORINATED DIBENZO-P-DIOXINS (PCDDs)					
Cook et al. 1986a,b,c	Cohort mortality	Male workers at Dow Chemical with potential exposure to PCDDs	Death certificates	0-42	2,192 exposed
Sobel et al. 1986	Case-control	Workers from Dow Chemical with potential exposure to PCDDs	Death certificates (histologically confirmed)	3-42	14 Cases STS 126 Controls
Lehnert and Szadowski 1985	Cohort mortality	Workers exposed to PCDDs as a result of an accident at the BASF plant in Ludwigshaven, FRG	Death certificates	32	133 exposed
D. STUDIES OF CANCER AMONG POPULATIONS EXPOSED TO CHLORINATED DIBENZO-P-DIOXINS AS A RESULT OF ENVIRONMENTAL CONTAMINATION					
Puntoni et al. 1986	Ecological	Residents of the area contaminated as a result of the ICMESA accident in Seveso, Italy	Hospital records (histologically confirmed)	0-5	59 Cases STS

NOTE: STS, soft-tissue sarcoma; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; FRG, Federal Republic of Germany; SEER, Surveillance, Epidemiology, and End Results; NCI, National Cancer Institute.

TABLE III-2

RESULTS OF STUDIES OF CANCER IN HUMANS EXPOSED TO PHENOXY HERBICIDES OR ASSOCIATED DIOXINS

Reference	Type of Study	Findings	Comments
		A. STUDIES OF CANCER AMONG VIETNAM VETERANS	
West Virginia Health Department 1986	Ecological mortality	3 deaths due to STS vs. 0 in non-Vietnam veterans. 5 deaths due to HD vs. 1 in non-Vietnam veterans. No other differences	Inadequate characterization of exposure. Possible selection bias. Inadequate latency. No confirmation of cause of death.
Kang et al. 1986	Case-control	Cases of STS no more likely to have served in Vietnam than controls	Inadequate characterization of exposure. Possible selection bias. Inadequate latency.
		B. STUDIES OF CANCER AMONG POPULATIONS WITH OCCUPATIONAL EXPOSURE TO PHENOXY HERBICIDES	
Hoar et al. 1986	Case-control	Relative risk of 6.0 for NHL among farmers exposed to herbicides for >20 days per year. No increased risk for STS or HD. Risk associated with 2,4-D exposure.	Relatively well designed and conducted. Exposure characterized on the basis of recall. Some possibility of confounding.
Woods et al. 1986	Case-control	Increased risk of NHL in farmers but risk was not associated with herbicide exposure. Statistically significant increased risk of NHL in men exposed for 15 years at least 15 years prior to cancer diagnosis. No increased risk of STS.	Relatively well designed and conducted. Exposure not well characterized.
Wiklund et al. 1986	Ecological	Cases of STS no more likely to have worked in forestry or agriculture or six sub-classifications than controls.	Inadequate characterization of exposure. No confirmation of cause of death. Inadequate latency. Possible selection bias.
Kirkpatrick et al. 1986	Ecological mortality	Mortality due to STS lower in agricultural workers than in general population.	Inadequate characterization of exposure. No confirmation of cause of death. Inadequate latency.
Morris et al. 1986	Case-control	Relative risk of 6.0 for multiple myeloma among individuals with occupational exposure to phenoxy herbicides.	Small number of individuals with occupational exposure to phenoxy herbicides raises possibility of spurious association. Possible confounding.
Coggins et al. 1986	Cohort mortality	No excess mortality due to STS or NHL. No statistically significant increase in mortality from cancer of any site.	Relatively well designed and conducted. Low statistical power. Control group not appropriate.

TABLE III-2 (Continued)

Reference	Type of Study	Findings	Comments
C. STUDIES OF CANCER AMONG POPULATIONS WITH OCCUPATIONAL EXPOSURE TO CHLORINATED DIBENZO-P-DIOXINS (PCDDs)			
Cook et al. 1986a,b,c	Cohort mortality	No statistically significant excess mortality due to cancer of any site except "other and unspecified." Mortalities due to stomach and lymphatic cancers were higher than expected, but not significantly so. Increased mortality due to cirrhosis of the liver in exposed cohort.	Relatively well designed and conducted. Inconsistent methods of exposure assessment for data analysis. Low statistical power.
Sobel et al. 1986	Case-control	All 14 cases of STS were unlikely to have been exposed to dioxins.	Relatively well designed and conducted. Inadequate statistical power.
Lehnert and Szadowski 1985	Cohort mortality	SMR for cancer = 170 (not statistically significant). High mortality due to stomach cancer and lung cancer.	Small cohort yields very low statistical power.
D. STUDIES OF CANCER AMONG POPULATIONS EXPOSED TO CHLORINATED DIBENZO-P-DIOXINS AS A RESULT OF ENVIRONMENTAL CONTAMINATION			
Putoni et al. 1986	Ecological	Increased incidence rate of STS in entire study area regardless of exposure.	Inadequate characterization of exposure. STS incidence rate equally high prior to ICMESA accident. Very short possible latency.

NOTE: STS, soft-tissue sarcoma; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease; SMR, standardized mortality ratio.

characteristic deficiency is the inability to determine exposure accurately. Because statistical power is proportional to the number of cases or individuals included in a study, those studies with the largest exposed cohorts, or the largest number of cases of the cancer of interest, have the greatest statistical power. In many cases, however, these large studies suffer from inadequate characterization of exposure, or the cohorts contain a significant portion of individuals who may not have been exposed and, whose inclusion may mask an increased risk of cancer among those with relatively heavy exposure. These limitations inherent in large studies will continue to plague epidemiologists in the future.

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C. GENETIC TOXICITY

1. Studies of Human Subjects

Mustonen et al. (1986) studied the frequency of chromosome aberrations induced by in vitro exposure of human lymphocytes to purified 2,4-D or commercial 2,4-D ("Vesakontuho Tasku"). They also determined the rate of chromosome aberrations in the lymphocytes of unexposed controls and of workers after 6 to 28 days of spraying "Vesakontuho DM", a 2:1 mixture of 2,4-D and 4-chloro-2-methylphenoxyacetic acid (MCPA). 2,4-D and MCPA concentrations from air samples from the breathing zone and in urine samples from the sprayers were also measured. Smoking status was considered.

The commercial 2,4-D tested in vitro produced significant increases in the average number of chromosome aberrations (with or without including gaps) per 100 cells and in the percentage of metaphases with aberrations over the range 0.5 to 1.25 mM. These concentrations of the pure 2,4-D were cytotoxic. Lower concentrations (0.125 to 0.350 mM) produced no indication of an increase in chromosome aberrations for pure 2,4-D, while the commercial product in this range of concentrations gave non-significant increases. The clastogenic activity of the commercial 2,4-D was attributed to chlorophenol contaminants.

The measured concentrations of 2,4-D plus MCPA in the air samples (0.03-0.04 mg/m^3) were considerably lower than the Finnish threshold limit value (TLV) for occupatonal exposure of 10 mg/m^3. The urinary levels of the phenoxy herbicides varied among the 19 sprayers from 0 to 10.9 mg/liter with an average of 2.7 mg/liter. The authors concluded that absorption occurred primarily by the dermal route, given the very low air concentrations. The cultured lymphocytes from the sprayers showed no delay in the cell cycle and no increase in the frequency of chromosome aberrations. There was no correspondence between number of days spraying, urinary concentration, and average number of aberrant metaphases.

This thorough study gives strong evidence that the 2,4-D in commercial preparations is not itself clastogenic in sprayers

exposed at moderate levels. It is, however, puzzling that the specific commercial formulation the sprayers were actually using was not the one selected for in vitro testing.

Bach et al. (1983) presented the results of three studies of chromosome aberrations in the peripheral lymphocytes of Vietnamese reportedly exposed or unexposed to herbicides sprayed during the war. The positive findings of one of these studies (Ton That Tung 1971) were reviewed in Volumes I and II of this review (see JRB 1981) and will not be discussed here. In the first of the newly reported studies, the chromosome aberration rates from three sets of "exposed" subjects studied before 1973 were compared to those from three sets of controls. The potentially exposed subjects were 27 adults who had been evacuated from a sprayed area between 1967 and 1972, 14 children born to mothers who lived in sprayed areas before and after the children were born, and 10 children whose mothers had left sprayed areas after the children's births (exactly how soon after was not stated). The control groups consisted of 7 adults who lived in unsprayed areas of South Vietnam, 50 adults from North Vietnam who also had not been exposed to X-rays or "chemical products," and 10 sick North Vietnamese children who did not have hereditary diseases or X-ray or chemical exposure. The means by which these individuals' exposures were ascertained and the selection criteria for the study were not stated. Standard methods for preparing and reading the samples appear to have been used, although the use of Student's t-test for evaluating the statistical significance of the findings is not appropriate for this type of data. The rates of cells with abnormal chromosomes did not differ significantly among the control groups (0.71%, 1.12%, and 0.55%, respectively), while the rates in all three possibly exposed groups were all significantly elevated (2.92%, 3.25%, and 2.26%, respectively). The observed abnormalities were predominantly chromatid gaps and breaks. The authors suggested that the elevated incidences in the children may be attributed in part to maternal exposure. However, in that case, the same parentally-derived defect should

have been expected to be present in virtually all the cells of a given child, which was not the case. The distinction between the postnatal exposure of the two groups of South Vietnamese children is not clear and may only have been a matter of degree rather than a complete lack of postnatal exposure in the second group.

The second new study was conducted after 1975 (at least 8 years after the period when herbicides were sprayed) and compared the chromosome aberration rates from adult civilians living in the sprayed provinces of Nghia Binh (59) and Quang Nam-Da Nang (22) to 100 "normal" Vietnamese. Again, it was not explained how these participants were selected. The percentages of cells with chromosome abnormalities in the exposed groups (3.69% and 1.59%, respectively) significantly exceeded the rate in the control group (0.15%), with most of the lesions being chromatid breaks.

Cung et al. (1983) studied the frequency of chromosome aberrations in cultured lymphocytes collected after 1975 from 31 people from the mountainous regions of Dong Nai and 25 people from the delta region of Ben Tre. These areas had been sprayed from one to five times between 1966 and 1969. Ten "normal" subjects from the mountain and delta regions of South Vietnam and of the same average age as the exposed individuals were used as controls. It was not explained how the subjects were identified, nor how their exposure category was determined. The methods indicate that procedures suitable for detecting chromosome aberrations were used, but that additional analyses requiring refined banding techniques and thorough karyotyping were also undertaken. The authors reported a significant excess in the proportion of cells with chromosome aberrations among exposed subjects (7.36%) as compared to the control rate (1.89%). Increased frequencies of chromatid and chromosome breaks were the major finding, but notable elevations in the rate of gaps, translocations, dicentrics, and rings were reported. Taking chromosome length into account, it was found that B and C Group chromosomes were disproportionately

affected. Cung et al. also reported a significant increase in the proportion of cells from exposed people with deviations from the normal number of chromosomes (11.15% versus 4.91% in the controls), e.g., hypoploidy (absence of individual chromosomes), hyperploidy (extra individual chromosomes), and polyploidy (presence of extra entire haploid sets of chromosomes), particularly due to endoreduplication. Cung et al. reported that the findings of endoreduplication and translocations between nonhomologous chromatids were confirmed in a subsequent study conducted in 1982 in which 12 subjects from the same sprayed regions were evaluated for chromosome aberrations.

The rather dramatic and internally consistent findings of the studies by Bach et al. (1983) and Cung et al. (1983) of Vietnamese people possibly exposed to Agent Orange stand in marked contrast to the findings of studies of animals exposed to 2,4-D, 2,4,5-T, or TCDD or of other human populations possibly exposed to the components of Agent Orange, individually or in combination. Assuming that the slide preparations and readings were conducted in an appropriate manner as reported, possible explanations might involve biased selection of exposed subjects, a unique susceptibility of the Vietnamese population to these effects from the herbicides, or the presence of another unidentified causative agent in that environment. Review of the slides by independent cytogeneticists might be of value.

2. Studies in Animals

Lundgren et al. (1986) treated groups of two to five female Sprague-Dawley rats with single oral doses of 0.3 to 30 μg/kg TCDD. These animals and controls were sacrificed 6 days later and their blood was cultured for 72 hours with or without 40 μM α-naphthoflavone (α-NF). The lymphocytes were then scored for sister chromatid exchanges (SCEs). Without α-NF, there was no increase in the baseline SCE frequency following treatment with TCDD. With α-NF, there was a dose-dependent increase in the frequency of SCEs from 0.3 to 3 μg/kg TCDD, followed by a plateau for the 10- and 30-μg/kg groups. In

animals treated similarly with TCDD, Lundgren et al. (1986) found that the dose-response relationship for increased AHH activity in liver microsomes paralleled that of SCEs in α-NF-treated lymphocytes from TCDD-treated animals and that α-NF was metabolized faster in TCDD-treated rats.

The increase in SCEs observed when α-NF treatment followed TCDD treatment was statistically significant, but very modest (a maximum increment of 5.3 SCEs per metaphase over a baseline frequency of 6.7 at 3 μg/kg). With the accompanying information on enzyme induction, these results are supportive of the idea that TCDD may induce genetic damage indirectly.

Carlson et al. (1983) used 2,4-D and 2,4,5-T of unknown TCDD content in a series of genetic and developmental studies in Drosophila. In an assay for sex-linked lethal mutations, 500 ppm of 2,4-D or 2,4,5-T or 150 ppm of a 1:1 mixture of the two did not produce an elevation over the control rate, but the control rate was unusually high and variable. Feeding a diet containing 500 ppm 2,4-D for a life cycle did not induce condensation of specific chromosomal regions, as did exposure to X-rays or quinacrine. Matings of stocks designed to detect non-disjunction (the improper segregation of chromosomes in cell division, which may lead to such conditions as Down's syndrome in humans) showed no evidence of this phenomenon when males were raised on feed containing 1,000 ppm 2,4-D. Equivalent frequencies of crossing-over (the exchange of segments between homologous chromosomes, which may increase following exposure to genotoxic agents such as X-rays) were observed in controls and females fed 500 ppm 2,4-D. 500 ppm 2,4-D in the feed did, however, produce a profound effect in prolonging the time to peak emergence of adult flies from 12 days to 20 days after parental flies were mated. (It was not stated whether 2,4,5-T was tested in the same fashion.) There was no increase in common teratogenic effects, but there was a nonsignificant increase in the frequency of hemithorax. A significant shift in the sex-ratio toward males was produced by 500 ppm 2,4-D, by 125 ppm 2,4,5-T, and by 150 ppm of a 1:1 mixture. A reduction

D. REPRODUCTIVE AND TERATOGENIC EFFECTS

1. Studies of Human Subjects

In previous volumes of this review, we have alluded to epidemiological studies on reproductive effects conducted by Vietnamese researchers on individuals from local populations thought to have been exposed or unexposed to herbicide spraying during the war. Because only summary results were available, we deferred evaluation of these studies until more detailed accounts were published. A book (Anonymous 1983) containing more extended discussions of these investigations has now become available. A set of abstracts pertaining to these studies was also included in the Proceedings of the Sixth International Symposium on Chlorinated Dioxins and Related Compounds held in Fukuoka, Japan, in September 1986. Unfortunately, these documents still do not provide sufficient information to appraise adequately and fairly the validity of the conclusions reached by the Vietnamese researchers. Information is lacking on the selection of the study populations and the nature of the questionnaires used in the interviews. Events reported by interviewers were generally not verified. Definitions of the end points are often unclear. The data gathered have consistently been analyzed incompletely and inappropriately. Use of incidences from registries of adverse reproductive outcomes gathered before or during the war is suspect because those statistics are believed to be incomplete or not comparable. Procedures for determining exposure status for individuals were largely undefined and, at best, were limited to characterizing the spraying history of the village in which they lived or, in the case of North Vietnamese soldiers, of the areas to which they traveled; no basis for quantitative estimations of exposure was given in these reports, although gradients of effect with dosage were claimed.

The reports of these epidemiology studies consistently assert that dramatic increases were found in adverse outcomes of pregnancy in groups possibly exposed to herbicides sprayed during the war. The enumerations by Nguyen Dinh Khoa (1983) of

childhood deaths and malformations in two sprayed South Vietnamese towns and by Ho Dang Nguyen (1983) of spontaneous abortions, stillbirths, premature deliveries, newborn deaths, congenital malformations, and molar pregnancies are quite startling in some respects but, at best, can only be considered descriptive and are likely to have been subject to many biases and confounding factors. In comparing rates in sprayed and unsprayed areas of South Vietnam, Nguyen Thi Ngoc Phuong and Le Thi Diem Huong (1983, abstract also, Nguyen Thi Ngoc Phuong et al. 1986) reported significant increases in fetal deaths, congenital malformations, and molar pregnancies associated with exposure to herbicide spraying. Similarly, Cung Binh Trung and T.C. Nguyen (1983) reported marked increases in spontaneous abortions and birth defects in sprayed areas relative to unsprayed areas and relative to pre-spraying rates. Nguyen Thi Ngoc Phuong et al. (1983) reported the results of two studies: a retrospective study (abstract also, Le Diem Huong et al. 1986) of adverse pregnancy outcomes compiled from existing records for 1952-1981, with notable gaps and questionable validity, and a "case-control" study (abstract also, Nguyen Thi Ngoc Phuong et al. 1986) said to show associations of congenital malformations and molar pregnancies with herbicide spraying, but having some of its largest differences in the factors that were supposed to be matching criteria (e.g., age and number of children).

The abstract by Nguyen Thi Xiem et al. (1986) reports positive findings from five studies of reproductive end points, for two of which more extensive discussions are available (Nguyen Can et al. 1983a,b); the other three cannot be addressed for lack of particulars. Nguyen Can et al. (1983a) conducted a large survey of 40,064 women in three North Vietnamese towns, gathering reproductive histories and information on their husbands' presence in South Vietnam during the war. Malformed children were examined by medical personnel, and other reported adverse pregnancy outcomes were verified in medical records. The statistical analysis treated all pregnancies as independent variables, (rather than grouping them by women), made no

adjustment for covariates (such as age), and apparently neglected a previously-mentioned distinction between pregnancies before and after a husband's stay in South Vietnam. The researchers reported that elevated incidences of spontaneous abortion and congenital malformation, but not stillbirth or molar pregnancy, were associated with the father's having been in South Vietnam during the war. The second study by Nguyen Can et al. (1983b) followed a case-control protocol. It apparently used as cases a subset of 61 mothers of malformed children considered in the previous study, and for this reason, it is questionable whether it can be considered a separate study. Each was matched by age and number of pregnancies to three women in the area who had normal children. The fathers' presence in South Vietnam was the antecedent of interest, and this characteristic was found to be significantly more frequent among fathers of the affected children.

Ton Duc Lang et al. (1983, abstract also 1986) found a strong positive relationship between the incidence of malformations among the children of North Vietnamese men who had been soldiers in South Vietnam and among the children of men who had not, and found a strong positive relationship. They also claimed that the degree of the fathers' exposure, determined by the region of South Vietnam in which they had served, was associated with the extent to which the incidence of malformations was increased.

Of all the Vietnamese studies, these two (Nguyen Can et al. 1983a and Ton Duc Lang et al. 1983) appear to have been conducted most nearly in accordance with accepted epidemiologic methods. They both support the hypothesis that paternal exposure to the components of Agent Orange can adversely affect the products of conceptions occurring considerably later.

As discussed previously in these reviews, no biological mechanism has been proposed that provides a plausible explanation for such an association. The most feasible is genetic damage to the father's germ line, but there is little experimental evidence that the components of Agent Orange cause genotoxicity or other effects on DNA. If the findings of the Vietnamese epidemiology studies are valid, the dramatic discrepancy between their findings and those from studies of other populations might be attributable to higher exposure to Agent Orange, a special susceptibility in the population, or another causative factor in the environment of Vietnam. It is also noteworthy that these studies repeatedly cite cleft lip and/or palate and anencephaly as being among the most common of the congenital malformations observed in the offspring of persons thought to have been exposed to Agent Orange.

2. Studies in Animals

Nau et al. (1986) investigated the transfer of TCDD from mothers to offspring by conducting cross-fostering experiments with NMRI mice treated orally or by intraperitoneal or subcutaneous injection with 25 µg/kg radiolabeled TCDD on day 16 of gestation. The concentrations of TCDD in the pups' livers were measured between 0 and 36 days after birth. The temporal patterns of TCDD concentrations did not differ markedly according to route of administration. The concentrations of TCDD in livers of pups nursed by their own treated mothers increased dramatically during the first week of life over the concentrations observed at birth. Pups of untreated mothers nursed by treated mothers had attained approximately the same TCDD concentrations in their livers one week after birth, but the concentrations dropped more rapidly over the next four weeks than they did in the pups that had been exposed *in utero*. Pups of treated mothers nursed by untreated mothers showed rapid declines in the TCDD concentrations in their livers within the first week of life. In the pups exposed *in utero*, concentrations

of TCDD were highest (approximately 10 ppb) in the liver and were an order of magnitude lower in other tissues that were sampled (skin, kidney, intestine, and lung). After 3 weeks of nursing, the tissue concentrations of TCDD in the exposed mothers had decreased by two to three orders of magnitude and were substantially lower than the levels in the pups they had nursed. These findings indicate that lactation is an important route of elimination of TCDD from the mother and of exposure for the newborn.

Nau et al. (1986) conducted an additional experiment in which mice were treated by gavage with 0 or 12.5 µg/kg TCDD on days 14 to 17 of gestation and their viable offspring were nursed by untreated mothers. (It was not stated whether the unexposed pups were cross-fostered also.) Greatly increased cumulative mortality (75% versus 6%) was observed through postnatal day 22 among the pups exposed in utero; among the surviving pups, weight gain was normal. This experiment demonstrates that exposure to a cumulative maternal dose of 50 µg/kg during gestation itself (but after the period when effects on palate formation might impair suckling) decreases fetal survival in mice. The effect on survival of exposure only during lactation by a similarly treated mother was not evaluated.

Krowke (1986) investigated the incidence of cleft palate on the 18th day of gestation in the offspring of NMRI mice treated orally with TCDD according to four different dosing regimens:

4-10 µg/kg/day on gestation days 6-15,
5-15 µg/kg/day on gestation days 9-13,
8-30 µg/kg/day on gestation day 11, and
20-60 µg/kg/day on gestation day 13.

(The indication of "ng" in the legend of Figure 2 is apparently in error.) In all four cases, a linear response was found between log-dose and the incidence of cleft palate on a probit scale and the logarithm of the dose. Krowke asserts that the dose-response relationship was steepest for the most extended dosing schedule; documentation of a statistical difference among the slopes was not provided, and the slopes of the graphed dose-response curves appear quite similar.

Krowke (1986) also compared the potency of 2,3,7,8-TCDD in inducing cleft palate with that of the chlorinated dibenzo-p-dioxin congeners 1,2,3,7,8-pentaCDD (P5CDD) and 1,2,3,4,7,8-hexaCDD (H6CDD) and of the chlorinated dibenzofuran 2,3,7,8-tetraCDF (T4CDF). Following subcutaneous treatment on days 9 to 11 of gestation, the females were sacrificed on day 18. On a molar basis, TCDD was found to be the most potent inducer of cleft palate. TCDD was administered according to the same treatment schedule in combination with each of the above three substances at doses of each substance individually observed to produce incidences of cleft palate in the range 5% to 32%. For each of the three combinations, the observed incidences were the same or only slightly larger than the sum of the incidences produced by the agents alone. Weber et al. (1985, reviewed in Volume VII) have reported greater-than-additive effects for this end point when TCDD and TCDF were administered to this strain of mice. More extensive testing is required to demonstrate whether this additive relationship, rather than inhibitory or synergistic effects, holds through a wider range of doses and to determine whether "subtoxic" doses of several of these substances administered together can result in a cumulative observable effect.

Lamb et al. (1986) investigated the possible interaction of TCDD and thyroid hormone in producing cleft palates in the offspring of C57Bl/6N mice treated by gavage on days 10 through 13 of gestation. It has been proposed that TCDD and thyroid hormones share a common receptor distinct from the Ah receptor (McKinney et al. 1985, reviewed in Volume VII). Separate experiments, each with eight treatment groups of 15 to 30 pregnant females, were run for triiodothyronine (T_3) and thyroxine (T_4). The treatment groups were vehicle control, TCDD alone (3 µg/kg/day), three levels of the thyroid hormone alone, and 3 µg/kg/day TCDD in combination with each of the three doses of thyroid hormone. The doses for T_3 were 120, 240, or 480 µg/kg/day and those for T_4 were 635, 1,250, or 2,500 µg/kg/day. The mice were sacrificed on gestation

day 18, and the fetal palates and kidneys were examined. None of these treatments produced more than minor maternal or fetal toxicity, i.e., scattered effects on maternal weight gain and liver-to-body weight ratio and on fetal weight and mortality. All of the fetuses exposed to TCDD had hydronephrosis, while none of the fetuses not exposed to TCDD had this condition. In neither experiment were any cleft palates observed among the vehicle controls (nor had any been observed in 154 control C57Bl/6N litters over the previous 2 years in this laboratory). In the two experiments, 7.4% and 8.3% of the fetuses treated with TCDD alone had cleft palates. In the fetuses treated with thyroid hormones only, there were several cases of cleft palate: 1.1%, 0.6%, and 0% for T_3 and 0%, 0%, and 1.2% for T_4. Simultaneous treatment with TCDD produced more-than-additive incidences of cleft palates, increasing with thyroid hormone dose: 15.9%, 20.6%, and 31.4% for the three T_3 doses plus TCDD, and 15.1%, 22.9%, and 27.2% for the three T_4 doses plus TCDD, respectively. In a separate experiment, 10 mg/kg/day T_3 (more than 20 times higher than the previous maximum dose) and 2.5 mg/kg/day T_4 (the previous maximum dose) were tested alone and together according to the previous treatment schedule. No maternal or fetal toxicity and no cleft palates were observed in any of the treatment groups. To investigate further the nature of the mechanism by which the more-than-additive increase in cleft palates had been produced, groups of 4 to 6 pregnant females were treated on gestational days 10 to 13 with vehicle, 3 µg/kg/day TCDD, 500 µg/kg/day T_3, or the combination of these doses of the two chemicals. They were sacrificed on day 14 of gestation, when the palatal shelves are closing in untreated fetuses. The distribution of the number of palates classified as "open", "near", "touching", or "closed" did not differ substantially between the TCDD only and the T_3-plus-TCDD groups, although both groups had considerably fewer palates in the closed configuration than the control or T_3-only groups.

Another group from the same laboratory conducted a similar set of experiments investigating how TCDD and hydrocortisone (HC) might interact in producing cleft palates (Birnbaum et al. 1986). The mechanisms by which these two substances produce this result are known to differ; HC inhibits proliferation of the palate's mesenchymal cells so that the shelves do not meet and cannot join, while TCDD prevents the programmed cell death of the palate's epithelial cells so that the shelves cannot fuse even though they have made contact (Pratt et al. 1984, Pratt 1985, reviewed in Volume VII). In comparison to other murine strains, C57Bl/6N mice are sensitive to induction of cleft palate by TCDD, but relatively insensitive to induction by HC.

Groups of 10 to 20 pregnant mice were treated orally with TCDD, subcutaneously with HC, or with vehicles on days 10 to 13 of gestation and sacrificed on day 18. In this experiment, no cleft palates were produced in the vehicle control groups or in the group receiving 3 µg/kg/day TCDD. HC at doses of 25, 50, and 100 mg/kg/day produced incidences of cleft palate of 4.5%, 9.5%, and 29.4%, respectively. TCDD in combination with any of these three HC doses produced cleft palate in 100% of the fetuses at risk. In a supplementary study, fetal palates were examined on day 14 of gestation after maternal treatment on days 10 to 13 with vehicle, 6 µg/kg/day TCDD, 100 mg/kg/day HC, or 3 µg/kg/day TCDD plus 25 mg/kg/day HC. The majority of the control palates were fused. None of the TCDD-treated palates was fused, but the shelves of most were touching. The great majority of the HC-treated palates were open, but there was an even larger proportion of open palates in the group treated with a lower dose of HC but also TCDD. These results suggest that TCDD enhances the activity of HC in producing cleft palate.

The above studies strongly indicate that TCDD, even at exposure levels so low that they might not produce effects in isolation, may interact with other substances to produce teratogenic effects in susceptible organisms.

Fetal mice are even more sensitive to the induction of renal effects than cleft palate following exposure to low levels of TCDD. Abbott et al. (1986) examined the kidneys of C57Bl/6N fetuses on days 14, 15, 16, 16.5, and 17.5 of gestation after the pregnant mice had been treated by an unspecified route on day 10 of gestation with 0 or 12 "g"/kg TCDD (it is assumed that "μg" was intended). This abstract reports that the ureteric lumens of the treated fetuses were progressively occluded, narrow, and tortuous, leading to pronounced hydroureter and true hydronephrosis by day 17.5. Without further details on experimental methods and results, this study cannot be evaluated.

In preliminary studies, Gallo et al. (1986) found that 6 μg/kg TCDD given to weanling C57Bl/6 female mice three times a week for a month reduced uterine weight and produced histological changes in the mucosa, stroma, and glands of the uterus. These effects were found to be more consistent in CD-1 mice, so additional studies of the interaction of TCDD and estradiol (E_2) were undertaken in this strain.

Weanling CD-1 females were dosed subcutaneously for 14 consecutive days with 0, 5, 10, 20, or 100 ng E_2, and on days 7, 9, 11, and 13 they were also gavaged with 0 or 10 μg/kg/day TCDD. After sacrifice on day 15, the mice were autopsied, the drained uteri were weighed, and microsomes were prepared from the livers of mice receiving 20 ng/day E_2 or less. The AHH activities, cytochrome P-450 levels and isozyme patterns, and epoxide hydroxylase activities were determined in microsomes pooled from groups of five mice. E_2 alone at doses of 20 or 100 ng/day produced marked increases in uterine weight; the addition of TCDD treatment reduced uterine weight to below normal levels except at the highest dose of E_2. Treatment with E_2 had no effect on AHH activity or amount of cytochrome P-450 present in the liver microsomes, but the TCDD treatment resulted in approximately a doubling of these parameters regardless of E_2 treatment. Epoxide hydroxylase activity was also increased by TCDD, but unaffected by E_2. A polyacrylamide gel was interpreted to show that the amount of a protein

co-migrating with epoxide hydroxylase and P-450a was decreased by coadministration of E_2 and TCDD. Treatment of a separate set of CD-1 mice with 0, 1, 3, or 10 µg/kg/day TCDD three times a week for a month did not stop their estrous cycles, but uterine weights were increased and ascites was evident in those receiving 3 µg/kg/day or more.

The findings presented by Gallo et al. (1986) show that E_2 does not compete with TCDD for the receptor leading to induction of epoxide hydroxylase, cytochrome P-450, or AHH, but at high doses can override TCDD's inhibitory affects on the uterus. The mechanism of this interaction remains unclear.

Rodwell et al. (1986) exposed groups of 30 male and 30 female Fischer 344 rats to 2,4-D (purity unspecified) at 0, 5, 20, or 80 µg/kg/day in their diets for 105 days prior to the first of two matings. (A 120-µg/kg/day dose group was terminated because of excessive maternal toxicity.) Offspring from the second of these matings were also bred twice. Treatment was continued throughout the experiment. The only adverse effect reported was reduced weights in the second set of litters by the F_0 20-µg/kg/day group, which was actually receiving nearly twice as much TCDD as intended; no mention was made of this effect in the 80-µg/kg/day group. Evaluation of the possibly important two-generation study on the reproductive effects of 2,4-D in rats reported in this abstract must await publication of detailed methods and results.

Mohammad and St. Omer (1985) used high-performance liquid chromatography to measure concentrations of norepinephrine, dopamine, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA) in the thalamus-hypothalamus, pons-medulla, and olfactory bulb of the brains of Sprague-Dawley rats at various times within a month of birth. The mothers of these rats had been gavaged with 0, 50, or 100 mg/kg/day of a 1:1 mixture of 2,4-D and 2,4,5-T containing 12.5 ppb TCDD on gestation days 6 to 15. Each data point represents the average of 4 to 6 pups; their distribution over litters was not stated. The methods section gives the impression that a more extensive study was carried out in terms

of postnatal sampling times, brain regions, and end points than was actually reported; results on only 22 of the 48 described combinations were presented. Pairwise comparison with control values showed several significant results at the 0.05 level, but there was no coherent pattern over dose or time. In both groups exposed in utero, dopamine levels were depressed in the olfactory bulb at 9 days of age (the only time reported) and in the thalamus-hypothalamus and the pons-medulla on day 7, but subsequent findings at 9 and 15 days of age were erratic even for the controls. At 25 days of age, serotonin and 5-HIAA were found to be reduced in the pons-medulla of the high-dose group, and 5-HIAA was reduced in the thalamus-hypothalamus in both dose groups. These rather fragmentary results appear to have been over-interpreted by the authors.

The pups in the above study were drawn from a larger study in which groups of 16 to 36 Sprague-Dawley rats were treated with 0, 50, 100, or 125 mg/kg/day of the 1:1 mixture of 2,4-D and 2,4,5-T on days 6-15 of gestation (Mohammad and St. Omer 1986). Data on developmental and behavioral effects resulting from in utero exposure were collected. They monitored pup weight, tooth eruption, eye opening, testes descent, and vaginal opening, in addition to conducting tests of rats' neurobehavioral development during the first two months of life.

The females in the 100- and 125-mg/kg/day dose groups showed significantly reduced weight gain during gestation and decreased litter size. The pups in the highest dose group gained slightly, but significantly, less weight than controls by 60 days of age. There were no differences among the treatment groups in the timing of occurrence of the markers of physical development. The development of the surface righting reflex was retarded in all three treatment groups at 4 and 5 days of age, as was negative geotaxis in the two higher dose groups between 9 and 11 days of age and in all dose groups between 15 and 17 days of age. Olfactory discrimination was reduced in the two higher dose groups at 9 days of age, but became less marked by 11 days of age. Running wheel activity did not differ among the

treatment groups at 21 or 35 days of age. This activity was significantly stimulated in 22- and 23-day-old male pups by 0.5 or 1.5 mg/kg amphetamine, but none of the treated groups showed an elevated response to amphetamine stimulation at 61 or 62 days of age.

In summary, Mohammad and St. Omer (1986) observed a number of behavioral effects prior to weaning in pups that had been exposed to 100 and 125 mg/kg/day doses of a 1:1 mixture of 2,4-D and 2,4,5-T on days 6 to 15 of gestation, which also produced overt signs of toxicity (reduced maternal weight gain and litter size). Effects on righting and geotaxis were seen in the low dose group (50 mg/kg/day) before weaning. Cross-fostering studies could address whether these effects were actually due to constitutional alterations in the offspring caused by in utero exposure or the effect of continued exposure via maternal milk. The data gathered in this study form a more complete experimental design and were more appropriately interpreted by analysis of variance than Mohammad and St. Omer's companion study (1985) on neurochemical concentrations.

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E. IMMUNOTOXICITY

In recent years, increasing research has focused on the effects of chlorinated dibenzo-p-dioxins on the immune system. TCDD has been shown to be a potent suppressor of both humoral and cell-mediated immunity in experimental animals. Some of the immunosuppressive effects of TCDD are thought to be mediated through the Ah receptor. Studies of humans exposed to phenoxy herbicides or chlorinated dibenzo-p-dioxins have not convincingly demonstrated any association between such exposures and impaired immune function. It is important to realize, however, that evaluation of immune function is not routinely included in morbidity studies. Of the human studies conducted in the past, two have indicated possible alterations in immune function. These studies are not consistent with each other. Sirchia (1982, see Volume III of this review) found evidence of possible stimulation of the immune system among children living in the vicinity of the ICMESA plant in Seveso, Italy, whereas Knutsen (1984, see Volume V of this review) reported a "trend" toward suppressed immune function in individuals from dioxin-contaminated areas of Missouri. Testing of immune function in a small subgroup of the Ranch Hand cohort showed no differences between exposed and control groups (see Lathrop et al. 1984a,b in Volume V of this review).

1. Studies of Immune Effects Among Populations Exposed to Chlorinated Dibenzo-p-dioxins Through Environmental Contamination

In a study discussed in detail in Section IIIA, Hoffman et al. (1986) evaluated several indicators of immune function in residents of the Quail Run Mobile Home Park, a location that was heavily contaminated with waste oil containing TCDD. According to the authors' interpretation, there was significantly more energy among the exposed population than among unexposed controls as judged by a skin test using seven recall antigens. There were also decreased percentages of T3, T4, and T11 lymphocytes in the exposed group. Lymphocytes from exposed subjects demonstrated an enhanced lymphoproliferative response

to pokeweed mitogen, but the responses to other mitogens were not altered. As indicated in Section III A, this study was subject to methodologic difficulties. Also, the significance of the findings for human health is unclear. The authors referred to the findings as indicators of "subclinical" immune alterations.

J.C. Cook et al. (1986) treated human thymic epithelial cells in culture with TCDD and observed a concentration-dependent inhibition of the responsiveness of cocultured thymocytes to the mitogens conconavilin A and phytohemagglutinin. The authors concluded that TCDD acted directly on human thymic epithelial cells to alter normal thymocyte maturation and that TCDD has the potential to produce immune dysfunction in humans.

2. Studies of the Effects of 2,4-D on Immune Function in Experimental Animals

Blakely (1986) administered the butyl ester of 2,4-D to female BDF_1 mice by gavage and evaluated several indicators of cell-mediated and humoral immunity. Acute (single dose) administration of 50-200 mg/kg 2,4-D enhanced antibody production against sheep red blood cells and stimulated the lymphoproliferative response to lipopolysaccharide, a B-lymphocyte mitogen. There was no effect on T-lymphocyte mitogenic responses. Oral administration of lower doses (10-100 mg/kg) of 2,4-D, 3 times a week for 3 weeks had no effect on any of the immune parameters measured. In the single dose study, immunostimulatory effects were seen at doses that caused histopathological changes in the central nervous system and clinical signs of toxicity. No such indications of toxicity were seen in the repeated dose study.

In a similar study, Blakely and Schiefer (1986) applied the butyl ester of 2,4-D to the shaved backs of female CD-1 mice. Single doses of 100-500 mg/kg or repeated doses of 100-300 mg/kg were evaluated. The highest doses, 200 and 500 mg/kg, in the single-dose study suppressed the antibody response to sheep red

blood cells but had no effect on the lymphoproliferative response measured. Repeated doses had no effect on the antibody response to sheep red blood cells but enhanced both the T-dependent and T-independent lymphoproliferative responses to conconavalin A and lipopolysaccharide. The authors considered the suppressed antibody response in the single-dose study to be secondary to the clinical toxicity elicited by this treatment.

In a third related study, Blakely and Blakely (1986) administered single oral doses of the butyl ester of 2,4-D to pregnant female mice on gestation day 11. The dams were allowed to deliver, and each litter was culled to four male and four female pups. At weaning, immune function was evaluated in a random sample of female offspring. Doses of 50-200 mg/kg had no effect on dams or pups in terms of clinical toxicity, organ weights, or histopathology of target organs. These treatments also had no effect on the antibody response to sheep red blood cells in the offspring. There was a decreased lymphoproliferative response to both conconavalin A and lipopolysaccharide, but these could be accounted for by a treatment-related decrease in thymidine uptake by lymphocytes in the absence of mitogen. The authors considered this finding to be of no immunotoxicological significance.

The authors of these studies considered the results to be of little or no toxicological significance because the effects seen were inconsistent and may have been secondary to clinical toxicity induced by the relatively high doses used. They emphasized that the doses tested were far in excess of doses that might be anticipated for humans exposed to 2,4-D during agricultural use.

3. Studies of the Effects of Chlorinated Dibenzo-p-dioxins on Immune Function in Experimental Animals

The majority of studies of the effects of chlorinated dibenzo-p-dioxins on the immune system that were published during the past year focused on the mechanism(s) by which TCDD exerts its immunosuppressive effect. Previous studies have

shown that TCDD has a broad range of effects on the immune system, suppressing both humoral and cell-mediated immunity in experimental animals. Evidence suggests that some, if not all, of these effects may be mediated through binding of TCDD to the Ah receptor.

Chastain and Pazdernik (1985) studied the effect of TCDD on immunity in C57Bl/6 mice and showed dose-dependent immune suppression at doses that caused body weight reductions and thymic atrophy. However, time course studies suggested that the immune suppression was not secondary to the wasting syndrome. They also showed that immature B-lymphocytes in the bone marrow were more sensitive to the immunosuppressive effects of TCDD than were mature B-lymphocytes in the spleen. This finding is consistent with earlier studies showing increased sensitivity of immature T-lymphocytes.

Tucker et al. (1986) investigated the effect of TCDD on T-dependent and T-independent immunity in responsive and nonresponsive mice. TCDD suppressed both types of immunity at doses below those that caused thymic atrophy, and it suppressed host resistance to Plasmodium yoelli infection in responsive mice. The ability of TCDD to suppress B-lymphocyte differentiation segregated with the Ah locus.

Vecchi et al. (1986) examined the interaction of TCDD with various inducers of microsomal enzymes on the immune system. Both 3-methylcholanthrene and ß-naphthoflavone interacted in an additive manner with TCDD in suppressing lymphoproliferative responses and humoral antibody production. Because the interaction of these compounds with TCDD in the induction of birth defects has been shown to be synergistic, the authors concluded that TCDD does not enhance proliferation and terminal differentiation in lymphocytes as it does in epidermal cells.

White et al. (1986) showed that subchronic oral administration of TCDD or 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin to female B6C3F1 mice caused a decrease in hemolytic complement activity (CH50) and in the third component of complement activity (C3) at doses as low as 10 ng/kg/day for 14 days. This effect on

complement activity was paralleled by decreased host resistance to Streptococcus pneumoniae infection, which is thought to be a manifestation of decreased complement activity. In an abstract of further work on this phenomenon, Lysy et al. (1986) provided evidence that the effect of TCDD on complement activity is mediated through binding of TCDD to the Ah receptor.

Holsapple et al. (1986) investigated the effect of 2,7-dichlorodibenzo-p-dioxin (DCDD) on humoral immune function in female B6C3F1 mice and found that, at the doses tested, it significantly suppressed the antibody response to sheep red blood cells (T-dependent antigen) and the antibody responses to DNP-Ficoll (T-independent antigen). The doses of DCDD used (0.1-10 μg/kg) had no effect on body weight, thymus weight, hepatic microsomal protein, cytochrome P-450, glutathione levels, aminopyrine-N-demethylase activity, or AHH activity.

Additional evidence that some of the immunotoxicological effects of TCDD and related chlorinated dibenzo-p-dioxins are mediated through the Ah receptor is provided by Luster et al. (1986), who showed that a competitive antagonist for binding of TCDD to the Ah receptor blocked the myelotoxic effects of TCDD, and by Silkworth and Antrim (1986), who showed that suppression of the antibody response in mice is dependent on the Ah genotype of the lymphoid tissue.

4. Summary and Conclusions

Although no study has provided direct evidence of immune suppression in humans exposed to chlorinated dibenzo-p-dioxins and/or phenoxy herbicides, the indirect evidence that human immune suppression might result from exposure to these compounds is increasing. The finding that TCDD interferes with thymocyte maturation in cultures of human thymic epithelial cells and the overwhelming evidence that TCDD and other chlorinated dibenzo-p-dioxins suppress or alter a variety of immune functions in experimental animals strongly suggest that the human immune system will be a target for these compounds. It is probable that subtle effects on immunocompetence in exposed human

populations may be difficult to detect because of great individual variability in immunocompetence and because a suppression of immune function would not be expected to result in the increased incidence of a single disease end point. Rather, decreased immune function would be expected to result in an increased prevalence of infections and a wide variety of diseases for which the immune system provides primary defense.

Of particular concern for human health is the potential role of decreased immune surveillance in the etiology of human cancer. The available evidence indicates that the use of immune suppressant drugs and immune deficiency leads to an increased incidence of human cancers and lends credence to the hypothesis that environmental contaminants that suppress immune function may result in increased risks of some forms of cancer.

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F. NEUROTOXICITY

No studies of neurobehavioral effects in humans as a result of exposure to phenoxy herbicides or chlorinated dibenzo-p-dioxins were published in 1986. Three studies on the neurobehavioral toxicity of 2,4-D in experimental animals were reported in the recent literature. Toyoshima et al. (1985) examined the effect of 2,4-D on deinnervated rat skeletal muscle. Mattsson et al. (1986b) subjected rats to repeated dermal exposure to 2,4-D and examined them for neuropathologic effects. In a second study, Mattsson et al. (1986a) examined rats for peripheral neuropathy or other signs of neurotoxicity following dermal exposure.

Toyoshima et al. (1985) exposed adult male Fischer rats by intraperitoneal injection to either vehicle or 100 mg/kg 2,4-D for 6 days/week for 24 days. The peroneal nerve to the extensor digitorum longus (EDL) muscle on one side was crushed just before the first dose was administered. An additional group served as an untreated (intact) control. The rats were examined daily for signs of altered motor or sensory function using gait or toe-spreading reflex, respectively. To assess the functional recovery from the nerve damage, the distance between the second and fourth digits was measured, and the distance on the affected side was expressed as a percentage of that on the control side. Muscle isometric twitch tension, twitch contraction time, half relaxation time, tetanic tension, twitch:tetanus ratio, distal motor nerve latency, and electromechanical transmission time were also measured. Recordings were made at 1, 10, 17, and 24 days after nerve crush.

Reinnervation of the peroneal nerve was observed 8-10 days into the study in both 2,4-D-treated and control rats. Motor function returned to normal within 3 weeks in both groups, as did the distance between the second and fourth digits. Body and EDL muscle weights were reduced following nerve crush and returned to normal more slowly in the animals treated with 2,4-D than in the controls. The twitch per muscle weight was significantly increased in treated versus control animals

following indirect stimulation at both 17 and 24 days on study. Similarly the twitch:tetanus ratio following indirect stimulation remained increased in treated animals as compared with controls or intact animals at 24 days. The twitch-to-tetanus ratio was increased in both groups compared with intact animals following direct stimulation at day 10 and remained increased in the 2,4-D-treated animals.

Toyoshima et al. (1986) noted that 2,4-D did not appear to alter the rate of peroneal nerve regeneration, peripheral nerve sprouting, or muscle reinnervation and suggested that their data indicate that 2,4-D is not toxic to peripheral nerves. However, the authors reported that 2,4-D was toxic to the muscle, affecting the contractile properties of the EDL. The authors further suggested that it was possible that proliferative changes observed in 2,4-D myopathy could account for the increased twitch per muscle weight and that the degenerative changes could account for muscle atrophy, reduced tetanus, and, hence, increased twitch-tetanus ratios. The authors also suggested that 2,4-D may affect calcium flux in the muscle and that this could also account for the observed effects.

The study appears to have been well conducted and to support the authors' conclusion that 2,4-D is not toxic to nerve during regeneration but seems to have an adverse effect on muscle tissue. As noted by the authors, further research is necessary to determine the mechanism of action for this effect.

Mattsson et al. (1986b) exposed groups of 9 male Fischer rats to a 24% aqueous solution of the dimethylamine salt of 2,4-D (2,4-D amine) by dermal application to their shaved legs. A similarly sized group of control animals was sham exposed. Because this concentration caused severe skin lesions, exposure was stopped after 2 weeks, and a second study using rats exposed to a 12% aqueous solution of 2,4-D amine was started. This study lasted the anticipated 3 weeks. Animals in both studies were exposed for 2 hours a day, 5 days a week. Body weights and grip strength were measured before treatment and then weekly throughout the study. All animals were necropsied, and the

kidneys were weighed. Sections of nerve, skin from the treated areas, liver, kidney, stomach, and muscle were examined microscopically.

Animals exposed to the 24% 2,4-D amine solution for 2 weeks and to the 12% solution for 3 weeks had significantly decreased body weights. Animals exposed to the 12% solution had significantly increased kidney weights, and rats exposed to the 24% solution also had increased kidney weights (not significant). Grip strength was significantly increased at week 3 in the 12% exposed group, but this may have been due to anomalously low values for the control group. Severe skin lesions were reported in the group exposed to the 24% 2,4-D amine solution, and less severe hyperkeratosis and parakeratosis were seen in the group exposed to the 12% solution. No treatment-related histologic changes were observed in the nervous tissue, liver, kidney, stomach, or skeletal muscle.

The authors concluded that 2,4-D amine did not cause central or peripheral nerve damage at dermal doses that caused skin lesions, lowered body weights, and elevated kidney weights. The authors also suggested that the increased kidney weights represented physical manifestation of a physiologic adaptation to active urinary excretion of 2,4-D. The study appears to have been well conducted and to support the authors' conclusions that short-term dermal exposure to 2,4-D is unlikely to cause neurotoxicity.

Mattsson et al. (1986a) conducted a second study in which groups of 15 male and female Fischer C344 rats were dermally exposed to a 12% solution of 2,4-D amine for 2 hours a day, 5 days a week for 3 weeks and then followed for a 1-month post-exposure period. Similarly sized groups of male and female control rats were sham exposed. Body weights and grip strength were measured before exposure and weekly throughout the study. Sciatic nerve action potentials, caudal nerve action potentials, accelerating rod performance, and H-reflex were measured preexposure and then 3, 17, and 31 days post-exposure. One-third of the rats in each group were necropsied after

3 weeks of treatment; the remaining rats were necropsied at the end of the study. Nervous tissue, skin from the treated areas, liver, kidneys, stomach, and muscle tissue were examined by light microscope. Cross-sections of tibial nerves were examined with an electron microscope.

Body weights were significantly decreased in exposed animals during the treatment period. Three 2,4-D-treated rats exhibited mild ulcerative dermatitis during the treatment period. No treatment-related microscopic (light or electron) changes were reported. No differences were observed between treated and control animals in grip strength, accelerating rod, or caudal nerve action potential. Observed differences were (1) the amplitude of the first sciatic nerve action potential of treated female rats at 3 weeks was smaller than controls; (2) H-reflexes were faster in treated male rats than in controls at 5 weeks; and (3) the second sciatic nerve action potential was slower in treated male rats than in controls at 7 weeks. The authors assumed that these differences were chance statistical occurrences (Type I errors) rather than treatment-related effects, because no clear trends were observed, and other contextual data did not support a treatment-related basis for the observed effects. The authors concluded that dermal exposure to 2,4-D amine caused weight loss and some minor reversible skin damage but had no neurotoxic effects.

Overall, the authors' conclusions appear to be supported by their data, and it seems likely that the statistically different neurological measurements were Type I errors. However, further research is necessary before it can be definitively stated that these observed differences were due solely to chance. Use of an additional exposed group would also have been helpful in determining the cause of the observed effects.

Taken together, these three studies provide no evidence that 2,4-D causes adverse neurological effects. However, some additional work is necessary before the neurotoxic potential of 2,4-D can be definitively determined.

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G. METABOLISM

Three recent studies provide information on the metabolism and pharmacokinetics of TCDD. Olson (1986) studied the metabolism and disposition of radiolabeled TCDD in guinea pigs and compared his results to those of studies conducted on other species. Poiger and Schlatter (1986) examined the pharmacokinetics of radiolabeled TCDD in a human volunteer. Finally, Wacker et al. (1986) reported on the pharmacokinetics of 1,2,3,7,8-pentachlorodibenzo-p-dioxin in the rat.

Olson (1986) studied the metabolism and disposition of TCDD in guinea pigs in an attempt to determine the reasons for the particular sensitivity of this species to the acute toxic effects of TCDD. Single doses of 0.56 µg radiolabeled (H^3) TCDD in olive oil were administered to 7 adult male Hartley guinea pigs by intraperitoneal injection. Fecal and urine samples from each animal were collected and weighed daily for 45 days. After 45 days, the animals were sacrificed and dissected, and individual organs were examined to determine the distribution of the TCDD in the body. About 29% of the administered dose was excreted during the 45-day study, with 3% being excreted in the urine and 26% in the feces. The author noted that elimination apparently followed first order kinetics with a half-time of 94 days. Only TCDD metabolites were detected in the urine and bile while unmetabolized TCDD represented 70-90% of the TCDD-derived radioactivity in the feces. Approximately 61% of the administered dose of TCDD was retained in the body after 45 days. About 36% was present in the adipose tissue, while the liver, pelt, skeletal muscle, and carcass each contained about 7%. Most of the TCDD-derived radioactivity in these tissues was unmetabolized TCDD, but 8%, 13%, and 28% of the dose in the perirenal adipose tissue, liver, and skeletal muscle, respectively, consisted of TCDD metabolites.

Olson (1986) noted that the tissue distribution of TCDD was consistent with that observed in earlier studies in the guinea pig, rat, mouse, monkey, and hamster. However, the presence of TCDD metabolites in the tissues had not been seen in earlier

studies in rats and hamsters. The author suggested that the enterohepatic circulation of TCDD metabolites may account for the presence of metabolites in tissues, but indicated that further study is necessary to explain the observation. Olson determined that the elimination of TCDD followed first order kinetics with a half-time in the body of 94 days, while in the only other metabolism study on guinea pigs, Gasiewicz and Neal (1979 as cited in Olson 1986) determined that elimination followed zero order kinetics with a half-time of 30 days. Olson suggested that the variability may be due to the younger age of the animals used by Gasiewicz and Neal or to the shorter duration of their study (23 days). He noted that, in any case, his results suggest that TCDD may be more persistent in the guinea pig than is suggested by the earlier study.

Olson (1986) suggested that the lack of unmetabolized TCDD in the bile combined with the fact that 74% of the TCDD eliminated in the feces was unchanged indicates the occurrence of direct intestinal elimination of TCDD. He noted that the mechanism by which direct intestinal elimination occurs is poorly understood, but for lipophilic compounds such as TCDD, passive diffusion is thought to be a major process. The author also noted that, in mice, rats, and hamsters, much less of the TCDD-derived radioactivity in feces (between 10% and 45%) was shown to represent unmetabolized TCDD.

The author concluded that the guinea pig is unique in its relative ability to metabolize and excrete TCDD and its metabolites. TCDD metabolites were detected in various guinea pig organs while only unmetabolized TCDD was reported in the same organs in other species. On the other hand, guinea pigs excreted a greater percentage of the fecally excreted TCDD in unmetabolized form than did other species. The author noted that these differences in metabolism and disposition may contribute to the extreme sensitivity of the guinea pig to the toxicity of TCDD.

The study reported by Olson (1986) appears to have been well conducted and appears to support his conclusions that guinea

pigs may treat TCDD in the body differently than other species. However, as noted by the author, further study is necessary before the differences can be clearly determined.

Poiger and Schlatter (1986) reported on the pharmacokinetics of TCDD in humans. In their study, a volunteer ingested a single oral dose of 1.14 ng/kg of tritium-labeled TCDD in corn oil. Feces and urine were collected and analyzed every 1-2 days for 35 days and fecal samples were pooled for 6-9 days and analyzed up to day 125. Adipose tissue biopsies were taken 14 days before and 13 and 69 days after dosing. Adipose tissue and excreta were analyzed for total radioactivity. Through the first 3 days, 11.5% of the administered radioactivity was excreted in the feces, and the authors concluded that over 87% of the administered dose was absorbed. No detectable radioactivity was found in the urine, but the authors noted that this was probably caused by a lack of sensitivity of the analytical techniques. Adipose tissue samples contained radioactivity equivalent to 3.0 and 2.8 parts per trillion (ppt) TCDD after 13 and 69 days, respectively. Very low levels of TCDD were detected in the blood during the initial phase of the experiment, and the levels fell below the detection limit after the first 5 days.

The authors used data on the body burden of radiolabeled TCDD from day 13 to 125 to calculate the half-life of TCDD in the body. Assuming first order kinetics and no urinary excretion, the authors calculated a half-life of 5.8 years for elimination of TCDD from the human body. The authors noted that if TCDD were also eliminated in the urine at the detection limit (9 pg/day) the half-life would be 4.5 years. This is much longer than the half-lives for TCDD reported in other species that have been studied, although non-human primates exhibit longer half-lives for elimination of TCDD than do rodents and dogs. The authors postulated that the greater persistence of TCDD residues in humans could have health implications, particularly in terms of long-term chronic effects. However, results from only one subject provide a weak basis for

generalization in light of probable large intraspecies variability. Moreover, the estimate of half-life from a period of observation of only 125 days (less than one sixteenth of the calculated half-life) is subject to very large uncertainty.

Wacker et al. (1986) studied the metabolism and pharmacokinetics of 1,2,3,7,8-pentachlorodibenzo-p-dioxin (1,2,3,7,8-pentaCDD) in rats. Three male and three female Sprague Dawley rats were administered single oral doses of 1.69-1.75 μg (approximately 0.6 uCi) of C-14 labeled penta CDD. Two bile-duct-cannulated female rats were administered single oral doses of 0.8 μCi of radiolabeled 1,2,3,7,8-pentaCDD. In the intact animals, between 19% and 71% of the administered dose appeared in the feces within 2 days, indicating incomplete and variable absorption. After the first 2 days, 2.16±0.17% and 0.18±0.03% of the body burden were excreted per day in the feces and urine, respectively. The rate of elimination was plotted against time and appeared to follow first order kinetics. Elimination was much less variable than absorption, with an average half-time of 29.5±2.7 days (range 27.2-33.1). About 25-30% of the body burden was located in the liver, and large amounts of radioactivity were also noted in the adipose tissue. Virtually all of the radioactivity in the liver was reported to be unchanged 1,2,3,7,8-pentaCDD.

The authors noted that 1,2,3,7,8-pentaCDD appears to behave in a manner similar to TCDD in the rat. However, absorption of 1,2,3,7,8-pentaCDD from the gut was incomplete and quite variable, whereas the absorption of TCDD in similarly designed experiments was apparently higher and less variable (84±11%). The average half-time reported (29.5 days) compared well with values reported in rats by one researcher for TCDD (31 days), but shorter half-times (17.4 days) have been reported by others. Finally, the authors reported that 1,2,3,7,8-pentaCDD is not likely to accumulate to a greater degree than TCDD in rats and speculated that this may not allow 1,2,3,7,8-pentaCDD to accumulate to toxic levels when animals are chronically exposed to low levels of the compound.

Wacker et al. (1986) did not report the duration of their study, but a figure presented in their text suggests that males were maintained for 25 days while females were maintained for 35 days or more. In addition, the authors did not report the health of the animals. Finally, the experiment does not appear sufficiently detailed to allow the authors to conclude that "in the body of rats accumulation of P_5CDD is not likely to occur to a greater extent than that of TCDD, which may not allow it to accumulate to toxic amounts when the animals are chronically exposed to low levels of the compound." Specifically, the fact that TCDD with reported half-times of 31 and 17.4 days has been shown to accumulate to toxic levels (DeCaprio et al. 1986) suggests that 1,2,3,7,8-pentaCDD with a reported half-time of 29.5 days may also behave in a similar manner. The authors' results do appear sufficient to indicate that 1,2,3,7,8-pentaCDD, like TCDD, accumulates primarily in the liver and adipose tissue, is present in the liver in unmetabolized form, and is excreted mainly in the feces.

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H. TISSUE RESIDUES OF CHLORINATED DIBENZO-P-DIOXINS

Past volumes of this review have not discussed studies of tissue levels of polychlorinated dibenzo-p-dioxins (PCDDs) in detail because of the limited relevance of such studies to human health effects. In the last few years scientific and regulatory interest in this subject has increased greatly. Included in the annotated bibliography that accompanies this review are approximately 30 citations to scientific articles or abstracts devoted to this topic. A major impetus for this interest is the lack of confidence among scientists in the results of conventional methods, i.e., interviews, employment records, and military records, for assessing exposure to these compounds. In studies of human populations potentially exposed to PCDDs, quantitative estimates of exposures can be derived from two sources: case histories or direct measurement of residues of PCDDs in the body. Case histories are compiled from interviews and various written records and, ideally, define the length of time the individual was exposed, the concentration of PCDDs in the medium of exposure, the types of activities in which the exposed individual was engaged, and the estimated amount of PCDDs entering the body through inhalation, ingestion, and dermal routes. Unfortunately, these estimates of exposure require information that is either difficult or impossible to obtain on an individual basis.

As a result, scientists are investigating direct measurements of tissue concentrations of PCDDs, coupled with an understanding of the pharmacokinetic parameters required to relate body residues to cumulative dose, in order to generate useful estimates of the extent of exposure. PCDDs are very lipophilic and are found in body compartments that are high in lipid content. The PCDDs detected in human samples are unique because only those congeners with 2,3,7,8-chlorine substitution patterns are found (Rappe et al. 1986, Ryan 1986). Residue measurements of PCDDs have been reported in human adipose tissue, breast milk, and blood. The primary disadvantage of measurements of residues in breast milk is that the study

population is limited to females within a limited age range. The primary disadvantage of adipose tissue sampling is that surgical procedures are required for taking samples. A biological specimen, such as blood, that may be obtained more easily from all study participants is highly desirable. However, the fat content of blood is much less than that of adipose tissue, and concentrations of PCDDs in blood are generally much lower than in adipose tissue. The analytical methods for blood analysis need to be particularly sensitive, as well as specific (Patterson et al. 1986a). In the context of these sampling and analytical difficulties, the results of recent reports regarding PCDD residues in humans are presented below. Results of studies investigating background residue concentrations and studies investigating contamination incidents are presented. In addition, difficulties in deriving predictive models relating body burdens to exposure are addressed.

1. Adipose Tissue

A number of authors have reported the results of residue analyses of human adipose tissue from autopsy and surgery cases. For these studies, the sampling has generally been without design and has been biased towards individuals who are admitted to hospitals or who have died, usually from accidents or various diseases. Exposure histories are not available for these individuals and there is inadequate evidence to determine if these results are representative of the general population. The results presented below indicate, however, that a significant percentage of the population of industrialized countries may carry background PCDD residues in their bodies at levels in the pg/g (parts per trillion) range.

Ryan (1986) reported the occurrence of 2,3,7,8-chlorine-substituted PCDDs and chlorinated dibenzofurans (PCDFs) in human adipose tissue obtained at autopsy from Canadian, American, and Japanese subjects. The arithmetic mean concentrations of 2,3,7,8-TCDD in the Canadian study group (n=46) were 6.4 pg/g (wet-tissue basis) and 7.0 pg/g (lipid basis) for the positive

samples (n=25) and 4.0 pg/g (wet-tissue basis) for all samples. The PCDD congener detected at the highest concentrations was octa-chlorodibenzo-p-dioxin (OCDD) at a mean concentration of 850 pg/g (wet-tissue basis). The concentrations of 2,3,7,8-TCDD were positively correlated with age; none of the other congeners showed this relationship.

Analyses for tetra- through octa-chlorinated PCDDs and PCDFs were completed for 46 pooled tissue samples from the National Human Adipose Tissue Survey (Stanley et al. 1986). Composites, deemed to be representative of U.S. census divisions and three age groups, were prepared from over 900 specimens. With the exception of pentachlorinated dioxin congeners, concentrations of the dioxin congeners increased with age; this trend was not tested statistically. The mean concentration of 2,3,7,8-TCDD was 5.0 pg/g (basis not specified).

Graham et al. (1986) analyzed adipose tissue from 35 deceased subjects in St. Louis, Missouri. The specimens were analyzed for 2,3,7,8-substituted tetra- through octachlorinated PDDs and tetra- and pentaPCDFs. Detectable amounts of all compounds were found in all samples; but concentrations were quantifiable in only nine. The geometric mean concentration of 2,3,7,8-TCDD in these samples was 7 pg/g (basis not specified). Concentrations of all PCDD and PCDF analytes were positively correlated with age at time of death.

The results of analyses for 2,3,7,8-TCDD of adipose tissue samples from 35 autopsy cases in Georgia and Utah were reported (Patterson et al. 1986a). The geometric means of the residues were 7.1 pg/g on a whole-weight basis and 9.6 pg/g on a lipid basis.

Subcutaneous adipose tissue from 31 persons was obtained from a hospital in Sweden (Rappe et al. 1986). No information was provided regarding the basis for their selection. All of the PCDD/PCDF isomers detected in adipose tissue were 2,3,7,8-chlorine substituted; 2,3,7,8-TCDD was detected at a mean concentration of 3 pg/g (basis not specified).

The results of the previous studies may not be representative of the general population because of the lack of random sampling (except in the study of Stanley et al. 1986), but the studies are mutually consistent. PCDDs and PCDFs appear to be present in the tissues of a significant portion of the population. Residues of 2,3,7,8-TCDD are present at mean background concentrations from just below the limit of quantitative detection to 10 pg/g; the more highly chlorine-substituted congeners are present at higher concentrations. The following studies report the results of studies of residues in adipose tissue of individuals exposed to PCDDs as a result of contamination.

Concentrations of the 2,3,7,8-TCDD congener were measured in the adipose tissue of individuals who believed they had a history of residential, recreational, or occupational exposure in Missouri (Patterson et al. 1986b,c). A central listing of individuals was created; determined by responses to questionnaires, the eligible exposed group consisted of approximately 400 persons. Thirty-nine people volunteered to donate subcutaneous abdominal adipose tissue. The control group was selected from individuals undergoing elective abdominal surgery in three midwestern hospitals and consisted of 57 subjects. All persons in both the exposed and control groups had detectable levels of 2,3,7,8-TCDD in their adipose tissues. After controlling for age and sex, the 2,3,7,8-TCDD levels in the exposed group were significantly higher than in the control group (geometric means of 21.8 pg/g versus 6.4 pg/g, respectively). Three individuals with residues greater than 100 pg/g reported that their most recent exposure to TCDD occurred from 12 to 14 years before their biopsy. Although preliminary, these results indicate that adipose tissue analysis may be an important exposure index. The exposed study group is probably not a representative sample of the exposed population. Because subjects were self-selected by volunteering, first for the central listing, and then, for the adipose tissue biopsy, there is likely to have been selection bias and true ranges of

2,3,7,8-TCDD residues in the population cannot be inferred from this study. Likewise, the control group was not selected in a randomized manner and may not be representative of "background" exposure in the regional population.

Schechter et al. (1986a) compared adipose tissue residues of 2,3,7,8-TCDD in persons living in the north or south of Vietnam. Adipose tissue from hospital patients in the north of Vietnam contained no detectable residues of 2,3,7,8-TCDD; of 15 hospital patients in the south of Vietnam, the adipose tissue of 12 contained detectable residues (mean, 28 pg/g on a lipid basis). Other PCDDs and PCDFs were measured at low levels in the subjects from the north and at much higher concentrations in subjects from the south. The nonrandom sampling makes the extrapolation of these results to the general Vietnamese population impossible. Schechter et al. (1986a) hypothesized that application of defoliants in the southern, but not northern, sectors of the country may be responsible for the elevated residues in adipose tissue of patients from the south. Insufficient individual exposure histories are provided to test this hypothesis.

2. Human Breast Milk

Mother's milk samples were collected from volunteers in Sweden and West Germany (Rappe et al. 1986). The isomer profiles in milk were qualitatively similar to those in fat presented earlier; the same 2,3,7,8-chlorine-substituted residues of PCDD and PCDF were found in similar proportions but at lower concentrations. The mean concentration of 2,3,7,8-TCDD in mother's milk from Sweden (n=4) was 0.6 pg/g and from Germany (n=5) was 1.9 pg/g.

Furst et al. (1986, abstract only) reported the results of analyses of 92 human milk samples from the Federal Republic of Germany. The samples contained a pattern of 2,3,7,8-chlorine-substituted PCDDs and PCDFs similar to these reported by Rappe et al. (1986). Because of a high detection limit (5 pg/g), 2,3,7,8-TCDD could not be quantified in any of the samples.

Breast milk samples obtained in 1973 and 1983 from subjects in the south of Vietnam, putatively exposed to defoliants, were analyzed for 2,3,7,8-TCDD residues by Schechter et al. (1986a). The three samples collected in 1973 contained mean concentrations of 2,3,7,8-TCDD of 4.1 pg/g (wet-weight basis) and 140 pg/g (lipid basis). Residues of 2,3,7,8-TCDD could not be detected (at detection limits less than 1 pg/g) from five 1983 breast milk samples. The lack of random sampling and detailed individual exposure histories precludes extrapolation of these results to the general Vietnamese population.

A review of PCDD and PCDF residues in human breast milk and the possible health implications is provided by Tarkowski and Yrjänheikki (1986). The reviewers emphasized that several congeners of PCDDs and PCDFs are present in milk, and, therefore, risk evaluation should concern all detected congeners and not only 2,3,7,8-TCDD.

3. Human Blood

Recent studies concerning serum concentrations of PCDDs and PCDFs have been incompletely reported in abstract form only. Kahn et al. (1986) compared blood and adipose tissue residues from veterans exposed to defoliants in Southeast Asia to nonexposed controls. The authors claim that a clear correlation exists between 2,3,7,8-TCDD residue levels and exposure status; The results were not presented in the available abstract. Patterson et al. (1986c) measured 2,3,7,8-TCDD residues in paired human serum and adipose tissue. The correlation between TCDD levels in adipose tissue and serum was not presented in the available abstract. Selenka (1986) reported in abstract form the results of a comparison of analyses of residues of PCDDs and PCDFs in blood samples from potentially exposed workers and a control group. Residues of PCDDs and PCDFs were found in 22% of the control group (n=89) and almost 100% of the workers (n=136). Residues of 2,3,7,8-TCDD were not detected.

4. Pharmacokinetic Parameters

The studies presented above indicate that analyses of adipose tissue, blood, and breast milk may, in principle, be useful indicators of exposure to PCDDs and PCDFs. However, measurements of body residues of these compounds provide no more than a semiquantitative measure of relative exposure in the absence of an understanding of the pharmacokinetic parameters required to relate tissue residues to cumulative dose.

A steady increase in adipose tissue concentrations of 2,3,7,8-TCDD with age was shown by Graham et al. (1986), Patterson et al. (1986c), Ryan (1986), and Stanley et al. (1986). It is apparent that 2,3,7,8-TCDD residues do not reach equilibrium in human tissues and that individuals may slowly accumulate 2,3,7,8-TCDD throughout their lifetime. The biological half-life has been estimated to range from approximately 200 days (Graham et al. 1986) to approximately 5-8 years (Poiger and Schlatter 1986, Patterson et al. 1986c). Graham et al. (1986) and Poiger and Schlatter (1986) assumed first-order kinetics, but by analogy with other organochlorines, a second excretion phase with a long half-life (comparable to lifetime) may be operative for 2,3,7,8-TCDD.

Until the pharmacokinetic parameters are more accurately defined, tissue residues of PCDDs and PCDFs are probably more appropriate as indicators of relative exposure than as measurements of cumulative dose. It is also likely that mean tissue levels determined from a representative sample of a given population are more indicative of exposure than are individual levels, due to large inter-individual variability in pharmacokinetics parameters.

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I. OTHER EFFECTS

1. Studies in Human Subjects

Previous studies of populations environmentally or occupationally exposed to chlorinated dibenzo-p-dioxins have shown elevated concentrations of D-glucaric acid in the urine of exposed individuals compared with unexposed controls (see Martin 1984 and Ideo 1984 in Volumes V and VI of this review). Increased D-glucaric acid in the urine is considered to be an indicator of hepatic microsomal enzyme induction. Steinberg et al. (1985) have subsequently speculated that urinary D-glucaric acid levels might be a sensitive indicator of dioxin exposure in humans and that measurement of this parameter might be useful for identifying exposed populations for epidemiological studies. These authors undertook a study to optimize the methodology for quantifying urinary D-glucaric acid quantification and to test their hypothesis among individuals who may have been exposed to chlorinated dibenzo-p-dioxins as a result of environmental contamination in Missouri.

First-morning-urine specimens were collected from 89 individuals who lived in dioxin-contaminated areas in Missouri. Of these individuals, 56 were considered to be at "high risk" because of exposure, and 33 persons were classified as being at "low risk." First-morning-urine specimens were also collected from 48 adult volunteers from the Centers for Disease Control and from 35 of their children. All samples were analyzed for D-glucaric acid. No significant differences were found between the Missouri residents and the CDC control groups nor between the "high" and "low" risk groups within the Missouri population.

The apparently negative findings of this study must be interpreted with caution. Actual exposure of the Missouri residents to chlorinated dibenzo-p-dioxins was not determined quantitatively, nor were tissue levels of chlorinated dibenzo-p-dioxins measured. Rather, duration of residence and participation in outdoor activities in the contaminated areas of Missouri were the criteria for inclusion in the exposed cohort. Furthermore, exposure of this cohort was likely to have been

relatively light as compared with relatively intense exposures in those cohorts where elevated urinary D-glucaric acid levels had been previously observed. Finally, the published report of this study does not contain information on possible confounding variables such as use of tobacco products and pharmaceuticals.

With the exception of isolated reports, exposure to phenoxy herbicides has not been associated with cardiovascular or pulmonary lesions. In order to investigate whether exposure to Agent Orange in Vietnam might be associated with such lesions, Pollei et al. (1986) conducted a study in which chest radiographs of 422 Vietnam veterans entered into the Agent Orange registry at the Albuquerque, New Mexico, Veterans Administration Medical Center were read and interpreted independently by three radiologists. The radiologists also read 105 chest radiographs obtained during routine physical examinations of Air Force personnel who did not serve in Vietnam. For the purpose of data analysis, a subset of 27 individuals from the 422 members of the Agent Orange registry cohort was identified as having recalled repeated handling of Agent Orange. Members of this subset were presumed to have relatively higher exposure to Agent Orange than others in the registry group.

There were no differences between the study group and control group either in the total number of abnormalities or in the types of abnormalities found in chest radiographs. Furthermore, the highly exposed subset of the study group had no increased frequency of abnormal findings, although this group was too small to allow meaningful statistical analysis. The authors concluded that Vietnam veterans are not at an increased risk for abnormalities that may be discernible on long-term follow-up chest radiographs. They noted that additional confidence in their findings was afforded by the fact that the control group was younger than the study group, which should bias the study toward finding excess abnormalities in the study group. The authors also recognized that the study group consisted of self-selected individuals, and enrollment in the

Agent Orange registry is not an accurate indication of Agent Orange exposure.

The negative findings of this study are not surprising in view of the lack of evidence that the cardiovascular and respiratory systems are primary targets of phenoxy herbicide toxicity in humans and other mammalian species. A much larger and more carefully controlled study than this, i.e., the Ranch Hand Study, has also failed to show significant changes that might be revealed by chest radiographs.

2. Studies in Experimental Animals

DeCaprio et al. (1986) studied the subchronic oral toxicity of TCDD in guinea pigs. Groups of 10 male and 10 female weanling Hartley guinea pigs were administered levels of 0, 2, 10, 76, or 430 ppt TCDD in their feed for 90 days, except for the high-dose animals, which were sacrificed early (males on day 46, females on day 60) because of excess mortality. Animals were observed daily, and feed consumption and body weights were determined weekly. Clinical chemistry was performed at the conclusion of the study. Animals were necropsied and examined histopathologically for lesions.

A recovery study was also conducted. Groups of male animals received 430 ppt TCDD in their feed for 11, 21, or 35 days and were then allowed to recover for 79, 69, or 55 days, respectively. Body weights and feed consumption were determined twice weekly for the first 60 days and weekly thereafter. Animals were sacrificed at 90 days but were not necropsied.

In the continuous feeding study, animals receiving 430 ppt TCDD in their diet exhibited a net body weight loss and increased mortality. Animals generally exhibited a severe decrease in body weight in the week before death and also exhibited abnormal eating behavior during the final 2 weeks of exposure. Animals receiving 76 ppt TCDD exhibited a significant decrease in the rate of body weight gain but no increased mortality. No clinical signs of toxicity were seen in animals receiving 2 or 10 ppt TCDD. Male but not female animals

receiving 76 ppt TCDD exhibited a significant decrease in absolute thymus and kidney weights compared to controls. Significant increases were reported for brain and liver weights in male animals and for liver weights in female animals. Organ weights were not reported for animals receiving 430 ppt, as an appropriate control population was not available. No effects on organ weights were observed in animals in the 2- or 10-ppt groups. Serum triglyceride levels were significantly elevated in males and elevated (not significantly) in females at the 76 ppt level. Again, clinical chemistry was not performed on animals in the 430-ppt group and animals receiving 2 or 10 ppt did not show any effects. Histopathologic examination revealed a significantly increased incidence of hepatocellular cytoplasmic inclusion bodies in female animals at 76 ppt; these inclusion bodies were observed in two of four high-dose female animals, but no such lesions were seen at lower doses. Atrophy of the thymic cortex was seen in one of four males and two of four females in the 430-ppt group. Several other lesions were observed in the 430- and 76-ppt groups, including fatty infiltration of the liver, lung edema, focal mineralization in the kidney and skeletal muscle, skeletal muscle degeneration, and focal inflammation of the thyroid.

In the recovery study, mortality was 10% in animals exposed to 430 ppt TCDD for 11 or 21 days and 70% in animals exposed for 35 days. An effective extended LD_{50} of 0.8 µg/kg TCDD was calculated from these results. Body weight loss, apparently caused by decreased food consumption, was observed in all groups during the first week of the study. Animals receiving TCDD for 11 days gained weight at the same rate as control animals after cessation of exposure, but their body weights remained depressed by about 20%. Animals exposed for 21 or 35 days to 430 ppt TCDD had severely depressed body weight gain and absolute body weights.

The authors noted that the no-observed-effect level (NOEL) of approximately 0.65 ng/kg/day that can be determined from this study is roughly one-tenth of the NOEL in rats, confirming the

greater sensitivity of the guinea pig to TCDD. The authors noted that animals given 76 ppt TCDD in their diet, equivalent to a daily dose of 4.9 ng/kg/day or a total dose of 0.44 µg/kg, exhibited toxic effects similar to those seen in guinea pigs following acute exposure. The authors suggested that their results indicate cumulative toxicity of TCDD in the guinea pig. Finally, the authors noted that guinea pigs in the recovery study failed to return to control body weights even over a 79-day observation period. The researchers noted that other studies also provide evidence that TCDD exposure may lower the body weight "set point" (Seefeld et al. 1984, as cited in DeCaprio et al. 1986).

Some additional histopathology on control and low-dose animals would have been useful in determining if the nonspecific lesions reported in the 76- and 430-ppt groups were compound-related or simply normal lesions for guinea pigs of that age. However, the study appears to have been well conducted overall.

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IV. BASIC RESEARCH ON TCDD TOXICITY

Volume VII of this review (Clement 1986) included a chapter on the relevance of experimental investigations of the mechanism of the biological action of TCDD and chemically/structurally related compounds. The results of this basic research continue to be published frequently. Such papers constitute a significant portion of the literature included in the annotated bibliography that accompanies this critical analysis of the literature. Although the relevance of this research to the assessment of human health effects of exposure to phenoxy herbicides is limited at present, such research may be of great value in the future if it reveals the mechanism(s) by which TCDD and related compounds cause biological responses in experimental animals and if it provides the basis for understanding interspecies differences in those responses. For example, TCDD causes cancer in experimental animals, but the evidence for such an effect in exposed humans is equivocal at best. This apparent interspecies difference may be an artifact due to inherent limitations of epidemiologic research or it may be a legitimate difference attributable to biochemical mechanisms that are operative in experimental animals but not in humans. Understanding the mechanism by which TCDD induces a neoplastic response in experimental animals may contribute to a resolution of this question. The remainder of this brief chapter is a review of literature published during 1986 that describes basic research on the mechanism of action of TCDD and related compounds.

Past research has suggested that, in experimental animals and perhaps humans, TCDD binds with high affinity to a stereospecific receptor protein located in the cytosol of cells in a wide variety of tissues. The TCDD-receptor complex then migrates into the nucleus and binds to DNA. This binding results in the expression of one or more structural genes and may also activate regulatory genes. One of the most thoroughly studied responses is stimulated transcription of cytochrome P450

genes leading to an accumulation of cytochrome P450 mRNA and increased aryl hydrocarbon hydroxylase activity in the affected cells. Whitlock (1986) published an excellent and comprehensive review of the regulation of cytochrome P450 gene expression, which includes a section on the genes that respond to polycyclic aromatic hydrocarbons, including TCDD. This review is complete through 1985.

Several studies were published in 1986 that provided insight into the nature of the cytochrome P450 genes that are induced by TCDD. P.B.C. Jones et al. (1986a,b) and Neuhold et al. (1986) used genetic engineering techniques to study the nature of the cytochrome P450 genes induced by TCDD in cultured mouse hepatoma cells. They identified at least two TCDD responsive domains, flanking the 5'-end of the gene, that function as enhancers of gene transcription. One of these domains contains a base pair segment that is substantially similar to a segment isolated from a human cytochrome P450 gene. Kimura et al. (1986) studied TCDD-induced P450 gene expression in the liver and five extrahepatic tissues of mice and found striking tissue-specific differences in transcriptional activation and mRNA stability. Quattrochi et al. (1986) cloned and isolated two cytochrome P450 cDNAs from a human liver cDNA library. Their results indicated that human liver cells contain at least two P450 genes that are highly homologous to genes induced by TCDD in rabbits and mice. These results suggest that humans are not fundamentally different from experimental animals in the mechanism by which TCDD induces aryl hydrocarbon hydroxylase activity.

A number of papers published in 1986 provided insight into the nature of the high affinity receptor for TCDD (the Ah receptor). Previous studies of the intracellular location of the receptor have given inconsistent results. Two studies published in 1986 independently provided confirming evidence that the Ah receptor is localized in the cytosol and only migrates to the nucleus after it is bound to the ligand (Denison et al. 1986a and Gudas et al. 1986). In addition, Hannah et al.

(1986) provided additional confirmation that TCDD must be bound to the receptor before the receptor will bind to nuclear DNA. Wilhelmsson et al. (1986) provided evidence that the Ah receptor (like the glucocorticoid receptor) binds heparin with high affinity and that the heparin binding site might be the same site that binds TCDD. Gudas and Hankinson (1986) showed that the Ah receptor may require energy in the form of ATP in order to exist in the active state.

Many of the more interesting properties of the Ah receptor mimic those of the glucocorticoid receptor, and research in past years has focused on these similarities. Closer investigation has revealed important differences between these two types of receptors. Poellinger et al. (1986a,b) have provided an excellent review of work in this area through 1984. In addition, Denison et al. (1986c) found the Ah receptor to be considerably less responsive than the glucocorticoid receptor to the stabilizing effect of molybdate. Taken together, these findings suggest that steroid hormones are not endogenous ligands for the Ah receptor.

The role played by the Ah receptor in mediating the biological effects of TCDD has been investigated vigorously in recent years. The results of structure-activity studies and/or studies using "responsive" and "nonresponsive" strains of mice suggest that a number of effects, including induction of hepatic microsomal enzymes, immunotoxicity, thymic atrophy, teratogenesis, epidermal hyperplasia, and hepatotoxicity, may require binding of TCDD to the Ah receptor as a step in the process. In 1986, Blank et al. (1986) provided evidence that B-lymphocyte differentiation may be mediated by the Ah receptor. Shara and Stohs (1986) found that the induction of lipid peroxidation by a number of chlorinated aromatic hydrocarbons obeyed the same structure-activity relationship as that seen for aryl hydrocarbon hydroxylase induction. On the other hand, Birnbaum (1986) found no important differences

between "responsive" and "nonresponsive" strains of mice in the rates and pathways of distribution, metabolism, and execretion of TCDD.

A hypothetical consequence of mediation of toxic effects by the Ah receptor is variable sensitivity to the toxic effects within and among species as a result of genetic differences in receptor levels or properties. Among different strains of mice, susceptibility to the toxic effects of TCDD appears to correlate with the presence of viable Ah receptors. However, researchers have had less success in attributing differences in sensitivity between different species to differences in receptor concentration or properties. Denison et al. (1986b,d) have found a wide range of receptor concentrations in tissues from a variety of mammalian and nonmammalian species. There is little evidence that these differences correlate with sensitivity to the toxicity of TCDD.

Limited studies of the concentrations of Ah receptors in human tissues have suggested large interindividual variability in these concentrations. Furthermore, these studies suggested that, on average, Ah receptor concentrations may be lower in human tissues than in comparable tissues from rats and mice. However, J.C. Cook et al. (1986) found uniformly high concentrations of Ah receptor in cultured human thymic epithelial cells and suggested that technical problems in isolating and quantifying Ah receptor in human tissues may have resulted in artificially low estimates of receptor concentrations in earlier studies.

It would be misleading to imply that all of the biological actions of TCDD and related chlorinated aromatic hydrocarbons are mediated through binding to the Ah receptor and that the nature of the receptor and its action are well understood. A number of anomalous findings were published during 1986. The chlorinated aromatic hydrocarbon, 2,2',4,4',5,5'-hexachlorobiphenyl, which neither binds to the Ah receptor nor induces AHH activity caused a dramatic increase in the number of Ah receptors in rats and mice and interacted synergistically with

TCDD in inducing AHH activity and causing toxicity (Bannister et al. 1986a). Another compound that has little or no affinity for the Ah receptor, 2,7-dichlorodibenzo-p-dioxin, suppressed immune function in mice without inducing AHH activity (Holsapple et al. 1986). Molloy et al. (1986) reported that TCDD caused proliferative responses in the skin of mice independent of the hr gene locus in direct contradiction of earlier findings of Poland et al. (1984) (see Clement 1986). Wong et al. (1986) looked for Ah receptor in human placenta and found only a low concentration of a receptor that was specific for TCDD but with substantially different physiological properties than the Ah receptor found in rodent tissues. Nevertheless, TCDD caused substantial induction of AHH activity in the placenta. This finding may be considered in conjunction with the report of J.C. Cook et al. (1986), who suggest that the human Ah receptor may be exceedingly labile and differ from the rodent receptor and thus be difficult to detect and quantitate in human tissues.

A number of papers published during 1986 described studies designed to elucidate the mechanisms by which TCDD causes cancer and other toxic effects in experimental animals. It is becoming increasingly clear that TCDD has profound effects on the endocrine system in experimental animals. A single dose of TCDD caused decreases in serum prolactin and follicle-stimulating hormone (Moore et al. 1986). DiBartolomeis et al. (1986a,b,c) found that TCDD actually inhibited AHH activity in adrenal cells and caused a decrease in adrenal steroidogenesis. It has been known that TCDD administration causes decreased androgen levels in male animals. Keys et al. (1986) reported that chlorinated dibenzo-p-dioxin induced hepatic testosterone 7α-hydroxylase and that the structure-activity relationship for this effect paralleled that for AHH induction. Mebus and Piper (1986) found that TCDD caused a decrease in testicular testosterone 17-hydroxylase and 17,20-lyase. In female animals, TCDD caused a decrease in uterine and hepatic estrogen receptors and decreased the estrogen responsiveness of the uterus (Romkes et al. 1986a,b; Gallo et al. 1986).

Taken together, the results of studies of the effects of TCDD and related compounds on the endocrine system must be considered as being preliminary, and no unifying hypothesis has been advanced. Whether or not some or all of these effects are primary effects of TCDD has not been established. The role of the endocrine system in modulating carcinogenic responses to chemical agents is well established, and, for this reason, research on the endocrine effects of TCDD may be very beneficial in increasing our understanding of the carcinogenic activity of this class of compounds.

Research in past years has indicated that acute administration of TCDD caused a dramatic decrease in circulating levels of thyroid hormone and that the "wasting syndrome" that is characteristic of acute TCDD intoxication resembles thyroid dysfunction. As a result, many research groups have focused their attention on the interaction of TCDD with the thyroid. The results of this research have provided no clear answers and are often inconsistent. For example, Kelling et al. (1986a) reported that TCDD did not affect the activity of two thyroid-responsive hepatic enzymes, α-glycerol phosphate dehydrogenase and malic enzyme. Roth et al. (1986), however, reported an increase in malic enzyme activity in rats after TCDD treatment, and Rickenbacher and McKinney (1986) found alterations in several enzyme activities and suggested a direct competitive interaction of TCDD with thyroxine in rat liver.

Potter et al. (1986a and b) concluded, from studies of thermogenesis and energy utilization in TCDD-treated thyroidectomized and intact rats, that altered thyroid status was not a major contributor to the acute "wasting syndrome". Henry and Gasiewicz (1986) investigated the effect of hypothyroidism on Ah receptor properties and enzyme induction by TCDD in rats and concluded that hypothyroidism does not modulate TCDD toxicity by altering the Ah receptor or its responsiveness. Kelling et al. (1986b) reported that the functional

thyroid status of the heart was not influenced by TCDD treatment. It would appear that the thyroid may not be a primary site of action for TCDD.

Another hypothetical mechanism that has been advanced to explain the acute toxicity of TCDD is that it causes an acute vitamin A deficiency. In support of this hypothesis, Hakansson et al. (1986) provided experimental evidence that TCDD severely depletes liver stores of vitamin A and interferes with the uptake and storage of newly administered vitamin A. Brouwer and van den Berg (1986) demonstrated that a metabolite of 3,3',4,4'-tetrachlorobiphenyl (a structural analogue of TCDD) inhibited the formation of a serum transport protein complex that carries both retinol and thyroxin. This result provides a possible connection between the thyroid and vitamin A hypothesis for the mechanism of TCDD toxicity.

Of particular relevance to the possible carcinogenic potential of TCDD is research on the mechanism by which TCDD promotes the carcinogenic response initiated by other carcinogenic agents. Morikawa et al. (1986) found that TCDD does not stimulate oxygen radical production by polymorphonuclear leukocytes, a mechanism for cancer promotion that has been hypothesized for phorbol esters. Kramer et al (1986a) reported that TCDD does not effect protein kinase C activity in cultured mouse thymoma cells. Goodrow et al. (1986) investigated the promotion of hepatocarcinogenesis by TCDD in rats initiated with diethylnitrosamine. They concluded that the interaction of TCDD with both Ah receptors and receptors for epidermal growth factor plays an important role in the mechanism by which TCDD promotes carcinogenesis.

In summary, the voluminous research on the mechanism of action of TCDD and related compounds underscores the complexity of the biological activity of this class of compounds. Virtually no system or tissue of the body is unaffected by these compounds. Little progress has been made in distinguishing direct and indirect effects or in identifying the primary target(s) of dioxin action. This is not to say, however, that

this research has not been of great scientific value. It has created a large and useful data base for further investigation. It has generated a number of working hypotheses, most of which are still viable. Perhaps of greatest value is the fact that this research has stimulated methodological and technological advances that will provide dividends for basic biomedical research in general.

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A. PICLORAM

Picloram (4-amino-3,5,6-trichloropicolinic acid) is a herbicide used on broad-leaved plants. It was a major active ingredient in Agent White. Clement (1984, 1985, 1986) and JRB (1981) have reviewed the limited information available in pre-1986 literature on the toxicology of picloram.

Two studies addressing the toxicology of picloram were reported in the literature in 1986. Hayes et al. (1986) conducted acute, 14-day, and 90-day subchronic toxicity studies in rats. In an abstract, Johnson et al. (1986) reported limited information on a 2-year chronic toxicity and carcinogenicity study in rats. Johnson et al. (1986) concluded that picloram increased liver and kidney weights in the high-dose groups but did not increase the incidence of tumors. A more detailed review of this study will be conducted in a subsequent volume, when more information becomes available.

Hayes et al. (1986) reported the results of three studies in CD rats. The first of these was an acute oral LD_{50} study. Groups of five male CD rats were dosed with 500, 600, 700, 750, 800, 840, 1,000, or 1,250 mg/kg potassium picloram by oral gavage. Groups of five female rats were administered doses of 600, 700, 750, 800, or 850 mg/kg. All animals were observed hourly during the first 9 hours after compound administration and twice daily for the next 14 days. Oral LD_{50} values of 954 mg/kg for males and 686 mg/kg for females were determined.

In the 14-day repeated dose study, groups of 10 male and 10 female CD rats were given doses of 0, 60, 190, or 600 mg kg/day picloram in their drinking water for 14 consecutive days. The animals were observed twice daily, and body weights were measured at the beginning, middle, and end of the study. Organ weights, urinalysis, and various clinical chemistry and hematological parameters were determined at the end of the

study. The only potentially compound-related effects observed in the 14-day study were caecal enlargement and decreased SGOT and SGPT.

In the 90-day subchronic study, male and female CD rats were divided into four groups of 20 rats of each sex and a high-dose group consisting of 10 rats of each sex. Groups were dosed with 0, 60, 190, 600, and 1,070 mg kg/day picloram in their drinking water for 90 consecutive days. Animals were observed twice daily and weighed weekly. Hematology and blood chemistry determinations and urinalysis were performed at sacrifice. Gross pathological examinations were performed, followed by weighing of selected organs and histopathological examination of kidneys, brains, and livers from a randomly selected subset of animals. Body weights were decreased in high-dose animals of both sexes, and mortality was increased in both 600- and 1,070-mg/kg dose groups (4/20 and 9/10 males died at 600 and 1,070 mg/kg, respectively; 2/20 and 7/10 females died at the same doses, respectively). Mild lesions in the kidneys were seen at all levels but particularly in males in the 600-mg/kg dose group. An increased incidence of mononuclear liver foci was observed in males given 190 or 600 mg/kg picloram, and the severity of mononuclear cell foci was increased in females in the 600-mg/kg group. However, the authors noted that these lesions are common in animals of that age, and it is unclear if these results reflect an exacerbation of the lesions by picloram or an unusually low incidence in vehicle control animals.

The authors noted that animals were able to survive a dose (1,070 mg/kg/day) equivalent to the LD_{50} for many weeks (mean time to death 6-8 weeks) when administered in drinking water. They hypothesized that this tolerance may be due to the different pharmacokinetics associated with the different methods of compound administration and the rapid excretion of picloram. The authors also noted that picloram does not appear to be highly toxic under the conditions of this study. Although as

noted by the authors, it is not possible to determine a no-observed-adverse-effect level from this study, it appears that picloram is not a cumulative toxicant.

B. CACODYLIC ACID

Cacodylic acid (dimethylarsenic acid) is a broad spectrum herbicide and was a major ingredient in Agent Blue. Information on its toxicology is limited. Clement (1984, 1985, and 1986) and JRB (1981) have reviewed the information available on the toxicology of cacodylic acid. No new studies on the health effects of cacodylic acid were published during 1986.

Hood (1985) recently prepared a monograph on the agricultural uses, environmental fate, and biological effects of cacodylic acid. The biological effects section of this monograph contains a fairly complete discussion of the animal toxicology, human toxicology, and pharmacology of cacodylic acid. In addition, Hood (1985) attempted to delineate the mechanism of action by which cacodylic acid produces toxic effects, and he provided recommendations for further research.

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REVIEW OF LITERATURE OF HERBICIDES, INCLUDING PHENOXY HERBICIDES AND ASSOCIATED DIOXINS

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BIBLIOGRAPHY

This volume is a bibliography of published and unpublished literature relevant to the human health effects of 2,4-D, 2,4,5-T, PCDD, cacodylic acid, and picloram that became available during 1986. The citations are arranged alphabetically by author. Each citation is followed by a series of keywords. These keywords describe the information contained in the paper including the health effects(s) or type of study, the route of administration/exposure, the chemical, the species, and the type of report.

Following the key words is a line that indicates those pages of the critical analysis (Volume IX) on which that document is discussed. Because many resources, e.g., review articles, new reports, and commentaries, are not cited in the critical review, short narrative statements describing the contents of those documents are included in the bibliography.

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Keywords: Miscellaneous study; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Review article

This is the summary and consensus conclusions of the International Symposium on Herbicides and Defoliants Used in War that was held in Ho Chi Minh City in January of 1983.

Anonymous. 1983b. [Report of Study Group P2: Epidemiology of Reproductive Abnormalities.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National D'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 142-144

Keywords: Reproductive toxicity; Birth defects; Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Human; Review article

This is the summary report of the working group on the epidemiology of reproductive abnormalities at the International Symposium on the Use of Herbicides and Defoliants in Warfare held in Ho Chi Minh City in January 1983. The group concluded that there appeared to be an increase in spontaneous abortions, certain congenital malformations, and hydatiform moles after exposure to herbicides and that further research was necessary to confirm or deny this apparent association.

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See Page 64.

Adena, M.A., Cobbin, D.M., Fett, M.J., Forcier, L., Hudson, H.M., Long, A.A., Nairn, J.R., and O'Toole, B.I. 1985. Mortality among Vietnam veterans compared with non-veterans and the Australian population. Med. J. Aust. 143:541-544

Keywords: Cancer; Epidemiological study; Cardiovascular toxicity; Neuro/behavioral effects; Other toxic effects; Occupational exposure; Phenoxy herbicide formulations; Human

This is the mortality study portion of the Australian Veterans' Health Studies in the form of a journal article. This study was discussed in detail in Volume V of this review (Clement 1985).

Ahlborg, U.G., Waern, F., and Hakansson, H. 1986. Interactive effects of PCDDs and PCDFs occuring in human mother's milk. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 61.

Keywords: Acute toxicity; Hepatotoxicity; Enzyme induction or inhibition; Tissue levels; Other toxic effects; Oral; Dioxins; Other contaminating compounds; Rat; Abstract

This abstract of a symposium presentation describes an acute oral toxicity study of a mixture of polychlorinated dibenzo-p-dioxins and dibenzofurans designed to resemble the profile of these compounds in human milk. Acute toxic potency was compared to that estimated by several different TCDD equivalent models.

Al-Bayati, Z.A., Stohs, S.J., and Al-Turk, W.A. 1986. TCDD, dietary iron and iron distribution in female rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:312

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; Other toxic effects; Unspecified route of exposure; Dioxins; Rat; Abstract

This is an abstract of a study of the effect of TCDD on the subcellular distribution of iron in the livers of rats. TCDD caused decreased iron content in the microsomes of treated rats. The authors concluded that TCDD-induced lipid peroxidation is not secondary to increased iron.

Albro, P.W., Corbett, J.T., and Schroeder, J.L. 1986. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on lipid peroxidation in microsomal systems in vitro. Chem. Biol. Interact. 57:301-313

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; In Vitro; Dioxins; Rat; Hamster

The authors investigated the effect of TCDD on lipid peroxidation in liver preparations from rats and hamsters and found that TCDD resulted in a decreased leakage of lysosomes. Iron stimulated lipid peroxidation but the results did little to reveal the interrelationship between lipid peroxidation, AHH induction and lethality.

Allison, A.C., and Lewis, R.A. 1986. Lack of health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA. 256:1446

Keywords: Epidemiological study; Hepatotoxicity; Immunological effects; Environmental exposure; Dioxins; Human; Commentary or opinion

See Page 11

American Academy of Clinical Toxicology. 1986. Commentary on 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD). Clin. Toxicol. 23:191-204

Keywords: Epidemiological study; Environmental exposure; Occupational exposure; Dioxins; Human; Review article

This review of the toxicology of TCDD prepared by the Scientific Review Committee of the AACT emphasizes the contradictory nature of the evidence regarding the human health effects of TCDD and describes on-going epidemiological investigations (43 references).

Antonov, N.S., and Burly, V.S. 1983. [The biomedical consequences of chemical warfare in Vietnam.] Proceedings of the International Symposium on the Use of Herbicides and Defoliant Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 41-45

Keywords: Miscellaneous study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Review article; Commentary or opinion

In this symposium presentation, the Russian authors summarize the history of the use of herbicides in South Vietnam and the human health and environmental consequences of that use (4 references).

Appel, K.E., Hildenbrandt, A.G., Lingk, W., and Kunz, H.W. 1986. Approaches to the health risk assessment of PCDD/PCDF. Chemosphere. 15:1825-1834

Keywords: Cancer; Environmental exposure; Dioxins; Human; Review article

In this symposium presentation, the authors review information on the mechanism by which 2,3,7,8-tetrachlorodibenzo-p-dioxin may cause cancer and the implications for risk assessment. The policy of the German Federal Health Office is described (19 references).

Astashkin, E.I., and Kiselev, M.P. 1983. [The effects of several pesticides and their impurities on porphyrin metabolism and hepatic microsomal enzymes.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 175-178

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Porphyria cutanea tarda; Phenoxy herbicide formulations; Dioxins; Review article

In this symposium presentation, the authors briefly review the evidence that halogenated aromatic hydrocarbons, especially TCDD, induce hepatic microsomal enzyme activity and change porphyrin metabolism (33 references).

Axelson, O., and Hardell, L. 1986. Storm in a cup of 2,4,5-T. Med. J. Aust. 144:612

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human; Commentary or opinion

In this letter to the editor, the authors provide evidence that Volume 4 of the Final Report of the Australian Royal Commission is almost identical to a submission to the Commission from Monsanto Australia, Ltd., and call into question the legitimacy of the entire Commission proceeding.

Bach, Q.T., Tran, T.T., Phung, X.B., Bach, K.H., Pham, T.L., and Vu, T.L. 1983. [Genetic effects of massive doses of herbicides and defoliants and chromosomal aberrations.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 166-174

Keywords: Epidemiological study; Genetic toxicity; Environmental exposure; Phenoxy herbicide formulations; Human

See Page 50.

Bannister, R., Mason, G., Kelley, M., and Safe, S. 1986a. The effects of cytosolic receptor modulation on the AHH-inducing activity of 2,3,7,8-TCDD. Chemosphere. 15:1909-1911

Keywords: Enzyme induction or inhibition; Mechanism of action; Injection; Dioxins; Rat; Mouse

Treatment of rats with 2,2',4,4',5,5'-hexachlorobiphenyl, a compound which does not induce AHH activity and which has minimal affinity for the Ah receptor, caused a marked increase in Ah receptor levels and acted synergistically with a subsequent dose of TCDD in inducing AHH activity. No mechanistic hypothesis was advanced.

See Page 109.

Bannister, R., Kelley, M., and Safe, S. 1986b. The effects of receptor modulation on the biologic and toxic actions of 2,3,7,8-TCDD. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:43

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Injection; Dioxins; Mouse; Abstract

This abstract describes the results of studies that have been published as a full paper elsewhere (see Bannister et al. 1986a).

Bannister, R., Kelley, M., and Safe, S. 1986c. The effects of receptor modulators on the AHH induction activity of 2,3,7,8-TCDD in C57BL/6 and DBA/2 mice. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds. September 16-19, 1986. Fukuoka, Japan. P. 56.

Keywords: Enzyme induction or inhibition; Mechanism of action; Injection; Dioxins; Mouse; Abstract

This abstract of a symposium presentation describes studies that are published as a full paper elsewhere (see Bannister et al. 1986a).

Barnes, D.G., Bellin, J., and Cleverly, D. 1986. Interim procedures for estimating risks associated with exposures to mixtures of chlorinated dibenzodioxins and dibenzofurans (CDDs and CDFs). Chemosphere. 15:1895-1903

Keywords: Cancer; Miscellaneous study; Environmental exposure; Dioxins; Other contaminating compounds; Human; Review article

This symposium presentation represents a preliminary version of the TCDD toxic equivalence approach to human health hazard assessment that is described in Bellin and Barnes 1985.

Beck, H., Eckart, K., Kellert, M., Mathar, W., and Ruhl, C.S. 1986. Levels of PCDF and PCDD in samples of human origin and food in the Federal Republic of Germany. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 134.

Keywords: Tissue levels; Environmental exposure; Dioxins; Human; Abstract

This abstract of a symposium presentation summarizes the methods, but provides no results, of a study of TCDD levels in 30 human milk samples and 8 cow's milk samples in West Germany.

Bellin, J.S., and Barnes, D.G. 1985. Health hazard assessment for chlorinated dioxins and dibenzofurans other than 2,3,7,8-TCDD. Toxicol. Ind. Health. 1:235-248

Keywords: Cancer; Miscellaneous study; Environmental exposure; Other contaminating compounds; Human; Review article

The authors propose a rationale for quantitative human health risk assessment for exposure to mixtures containing various polychlorinated dibenzo-p-dioxin and dibenzofuran congeners using a TCDD-equivalent approach (34 references).

Berman, E.F., Schaus, P., and Fujimoto, J.M. 1986. Comparison of the inhibition of biliary excretion produced by certain inducing agents including 2,3,7,8-tetrachloro-dibenzo-p-dioxin. J. Toxicol. Environ. Health. 17:395-403

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; Injection; Dioxins; Rat

The authors studied the effect of TCDD on biliary transport and excretion of morphine, imipramine, and ouabain. TCDD inhibited the canalicular transport of morphine and imipramine glucuronides and the transport of ouabain into the bile. The human health significance of these findings is unclear.

Birmingham, B., Clement, R., Harding, D., Pearson, R., Rokosh, D., Smithies, W., Szakolcai, A., Thorpe, B.H., Tosine, H., and Wells, D. 1986. Chlorinated dioxins and dibenzofurans in Ontario - Analysing and controlling the risks. Chemosphere. 15:1835-1850

Keywords: Cancer; Miscellaneous study; Environmental exposure; Dioxins; Human; Review article

In this symposium presentation, the authors describe the procedures and results of an analysis of human health risks due to environmental exposure to chlorinated dibenzo-p-dioxins and dibenzofurans in the Province of Ontario, Canada. The expert committee adopted a threshold model for risk extrapolation (30 references).

Birnbaum, L.S. 1986. Distribution and excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin in congenic strains of mice which differ at the Ah locus. Drug Metab. Dispn. 14:34-40

Keywords: Mechanism of action; Absorption, distribution, metabolism, and excretion; Injection; Dioxins; Mouse

The author studied the distribution, metabolism, and excretion of TCDD after intraperitoneal injection in "responsive" and "nonresponsive" strains of mice. There were no important differences between strains in the tissue distribution or in the rate and route of excretion, indicating that the Ah receptor or the Ah genetic locus play no role in this function. The authors conclude that other genetic loci are responsible for interspecies or interstrain differences in the pharmocokinetics of TCDD.

Birnbaum, L.S., and Couture, L.A. 1986. Disposition of octachlorodibenzo-p-dioxin (OCDD) in rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:310

Keywords: Absorption, distribution, metabolism, and excretion; Injection; Oral; Dioxins; Rat; Abstract

This abstract describes a study of the absorption, metabolism, and excretion of octachlorodibenzo-p-dioxin following intravenous and oral administration to male F344 rats. OCDD is slowly absorbed from the gut, is concentrated in the liver, and is excreted unchanged in the feces with a half life of one to three months.

Birnbaum, L.S., Harris, M.W., Miller, C.P., Pratt, R.M., and Lamb J.C., 1986. Synergistic interaction of 2,3,7,8,-tetrachlorodibenzo-p-dioxin and hydrocortisone in the induction of cleft palate in mice. Teratology. 33:29-35

Keywords: Acute toxicity; Mechanism of action; Reproductive toxicity; Birth defects; Oral; Dioxins; Mouse

See Page 63.

Blakley, B.R. 1986. The effect of oral exposure to the n-butylester of 2,4-dichlorophenoxyacetic acid on the immune response in mice. Int. J. Immunopharmac. 8:93-99

Keywords: Immunological effects; Oral; 2,4-D; Mouse

See Page 72.

Blakley, B.R., and Blakley, P.M. 1986. The effect of prenatal exposure to the n-butylester of 2,4-dichlorophenoxyacetic acid (2,4-D) on the immune response in mice. Teratology. 33:15-20

Keywords: Birth defects; Immunological effects; Oral; 2,4-D; Mouse

See Page 73.

Blakley, B.R., and Schiefer, B.H. 1986. The effect of topically applied n-butylester of 2,4-dichlorophenoxyacetic acid on the immune response in mice. J. Appl. Toxicol. 6:291-295

Keywords: Acute toxicity; Immunological effects; Dermal; 2,4-D; Mouse

See Page 72.

Blank, J., Tucker, A., Sweatlock, J., and Gasiewicz, T. 1986. Protective effect of alpha-naphthaflavone on TCDD-induced immunosuppression. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:312

Keywords: Immunological effects; Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture; Abstract

This abstract describes studies to investigate the mechanism by which TCDD suppresses differentiation of B-lymphocytes into antibody producing cells. Using cultured lymphocytes the authors provide evidence that the effect is mediated by binding to the Ah receptor.

Bombick, D.W., Madhukar, B.V., Brewster, D.W., and Matsumura, F. 1986. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) causes increased protein kinase C activity in the hepatic plasma membrane of the rat and guinea pig. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:42

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; Unspecified route of exposure; Dioxins; Rat; Guinea pig; Abstract

This abstract describes studies that have been published previously as a full paper (see Bombick et al. 1985 in Volume VIII of this review).

Bond, G.G., Cook, R.R., Brenner, F.E., Ducommun, D., and McLaren E.A. 1986. Evaluation of mortality patterns among chemical workers with chloroacne. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 190.

Keywords: Chloracne; Cancer; Epidemiological study; Occupational exposure; Dioxins; Phenoxy herbicide formulations; Human; Abstract

Breslin, P., Kang, H., and Shepard, B. 1986. Mortality pattern among Vietnam era veterans - A look at the suicide issue. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 188.

Keywords: Epidemiological study; Other toxic effects; Occupational exposure; Phenoxy herbicide formulations; Human; Abstract

This abstract of a symposium presentation presents preliminary results of a proportionate mortality study among veterans who served in Vietnam. The authors found less than the expected number of suicides among Vietnam veterans and a small excess of deaths due to motor vehicle and other accidents.

Brewster, D.W., and Matsumura, F. 1986. 2,3,7,8-Tetrachlorodibenzo-p-dioxin alters contraction force in isolated guinea pig atria. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:41

Keywords: Acute toxicity; Cardiovascular toxicity; Mechanism of action; Lethality; Unspecified route of exposure; Dioxins; Guinea pig; Abstract

This abstract describes a study of the effect of orally administered TCDD, at nearly lethal doses, on the response of atrial heart muscle to isoproterenol in guinea pigs. TCDD dramatically depressed the contractile response of guinea pig atria to catecholamines. The authors speculate that this might contribute to lethality.

Brouwer, A., and Van Den Berg, K.J. 1986. Binding of a metabolite of 3,4,3',4'-tetrachlorobiphenyl to transthyretin reduces serum vitamin A transport by inhibiting the formation of the protein complex carrying both retinol and thyroxin. Toxicol. Appl. Pharmacol. 85:301-312

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Injection; Other contaminating compounds; Rat

See Page 111.

Brownlee, L.J., and Hollebone, B.R. 1986. A correlation of induced mixed-function oxidase specific activity to C-H bond strengths in partially chlorinated monocyclic hydrocarbons. J. Appl. Toxicol. 6:61-66

Keywords: Enzyme induction or inhibition; Mechanism of action; Oral; Dioxins; Rat

This paper and a companion paper (Brownlee et al. 1986) describe a systematic study of structure-activity in relation to AHH induction by chlorinated aromatic hydrocarbons including polychlorinated dibenzo-p-dioxins.

Brownlee, L.J., Evans, C.H., and Hollebone, B.R. 1986. The relative induction of mixed-function oxidase specific activity to C-H and C-CL bond strengths in polychlorinated derivatives of dibenzo-p-dioxin (PCDDs). J. Appl. Toxicol. 6:67-71

Keywords: Enzyme induction or inhibition; Mechanism of action; Unspecified route of exposure; Dioxins; Rat

This is a companion paper to Brownlee and Hollibone (1986).

Carlson, E.A., Ciccarone, D.H., Jay, G.D., Moss, L.J., Levy, R.S., and Meyers, T.K. 1983. Biological effects of phenoxy herbicides on Drosophila melanogaster. Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. 3:190-199

Keywords: Genetic toxicity; Other routes of exposure; 2,4-D; 2,4,5-T; Other species

See Pages 53 and 54.

Chastain, J.E., and Pazdernik, T.L. 1985. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced immunotoxicity. Int. J. Immunopharmac. 7:849-856

Keywords: Immunological effects; Mechanism of action; Injection; Dioxins; Mouse

See Page 74.

Christophers, A.J. 1986. Storm in a cup of 2,4,5-T. Med. J. Aust. 145:298

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Dioxins; Phenoxy herbicide formulations; Human; Commentary or opinion

In this letter to the editor, the author contests the allegation by Axelson and Hardell (1986) that the scientific credibility of the Australian Royal Commission was compromised by its heavy reliance on a submission by Monsanto Australia, Ltd. A reply by Axelson and Hardell is also included.

Clark, G.C., Germolec, D., and Luster, M.I. 1986. Effects of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on protein phosphorylation in B lymphocytes. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:167

Keywords: Immunological effects; Mechanism of action; In Vitro; Dioxins; Human; Mammalian cells in culture; Abstract

This abstract summarizes a study of the mechanism by which TCDD suppresses B-cell differentiation in response to lipopolysaccharide. The results of in vitro studies suggest that TCDD may exert this effect by interfering with protein phosphorylation.

Clement Associates, Inc, (Clement). 1986. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. Vol. VII: Analysis of recent literature on health effects, and Vol. VIII: Annotated bibliography of recent literature on health effects. U.S. Veterans Administration, Dept. of Medicine and Surgery, Washington, D.C. 219 pages.

Keywords: Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Dioxins; Review article

This review represents the third complete update of scientific literature relevant to the health effects of phenoxy herbicides and their chlorinated dibenzo-p-dioxin contaminants, and it covers the literature that became available in 1985.

See Pages 21, 105, 109, 118, and 120.

Coggon, D., Pannett, B., Winter, P.D., Acheson, E.D., and Bonsall, J. 1986. Mortality of workers exposed to 2-methyl-4-chlorophenoxyacetic acid. Scand. J. Work Environ. Health. 12:448-454

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human

See Page 28.

Cohen, F.L. 1986. Paternal contributions to birth defects. Nurs. Clin. North Am. 21:49

Keywords: Epidemiological study; Mechanism of action; Reproductive toxicity; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Human; Review article

This article reviews the possible mechanisms by which paternal exposure to various agents may effect reproductive outcome, with emphasis on genetic means. A brief summary on Agent Orange and its components concludes that the data are inconclusive.

Colton, T. 1986. Herbicide exposure and cancer. JAMA. 256:1176-1177

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human; Commentary or opinion

In this editorial, which appeared in the same issue of JAMA as did the case-control epidemiology study of cancers in Kansas farmers (Hoar et al. 1986), the author critically reviews the available evidence on the association between phenoxy herbicide exposure and non-Hodgkin's lymphoma, Hodgkin's disease, and soft-tissue sarcoma.

Connett, P. 1986. Letter to the Editor: In response to Tschirley's article "Dioxin" [Sci. Am., Feb. 1986]. Sci. Am. Pp. 4-6.

Keywords: Acute toxicity; Cancer; Epidemiological study; Dioxins; Commentary or opinion

The author of this letter to the editor takes issue with the conclusion of Tschirley (1986) that TCDD is not a significant human health hazard.

Conso, F. 1986. Evaluation of the human health risks from polychlorinated biphenyls (PCB), polychlorinated dibenzodioxins and dibenzofurans. Arch. Mal. Prof. 47:27-34

Keywords: Chloracne; Cancer; Immunological effects; Hepatotoxicity; Reproductive toxicity; Dioxins; Other contaminating compounds; Review article

This is a superficial review of the toxicology and environmental properties of polychlorinated aromatic hydrocarbons including polychlorinated dibenzo-p-dioxins. The author emphasizes the lack of conclusive evidence of adverse human health effects other than short-term effects such as chloracne and neurological effects (32 references).

Constable, J.D. 1986. An historical survey of Agent Orange/dioxin research in Vietnam from the AAAS Assessment Commission in 1970 until the present. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxin and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 193.

Keywords: Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human; Review article; Abstract

In this abstract of a symposium presentation, the author describes how he became aware of studies of birth defects among women in Vietnam who may have been exposed to Agent Orange.

Cook, J.C., Dold, K.M., and Greenlee, W.F. 1986. Evidence that human thymic epithelial (HuTE) cells are a target for 2,3,7,8,-tetrachlorodibenzo-p-dioxin (TCDD). Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:172

Keywords: Immunological effects; Mechanism of action; In Vitro; Dioxins; Human; Mammalian cells in culture; Abstract

See Pages 72, 108, and 109.

Cook, R.R., Bond, G.G., Olson, R.A., Ott, M.G., and Gondek, M.R. 1986a. Evaluation of the mortality experience of workers exposed to the chlorinated dioxins. Chemosphere. 15:1769-1776

Keywords: Cancer; Epidemiological study; Occupational exposure; Dioxins; Phenoxy herbicide formulations; Human

See Page 32.

Cook, R.R., Bond, G.G., Olson, R.A., and Ott, M.G. 1986b. Update of mortality experience of workers exposed to chlorinated dioxins. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 189.

Keywords: Cancer; Epidemiological study; Occupational exposure; Dioxins; Phenoxy herbicide formulations; Human; Abstract

See Pages 32 and 34.

Cung, B.T., and Nguyen, T.C. 1983. [The incidence of spontaneous abortions and congenital malformations in several communities (within Giong Trom District, Ben Tre Province, Vietnam) subjected to spraying with toxic chemicals.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation de Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 99-103

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human;

Cung, B.T., Vu, V.D., Nguyen, V.C., Nguyen, H.B., Nguyen, V.Q., and Huynh, T.L. 1983. [Chromosomal aberrations among victims of the spraying of toxic herbicides and defoliants in Vietnam.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation de Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 155-160

Keywords: Epidemiological study; Genetic toxicity; Environmental exposure; Phenoxy herbicide formulations; Human

See Pages 51 and 52.

Czeskleba-Dupont, R. 1986. A comparison of risk assessments for chlorinated dioxins by ADI values and by incremental cancer risk estimates. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 198.

Keywords: Cancer; Miscellaneous study; Environmental exposure; Dioxins; Human; Review article; Abstract

This is an abstract of a symposium presentation in which the author discussed the relative merits of using threshold and non-threshold models for quantitative risk assessment for TCDD.

Dai, L.C., and Quynh, H.T. 1986. The organization of Vietnamese scientific research on the consequences of the use of herbicides and defoliants during wartime. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 177.

Keywords: Miscellaneous study; Environmental exposure; Phenoxy herbicide formulations; Human; Abstract; Review article

This is an abstract of a symposium presentation in which the authors describe the organization of research on the health effects of exposure to phenoxy herbicides in Vietnam.

Dai, L.C., and Quynh, H.T. 1986. Overview of Vietnamese scientific studies on the consequences of the use of herbicides and defoliants during wartime. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 176.

Keywords: Cancer; Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human; Review article; Abstract

This is an abstract of a symposium presentation in which the authors summarize studies of the health effects of phenoxy herbicide exposure that were conducted by Vietnamese scientists.

DeCaprio, A.P., McMartin, D.N., O'Keefe, P.W., Rej, R., Silkworth J.B., and Kaminsky, L.S. 1986. Subchronic oral toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the guinea pig: Comparisons with a PCB-containing transformer fluid pyrolysate. Fundam. Appl. Toxicol. 6:454-463

Keywords: Subchronic toxicity; Hepatotoxicity; Other toxic effects; Oral; Dioxins; Guinea pig

See Pages 88, 101, and 103.

Dencker, L. 1985. The role of receptors in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxicity. Arch. Toxicol. Suppl. 8:43-60

Keywords: Mechanism of action, Dioxins; Review article

In this review article, the author describes the physiological properties of the Ah receptor and summarizes the evidence that some of the toxic effects of TCDD are mediated through this receptor (64 references).

Denison, M.S., Harper, P.A., and Okey, A.B. 1986a. Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin: Codistribution of unoccupied receptor with cytosolic marker enzymes during fractionation of mouse liver, rat liver and cultured Hepa-1c1 cells. Eur. J. Biochem. 155:223-229

Keywords: Mechanism of action; Acute toxicity; In Vitro; Dioxins; Rat; Mouse; Mammalian cells in culture

Using data from studies in rats, mice, and cultured mammalian cells, the authors provide evidence that the Ah receptor is primarily localized in the cytoplasm when it is unoccupied.

See Page 106.

Denison, M.S., Vella, L.M., and Okey, A.B. 1986b. Structure and function of the Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Biol. Chem. 261:3987-3995

Keywords: Mechanism of action; In Vitro; Dioxins; Rat; Mouse

In this study, the molecular properties of the Ah receptors from the livers of rats and receptive mice were characterized and compared. Based on criteria of molecular size, response to high ionic strength environments, and affinity for various ligands, the receptors from these species are similar but not identical.

See Page 108.

Denison, M.S., Vella, L.M., and Okey, A.B. 1986c. Hepatic Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Biol. Chem. 261:10189-10195

Keywords: Acute toxicity; Other toxic effects; Mechanism of action; In Vitro; Dioxins; Rat; Mouse

Denison, M.S., Wilkinson, C.F., and Okey, A.B. 1986d. Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin: Comparative studies in mammalian and nonmammalian species. Chemosphere. 15:1665-1672

Keywords: Mechanism of action; In Vitro; Dioxins; Other spe- cies; Bird; Fish; Human; Monkey; Mouse; Rat; Rabbit

Using radiolabelled TCDD, the authors conducted in vitro assays to determine the properties of the Ah receptor in hepatic cytosol from diverse animal species. Receptor was detectable in most mammalian species and not detectable in fish, amphibians, and invertebrates. Receptor properties varied among species.

See Page 108.

DiBartolomeis, M.J., Christou, M., and Jefcoate, C.R. 1986a. Regulation of rat and bovine adrenal metabolism of polycyclic aromatic hydrocarbons by adrenocorticotropin and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch. Biochem. Biophys. 246:428-438

Keywords: Mechanism of action; Other toxic effects; Injection; In Vitro; Dioxins; Rat; Mammalian cells in culture

See Page 109.

DiBartolomeis, M.J., Moore, R.W., and Peterson, R.E. 1986b. Hypercholesterolemia and the regulation of adrenal steroidogenesis in 2,3,7,8-tetrachlorodibenzo-p-dioxin treated rats. Toxicol. Appl. Pharmacol. 85:313-323

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Oral; Dioxins; Rat

See Page 109.

DiBartolomeis, M.J., Williams, C., and Jefcoate, C.R. 1986c. Inhibition of ACTH action on cultured bovine adrenal cortical cells by 2,3,7,8-tetrachlorodibenzo-p-dioxin through a redistribution of cholesterol. J. Biol. Chem. 261:4432-4437

Keywords: Mechanism of action; Other toxic effects; In Vitro; Dioxins; Mammalian cells in culture

See Page 109.

Dibartolomeis, M.J., Williams, C., and Jefcoate, C.R. 1986d. 2,3,7,8-Tetrachlorodibenzo-p-dioxin redirects ACTH stimulation of bovine adrenal cortical cells in vitro. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:275

Keywords: Mechanism of action; Other toxic effects; In Vitro; Dioxins; Mammalian cells in culture; Abstract

This abstract describes a study that has subsequently been published as a full article (see DiBartolomeis, M..J. et al. 1986c).

DiDomenico, A., and Zapponi, G.A. 1986. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) in the environment: Human health risk estimation and its application to the Seveso case as an example. Regul. Toxicol. Pharmacol. 6:248-260

Keywords: Cancer; Environmental exposure; Dioxins; Human; Review article

Using data from animal experiments and various mathematical models and assumptions for low-dose and interspecies extrapolation, the authors estimate the risk of cancer among residents of zones B and R in the vicinity of Seveso. The authors conclude that even under worst case exposure scenarios lifetime cancer risks are 10^{-5} or lower.

Do, D.V. 1983. [Primary liver cancer and chemical warfare in Vietnam.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 2. Pp. 18-22

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human

See Pages 37 and 38.

Do, T.T., Nguyen, L., Nguyen, V.T., Truong, T.M.D., and Lee, T. 1983. [Investigation of pathological characteristics within an area affected by toxic chemicals applied from 1966 to 1968.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 33-40

Keywords: Epidemiological study; Hematologic effects; Hepatotoxicity; Neuro/behavioral effects; Review article; Other toxic effects; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human

See Page 37.

Doan, T.B., Nguyen, L.H., Pham, H.P., Trinh, K.A. 1983. [Investigation of health and morbidity in a cohort and the general population of Tay Ninh Province.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 29-33

Keywords: Cardiovascular toxicity; Epidemiological study; Neuro/behavioral effects; Other toxic effects; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human

See Page 37.

Dwyer, J.H., Lang, T.D., Van, D.D., Flamenbaum, C. Dwyer, K.M., and Fantini, D. 1983. Health problems as a result of exposure to herbicides: Preliminary results of an investigation of the families of 432 North Vietnamese combat veterans. Proceedings of the International Symposium on the Use of Herbicides and Defoliants on Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. 3:9-23

Keywords: Epidemiological study; Reproductive toxicity; Other toxic effects; Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Human

Eisen, H.J., and Schecter, A. 1986. Actions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the human hepatoblastoma $HepG_2$ tissue culture cell line: Functional and electron microscopic observations. Chemosphere. 15:1965-1970

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture

In this study, the authors studied the effect of TCDD on the structure and function of human hepatoblastoma cells in culture and found no morphological alterations like those found in mouse hepatoma cells or liver cells from humans who were exposed in vivo. The authors speculate that morphological alterations are indirect effects of TCDD.

Engelse, D.L., Floot, B.G.J., Menkveld, G.J., and Tates, A.D. 1986. Enhanced repair of O6-methylguanine in liver DNA of rats pretreated with phenobarbital, 2,3,7,8-tetrachlorodibenzo-p-dioxin, ethionine, or N-alkyl-N-nitrosoureas. Carcinogenesis. 7:1941-1947

Keywords: Cancer; Mechanism of action; Injection; Dioxins; Rat

TCDD is one of several inducers and promoters of hepatocarcinoma in rats that are tested for their capacity to enhance O6-methylguanine repair. This effect was not secondary to hepatocellular proliferation or direct interaction with DNA. The authors conclude that the enhancement of O6-methylguanine repair is a common property of compounds that induce or promote liver cancer.

Epstein, S.S. 1983. American Veterans and Agent Orange. Proceeding of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. 2:28-40

Keywords: Miscellaneous study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Review article; Commentary or opinion

In this symposium presentation, the author discusses the ongoing efforts within the United States to investigate possible associations between exposure to Agent Orange in Vietnam and long-term adverse health effects (14 references).

Evatt, P. 1985. Final Report of the Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam. July, 1985. Australian Government Publishing Service, Canberra, Australia. 9 volumes.

Keywords: Cancer; Epidemiological study; Neuro/behavioral effects; Reproductive toxicity; Birth defects; Other toxic effects; Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Human; Review article

This document is the end product of a two-year inquiry into the potential long-term adverse health effects of exposure to phenoxy herbicides and related compounds on Australian troops who were on active duty in Vietnam during the period when defoliants were used in that country. In addition to critical reviews of scientific literature and summaries of testimony by expert witnesses, the report contains a great deal of procedural information and philosophical discussion.

Farrell, K., and Safe, S. 1986a. 2,3,7,8-Tetrachloro-dibenzo-p-dioxin: Relationship between toxicity and the induction of aryl hydrocarbon hydroxylase and ornithine decarboxylase. Chemosphere. 15:1971-1976

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Injection; Dioxins; Rat

The authors study the induction of ornithine decarboxylase (ODC) in rat liver by TCDD showing that the time course for induction is different from that of AHH induction and that ODC inhibition can be blocked without effecting AHH induction or thymic atrophy. The authors conclude that ODC induction is not related to AHH induction or toxicity.

Farrell, K., and Safe, S. 1986b. Lack of cooperativity in the binding of 2,3,7,8-TCDD to the Ah receptor. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:43

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture; Abstract

This is an abstract of a kinetic study of TCDD binding to the Ah receptor which demonstrates a lack of positive cooperativity, i.e., increased affinity of the receptor for the substrate as a result of substrate binding.

Fishbein, L. 1986. Limitations of health-risk estimates for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere, 15:1883-1893

Keywords: Cancer; Environmental exposure; Dioxins; Human; Review article

In this symposium presentation, the author critically examines the standard assumptions contained in quantitative estimates of human cancer risk due to exposure to polychlorinated dibenzo-p-dioxins and shows how such assumptions lead to an overestimate of risk (18 references).

Fokin, A.B. 1983. [The long term consequences of the use of 2,3,7,8-tetrachlorodibenzo-p-dioxin by the U.S. Army in South Vietnam.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 145-155

Keywords: Miscellaneous study; Environmental exposure; Dioxins; Human; Review article; Commentary or opinion

In this symposium presentation, the author reviews the toxicology of 2,3,7,8-tetrachlorodibenzo-p-dioxin and speculates on the consequences of the use of dioxin-contaminated herbicides in Vietnam (references not included).

Ford, A.M., and McCarville, W.J. 1986. Dioxin risk. Nature. 323:576

Keywords: Cancer; Epidemiological study; Occupational exposure; Dioxins; Phenoxy herbicide formulations; Human; Commentary or opinion

In this brief letter to the editor, the authors object to the publication of an earlier letter by Hay and Silbergeld because they did not disclose their "hidden affiliation" with plaintiffs in a lawsuit. A reply by Hay and Silbergeld and an editor's comment are also included.

Fulop, Z., and Mate, L. 1983. [The medical problems and long term human health effects of TCDD-contaminated herbicides used by U.S. military forces in Vietnam.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 133-142

Keywords: Miscellaneous study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human; Review article; Commentary or opinion

In this symposium presentation the authors review the health effects of phenoxy herbicides and chlorinated dibenzo-p-dioxin and argue that the use of phenoxy herbicides in Vietnam has caused an epidemic of congenital malformations (28 references).

Furst, P., Meemken, H.A., Kruger, C., and Groebel, W. 1986. Polychlorinated dibenzodioxins and dibenzofurans in human milk samples from western Germany. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 136.

Keywords: Tissue levels; Environmental exposure; Dioxins; Human; Abstract

See Page 94.

Furuhashi, N., Kurl, R.N., Wong, J., Villee, C.A. 1986. A cytosolic binding protein for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the uterus and deciduoma of rats. Pharmacology. 33:110-120

Keywords: Enzyme induction or inhibition; Mechanism of action; Reproductive toxicity; Birth defects; In Vitro; Dioxins; Mouse

The authors isolated receptors for TCDD from the uterus and deciduoma of rats. The binding of TCDD to this receptor was not affected by steroid hormones.

Gallo, M.A., Hesse, E.J., MacDonald, G.J., and Umbreit, T.H. 1986. Interactive effects of estradiol and 2,3,7,8-tetrachlorodibenzo-p-dioxin on hepatic cytochrome P-450 and mouse uterus. Toxicol. Lett. 32:123-132

See Pages 64, 65, and 109.

Keywords: Enzyme induction or inhibition; Mechanism of action; Reproductive toxicity; Injection; Dioxins; Mouse

Gasiewicz, T.A., Henry, E.C., Baggs, R.B., Rucci, G., and Schecter A., 1986a. Temporal and dose-related characteristics of biochemical and morphological alterations in the hamster induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere. 15:1749-1752

Keywords: Acute toxicity; Enzyme induction or inhibition; Lethality; Mechanism of action; Other toxic effects; Injection; Dioxins; Hamster

In this and a companion paper (Gasiewicz et al. 1986b) the authors describe studies of the actions of acute doses of TCDD in Syrian Golden hamsters. This species is as sensitive as rats and mice to the AHH inducing and hepatotoxic effects of TCDD yet it is much more resistant to the acute lethal effects including the "wasting syndrome" possibly as a result of differences in thyroid response.

Gasiewicz, T.A., Rucci, G., Henry, E.C., and Baggs, R.B. 1986b. Changes in hamster hepatic cytochrome P-450, ethoxycoumarin O-deethylase, and reduced NAD(P):Menadione oxidoreductase following treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Biochem. Pharmacol. 35:2737-2742

Keywords: Acute toxicity; Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; Injection; Dioxins; Hamster

This is a companion article to Gasiewicz et al. 1986a.

Geyer, H.J., Scheunert, I., Filser, J.G., and Korte, F. 1986. Bioconcentration potention (BCP) of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) in terrestrial organisms including humans. Chemosphere. 15:1495-1502

Keywords: Tissue levels; Environmental exposure; Dioxins; Human; Review article

Using experimental data, the authors calculate bioconcentration factors for TCDD in the adipose tissue of rats, cows, and monkeys. They also estimate that bioconcentration factors in human tissue range from approximately 100 to 200, based on indirect evidence.

Gillner, M., Fernstrom, B., and Gustafsson, J. 1986. A new structure-affinity relationship for TCDD receptor binding. Chemosphere. 15:226-230

Keywords: Mechanism of action; In Vitro; Other contaminating compounds; Dioxins; Mammalian cells in culture

The authors studied the capacity of a series of indoles to inhibit binding of TCDD to the Ah receptor in rat liver cytosol. Using computer analyses the authors developed a structural requirement for the active site of the receptor.

Goodrow, T., Sunahara, G., Sloop, T., Lucier, G., and Nelson, K. 1986. Evaluation of early receptor and histochemical changes in TCDD-promoted hepatocarcinogenesis. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:311

Keywords: Cancer; Hepatotoxicity; Enzyme induction or inhibition; Mechanism of action; Unspecified route of exposure; Dioxins; Rat; Abstract

This abstract describes studies designed to elucidate the mechanism by which TCDD promotes hepatocarcinogenesis. Treatment of rats with diethylnitrosamine followed by repeated treatment with TCDD resulted in an increased number of GGT-positive foci and DNA synthesis compared to all control treatments. DEN initiation resulted in increased numbers and phosphorylation of epidermal growth factor receptors suggesting that both these receptors and Ah receptors play a role in TCDD carcinogenesis.

See Page 111.

Gorski, J.R., and Rozman, K. 1986. Characterization of thyroid homeostasis in TCDD-treated rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:88

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Injection; Dioxins; Rat; Abstract

This is an abstract of a study of the response of circulating thyroid hormone levels in rats following treatment with TCDD. The authors found the changes to be incompatible with those for animals in a state of reduced food intake.

Gough, M. 1986. Dioxin, Agent Orange. 1986. Plenum Publishing Co., New York. P. 288 pages.

Keywords: Cancer; Epidemiological study; Mechanism of action; Miscellaneous study; Reproductive toxicity; Birth defects; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Human; Review article

In this comprehensive book written for the lay reader, the author reviews the history of scientific and public inquiry into the health effects of phenoxy herbicides and their contaminating chlorinated dioxin impurities. Chapters are devoted to the Vietnam experience, the Seveso incident, the Missouri contamination problems; and to industrial exposures to dioxins.

Graham, M., Hileman, F.D., Orht, R.G., Wendling, J.M., and Wilson, J.D. 1986. Chlorocarbons in adipose tissue from a Missouri population. Chemosphere. 15:1595-1600

Keywords: Tissue levels; Environmental exposure; Dioxins; Human

See Pages 92 and 96.

Grover, R., Cessna, A.J., Muir, N.I., Riedel, D., Franklin, C.A., and Yoshida, K. 1986a. Factors affecting the exposure of ground-rig applicators to 2,4-D dimethylamine salt. Arch. Environ. Contam. Toxicol. 15:677-686

Keywords: Absorption, distribution, metabolism, and excretion; Miscellaneous study; Occupational exposure; 2,4-D; Human

The authors studied the exposure of farmers to 2,4-D during the application of 2,4-D dimethlyamine salt formulation to wheat fields using tractor-drawn ground rigs. Inhalation was a minor route of exposure with deposition on the hands representing the major route. Only a small percentage of the theoretical dermal dose was excreted in the urine.

Grover, R., Franklin, C.A., Muir, N.I., Cessna, A.J., and Riedel, D. 1986b. Dermal exposure and urinary metabolite excretion in farmers repeatedly exposed to 2,4-D amine. Toxicol. Lett. 33:73-83

Keywords: Absorption, distribution, metabolism, and excretion; Miscellaneous study; Occupational exposure; 2,4-D; Human

The authors determined dermal exposure to, and urinary excretion of, 2,4-D among farmers exposed during routine application using tractor-drawn spray rigs. They concluded that only a very small portion of the 2,4-D deposited on the skin was absorbed.

Gudas, J.M. 1985. Biochemical and Genetic Regulation of the Ah Receptor for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin in Rodent Hepatoma Cells. Ph.D. Dissertation, University of Michigan, Ann Arbor, MI. 123 pages.

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture

This Ph.D. dissertation describes a systematic investigation of the interaction of TCDD with the Ah receptor in cultured Hepa-1 cells. Much of this work has been published in journal articles (see Gudas and Hankinson 1986 and Gudas et al. 1986).

Gudas, J.M., and Hankinson, O. 1986. Reversible inactivation of the Ah receptor associated with changes in intracellular ATP levels. J. Cell. Physiol. 128:449-456

Keywords: Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture

Experimental evidence is provided for the hypothesis that ATP, or another energy dependent molecule, is required to maintain the Ah receptor in an active state.

See Page 106.

Gudas, J.M., Karenlampi, S.O., and Hankinson, O. 1986. Intracellular location of the Ah receptor. J. Cell. Physiol. 128:441-448

Keywords: Hepatotoxicity; Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture

The authors provide additional evidence that the Ah receptor is localized in the cytoplasm of cells.

Hakansson, H., Ahlborg, U.G., and Gottling, L. 1986. The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the distribution and excretion of the endogenous pool of vitamin A in rats with low liver vitamin A stores. Chemosphere. 15:1715-1723

Keywords: Acute toxicity; Mechanism of action; Hepatotoxicity; Other toxic effects; Oral; Dioxins; Rat

See Page 111.

Hall, W. 1986. The Agent Orange controversy after the Evatt Royal Commission. Med. J. Aust. 145:219-225

Keywords: Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Dioxins; Human; Review article; Commentary or opinion

The author describes the history of the Australian Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam and summarizes the final report of that Commission. The author argues for unqualified acceptance of the Commission's conclusions (20 references).

Hannah, R., Lund, J., Poellinger, L., Gillner, M., and Gustafsson J., 1986. Characterization of the DNA-binding properties of the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Biochem. 156:237-242

Keywords: Acute toxicity; Mechanism of action; In Vitro; Dioxins; Rat

Chromatography on DNA-cellulose columns was used to study the nature of the binding of the TCDD-Ah receptor complex to DNA. The receptor must first bind TCDD before it will bind to DNA and both electrostatic and configurational interactions are involved in the binding to DNA.

See Pages 106 and 107.

Hardell, L., and Eriksson, M. 1986. Soft-tissue sarcoma and exposure to dioxins. The Lancet. P. 868.

Keywords: Cancer; Epidemiological study; Environmental exposure; Dioxins; Human; Commentary or opinion

In this letter to the editor, the authors comment on the earlier letter of Puntoni et al. (1986) describing an increased incidence of soft-tissue sarcoma among residents of Seveso.

Hatch, M.C. 1983. The reproductive effects of exposure of humans to phenoxy herbicides and/or chlorinated dioxins. Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. 3:70-79

Keywords: Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human; Review article

The author briefly reviews the methodological problems of the existing studies of Agent Orange's possible effects on reproduction and the theoretical problems of interpreting the generated data. She finds the existing information largely inconclusive and suggests approaches for further study in Vietnam.

Hatch, M.C., and Stein, Z.A. 1986. Agent Orange and risks to reproduction: The limits of epidemiology. Teratogenesis Carcinog. Mutagen. 6:185-202

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Human; Review article

This excellent review evaluates the evidence from the Australian Veterans study, the CDC Atlanta birth defects study and the Ranch Hand study concerning adverse reproductive outcomes resulting from possible paternal exposure to Agent Orange. The criteria of epidemiologic "proof" are systematically applied to these data and the conclusion reached that paternal exposure in Vietnam may have resulted in small increased risk of adverse reproductive effects. Without more basic research to generate specific hypotheses for epidemiologists to test, it is unlikely that any more definitive answers will be obtained.

Hay, A., and Silbergeld, E. 1986. Dioxin exposure at Monsanto. Nature. 320:569

Keywords: Epidemiological study; Cancer; Occupational exposure; Dioxins; Commentary or opinion

In this letter to the editor, the authors continue an ongoing debate regarding the design and interpretation of epidemiologic studies of workers exposed to chlorinated dibenzo-p-dioxins during employment by the Monsanto Co. in Nitro, West Virginia. These authors argue that those studies do not rule out excess deaths due to cancer and heart disease among the exposed workers.

Hay, A.W.M., Ashby, J., Styles, J.A., and Elliot, B. 1983. The mutagenic properties of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. 3:160-166

Keywords: Genetic toxicity; Dioxins; Review article

The data discussed in this review (Ames test, BHK transformation assay, and BNA intercolation assays) are supportive of TCDD's role in carcinogenesis being that of a promoter, rather than a mutagenic initiator.

Hayes, J.R., Condie, L.W., and Borzelleca, J.F. 1986. Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of potassium picloram. Fundam. Appl. Toxicol. 7:464-470

Keywords: Acute toxicity; Lethality; Hepatotoxicity; Renal toxicity; Oral; Picloram; Rat

See Page 118.

Hebert, C.D., and Birnbaum, L.S. 1986. Age-related changes in TCDD absorption. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:310

Keywords: Absorption, distribution, metabolism, and excretion; In Vitro; Dioxins; Rat; Abstract

In this abstract, the authors describe a study of the absorption of radiolabelled 2,3,7,8-TCDD from the intestine and the effect of age on the rate of that absorption. The rate of absorption decreased in going from young to mature to senescent rats

Henderson, J., Baker, H.W.G., and Hanna, P.J. 1986. Occupation-related male infertility: A review. Clin. Reprod. Fertil. 4:87-106

Keywords: Epidemiological study; Reproductive toxicity; Occupational exposure; Phenoxy herbicide formulations; Dioxins; Human; Review article

In a brief review of the data concerning TCDD and the products it may contaminate, the authors conclude that there is no indication of adverse reproductive outcomes affecting men exposed to these substances occupationally.

Henry, E.C., and Gasiewicz, T.A. 1986. Effect of thyroid status on Ah receptor and enzyme inducibility by 2,3,7,8-TCDD in rat liver. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:308

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Injection; Dioxins; Rat; Abstract

See Page 110.

Hiremath, C., Bayliss, D., and Bayard, S. 1986. Qualitative and quantitative cancer risk assessment. Chemosphere. 15:1815-1823

Keywords: Cancer; Environmental exposure; Dioxins; Human; Review article

In this symposium presentation, the authors summarize an assessment of the probability that 2,3,7,8-tetrachlorodibenzo-p-dioxin is a human carcinogen and of the quantitative risk associated with exposure by TCDD. This risk assessment was performed by the Cancer Assessment Group at the U.S. Environmental Protection Agency and is incorporated in the Health Assessment Document for Polychlorinated Dibenzo-p-dioxins (USEPA 1986) (35 references).

Ho, D.N. 1983. [Births at the Tay Ninh Province Medical Center.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 116-120

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human

Hoang, D.C. 1983. [Long-term effects of chemical warfare on human health.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 1. Pp. 29-33

Keywords: Cancer; Epidemiological study; Genetic toxicity; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Human; Review article; Commentary or opinion

In this symposium presentation, the author summarizes the history of the use of phenoxy herbicide formulations by the U.S. military in Vietnam and the results of studies of long-term health consequences conducted by Vietnamese scientists.

Hoar, S.K., Blair, A., Holmes, F.F., Boysen, C.D., Robel, R.J., Hoover, R., and Fraumeni, J.F. 1986. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA. 256:1141-1147

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human

See Pages 5, 20, 24, and 39.

Hoffman, R.E., Belser, W.T., Patterson, D.G., Bagby, J.R., and Needham, L.L. 1986a. Assessment of human exposure to 2,3,7,8-TCDD through biological monitoring: A case study. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 159.

Keywords: Epidemiological study; Tissue levels; Environmental exposure; Dioxins; Human; Abstract

This is an abstract of a symposium presentation of a case study of tissue levels of TCDD in an individual who may have been exposed to chlorinated dibenzo-p-dioxins as a result of environmental contamination in Missouri. No data are contained in the abstract.

See Page 71.

Hoffman, R.E., Stehr-Green, P.A., Webb, K.B., Evans, R.G., Knutsen, A.P., Schramm, W.F., Staake, J.L., Gibson, B.B., and Steinberg, K.K. 1986b. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA. 255:2031-2038

Keywords: Epidemiological study; Hematologic effects; Hepatotoxicity; Immunological effects; Neuro/behavioral effects; Porphyria cutanea tarda; Environmental exposure; Dioxins; Human

See Pages 5, 8, and 81.

Holsapple, M.P., McCay, J.A., and Barnes, D.W. 1986a. Immunosupression without liver induction by subchronic exposure to 2,7-dichlorodibenzo-p-dioxin in adult female B6C3F1 mice. Toxicol. Appl. Pharmacol. 83:445-455

Keywords: Acute toxicity; Enzyme induction or inhibition; Immunological effects; Mechanism of action; Subchronic toxicity; Other toxic effects; Oral; Dioxins; Other contaminating compounds; Mouse

See Page 109.

Holsapple, M.P., White, K.L., Bradley, S.G., and Munson, A.E. 1986b. Immunotoxicological studies of hexachlorinated dioxins. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:63

Keywords: Immunological effects; Unspecified route of exposure; Dioxins; Mouse; Abstract

This abstract summarizes the results of a study in which daily oral administration of 1,2,3,6,7,8-hexachloro-dibenzo-p-dioxin to B6C3F1 mice suppressed the antibody response to sheep red blood cells. Cell-mediated immunity was relatively unaffected while host resistance to Streptococcus pneumoniae was decreased.

See Page 109.

Hood, R.D. 1986. Cacodylic Acid: Agricultural Uses, Biologic Effects, and Environmental Fate. December 1985. U.S. Government Printing Office, Washington, D.C. 164 pages.

Keywords: Acute toxicity; Chronic toxicity; Subchronic toxicity; Cancer; Birth defects; Reproductive toxicity; Genetic toxicity; Mechanism of action; Cacodylic acid; Review article

See Page 5.

Houk, V.N. 1986a. Uncertainties in dioxin risk assessment. Chemosphere. 15:1875-1881

Keywords: Cancer; Environmental exposure; Dioxins; Human; Review article

In this symposium presentation the author reviews the human health risk assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin conducted by the U.S. Centers for Disease Control, emphasizing key assumptions and sources of uncertainty. The risk assessment was published previously (see Kimbrough et al. 1984 in Volume VIII of this review).

Houk, V.N. 1986b. Status of Centers for Disease Control dioxin studies of U.S. population. Chemosphere. 15:1765-1768

Keywords: Cancer; Epidemiological study; Miscellaneous study; Absorption, distribution, metabolism, and excretion; Environmental exposure; Dioxins; Human; Review article

In this symposium presentation, the author summarizes the status of studies being conducted by the U.S. Centers for Disease Control to investigate possible associations between adverse human health effects and exposure to chlorinated dibenzo-p-dioxins.

Hryhorczuk, D.O., Wallace, W.H., Perksy, V., Oleske, D., and Haselhorst, B. 1986. Design and implementation of the W.G. Krummrich study. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 181.

Keywords: Chloracne; Cancer; Cardiovascular toxicity; Epidemiological study; Hematologic effects; Immunological effects; Neuro/behavioral effects; Porphyria cutanea tarda; Renal toxicity; Respiratory toxicity; Occupational exposure; Phenoxy herbicide formulations; Dioxins; Human; Abstract

In this abstract of a symposium presentation, the authors summarize the methodology being used in a cohort epidemiologic study of workers at a plant in Sauget, Illinois where chlorophenols and phenoxy herbicides were manufactured from 1923-1983. The results of this study are not yet available.

Humphrey, G.F. 1986. Storm in a cup of 2,4,5-T. Med. J. Aust. 144:611

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human; Commentary or opinion

The author of this letter to the editor comments on the editorial by Armstrong (1986) regarding the Australian Royal Commission. He proposes steps to ensure that future proceedings are inquisitional instead of adversarial and recommends that scientists who appear as expert witnesses in such proceedings have independent counsel.

Huong, L.D., Phuong, N.T.N., Thuy, T.T., and Hoan, N.E. 1986. A retrospective study on the incidence of birth defects and other reproductive anomalies in the obstetrical and gynecological hospital of Ho Chi Minh City from 1952 to 1985. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 172.

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human; Abstract

See Page 57.

Hutzinger, O. 1985. Dioxins and furans in the environment: Evaluating toxicological risk from different sources by multi-criteria analysis. In Kamrin, M.A. and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 9-32.

Keywords: Miscellaneous study; Environmental exposure; Occupational exposure; Dioxins; Review article

In this conference presentation, the author reviews data on the sources and toxicity of various polychlorinated dibenzo-p-dioxins in the human environment and develops a systematic approach for classifying potential sources on the basis of relative human health risk (106 references).

Jerusalem, C., and Kubat, K. 1983. [Pathological notes on hepatocellular carcinoma in Vietnamese exposed to military phenoxy-herbicides contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 53-62

Keywords: Cancer; Mechanism of action; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Human

See Page 38.

Johnson, K.A., Landry, T.D., Gorzinski, S.J., Cieszlak, F.S., Kropscott, B.E., and Wolfe, E.L. 1986. Picloram: A two-year chronic toxicity and oncogenicity study in Fischer 344 rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:83

Keywords: Cancer; Hepatotoxicity; Renal toxicity; Oral; Picloram; Rat; Abstract

A 2-year chronic feeding study was conducted in Fisher 344 rats. Increased liver and kidney weights were noted in the high dose groups; no increase in tumor incidence related to picloram ingestion was reported.

See Page 118.

Jones, M.K., Weisenburger, W.P., Sipes, I.G., and Russell, D.H. 1986. Serum prolactin (PRL) and PRL-stimulated ornithine decarboxylase (ODC) alterations in response to TCDD. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:43

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Injection; Dioxins; Rat; Abstract

This is an abstract of a study of the effect of acutely toxic doses of TCDD on serum prolactin levels in rats. TCDD decreased serum prolactin levels within four hours of administration and the authors suggest that other responses, such as decreased ornithine decarboxylase activity, may be secondary to the hormonal effects of TCDD.

Jones, P.B.C., Durrin, L.K., Fisher, J.M., and Whitlock, J.P. 1986a. Control of gene expression by 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Biol. Chem. 261:6647-6650

Keywords: Mechanism of action; Enzyme induction or inhibition; In Vitro; Dioxins; Mammalian cells in culture

See Page 106.

Jones, P.B.C., Durrin, L.K., Galeazzi, D.R., and Whitlock, J.P. 1986b. Control of cytochrome P1-450 gene expression: Analysis of a dioxin-responsive enhancer system. Proc. Natl. Acad. Sci. USA. 83:2802-2806

Keywords: Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture

See Page 106.

Jones, R.E., and Chelsky, M. 1986. Further discussion concerning porphyria cutanea tarda and TCDD exposure. Arch. Environ. Health. 41:100-103

Keywords: Epidemiological study; Porphyria cutanea tarda; Occupational exposure; Environmental exposure; Dioxins; Review article; Human

The authors, who are employees of Diamond Shamrock Corporation, review epidemiological evidence that occupational exposure to TCDD is associated with porphyria cutanea tarda and conclude that the evidence is unconvincing, with the more likely etiologic agent in two well-publicized incidents being hexachlorobenzene. The authors do not address the body of evidence from animal studies showing that TCDD inhibits uroporphyrinogen decarboxylase.

Kahn, P.C., Gochfeld, M., Rappe, C., Nygren, M., Hansson, M., Velez H., Ghent-Guenther, T., and Wilson, W.P. 1986. Analysis of adipose tissue and blood samples from Vietnam veterans: Project outline and preliminary results. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 6.

Keywords: Tissue levels; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Human; Abstract

See Page 95.

Kamrin, M., and Matsumura, F. 1985. Human health and toxicity - Workshop summary. In Kamrin, M.A. and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 285-295.

Keywords: Cancer, Acute toxicity; Reproductive toxicity; Birth defects; Enzyme induction or inhibition; Dioxins; Review article

This summary represents the consensus of participants at a workshop on the health effects of chlorinated dibenzo-p-dioxins that was part of a conference on dioxins in the environment held at Michigan State University in 1983 (70 references).

Kamrin, M.A., and Rodgers, P.W. (eds.). 1985. Dioxins in the Environment. In Kamrin, M.A. and Rodgers, P.W. 1985. Hemisphere Publishing Corp., Washington, D.C. P. 318 pages.

Keywords: Miscellaneous study; Dioxins; Review article

This book is the published proceedings of a conference on dioxins in the environment held at Michigan State University on December 6-9, 1983.

Kang, H., and Shepard, B. 1986. Retrospective study of dioxins and furans in human adipose tissue. Abstract of a paper presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 47.

Keywords: Epidemiological study; Tissue levels; Occupational exposure; Phenoxy herbicide formulations; Human; Abstract

This abstract of a symposium presentation describes the protocol of a study of adipose tissue levels of TCDD in Vietnam veterans as compared to veterans who did not serve in Vietnam and non-veterans. This study is being conducted by the Veterans Administration and no results are available to date.

See Page 17.

Kang, H., Enzinger, F., Breslin, P., Feil, M., Lee, Y., and Shepard, B. 1986. Soft tissue sarcoma and military service in Vietnam: A case control study. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986. P. 191.

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human; Abstract

This is an abstract of a symposium presentation describing a case-control study of soft-tissue sarcoma among veterans in the United States.

Kang, H.K., Weatherbee, L., Breslin, P.P., Lee, Y., and Shepard, B.M. 1986. Soft tissue sarcomas and military service in Vietnam: A case comparison group analysis of hospital patients. J. Occup. Med. 28:1215-1218

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human

Kelley, M., and Vessey, D.A. 1986. Interaction of 2,4-dichlorophenoxyacetate (2,4-D) and 2,4,5-trichlorophenoxyacetate (2,4,5-T) with the acyl-CoA:Amino acid N-acyltransferase enzymes of bovine liver mitochondria. Biochem. Pharmacol. 35:289-295

Keywords: Mechanism of action; Enzyme induction or inhibition; Absorption, distribution, metabolism, and excretion; In Vitro; 2,4-D; 2,4,5-T; Other species

Kelling, C.K., Menahan, L.A., and Peterson, R.E. 1986a. Patterns of hepatic enzyme activities following 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) treatment in the rat. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:308

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; Other toxic effects; Unspecified route of exposure; Dioxins; Rat; Abstract

See Page 110.

Kelling, C.K., Menahan, L.A., and Peterson, R.E. 1986b. Influence of isoproterenol on tension development and rate in atria isolated from rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:312

Keywords: Acute toxicity; Cardiovascular toxicity; Mechanism of action; Other toxic effects; In Vitro; Oral; Dioxins; Rat; Abstract

See Page 110.

Kerkvliet, N.I., and Brauner, J.A. 1986. Cellular targets of dioxin-induced humoral immune suppression. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:62

Keywords: Immunological effects; Mechanism of action; Unspecified route of exposure; Other contaminating compounds; Dioxins; Mouse; Abstract

This is an abstract of a study of the effect of 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin on the antibody response to sheep red blood cells in mice. Results indicated that humoral immune suppression was probably mediated through T-cells.

Keys, B., Hlavinka, M., Mason, G., and Safe, S. 1985. Modulation of rat hepatic microsomal testosterone hydroxylases by 2,3,7,8-tetrachlorodibenzo-p-dioxin and related toxic isostereomers. Can. J. Physiol. Pharmacol. 63:1537-1542

Keywords: Acute toxicity; Mechanism of action; Reproductive toxicity; Injection; Dioxins; Other contaminating compounds; Rat

Kilpatrick, R., Knowelden, J., and Martin, D. 1986. Mortality from malignant disease of connective and other soft tissue in agricultural workers in England and Wales (1972-1981). Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 185.

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human; Abstract

See Page 27.

Kimura, S., Gonzalez, F.J., and Nebert, D.W. 1986. Tissue-specific expression of the mouse dioxin-inducible P1-450 and P3-450 genes: Differential transcriptional activation and mRNA stability in liver and extrahepatic tissues. Mol. Cell. Biol. 6:1471-1477

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Injection; Dioxins; Mouse

See Page 106.

Kramer, C.M., Sando, J.J., and Holsapple, M.P. 1986a. Lack of direct effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on protein kinase C activity in EL4 cells. Biochem. Biophys. Res. Commun. 140:267-272

Keywords: Cancer; Mechanism of action; Other toxic effects; In Vitro; Dioxins; Mammalian cells in culture

In order to study the effect of TCDD on protein kinase C, EL4 thymoma cells (cells high in protein kinase C) were incubated with TCDD. TCDD had no effect on a number of measures of protein kinase C function and activity leading the authors to conclude that TCDD does not activate this enzyme in EL4 cells.

See Page 111.

Kramer, C.M., Sando, J.J., and Holsapple, M.P. 1986b. The effect of 2,3,7,8-TCDD on protein kinase C activity in EL4 cells. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:170

Keywords: Mechanism of action; Other toxic effects; In Vitro; Dioxins; Mammalian cells in culture; Abstract

This abstract of a meeting presentation describes studies that were published as a full paper (see Kramer et al. 1986a).

Krowke, R. 1986. Studies on distribution and embryotoxicity of different PCDD and PCDF in mice and marmosets. Chemosphere. 15:2011-2022

Keywords: Absorption, distribution, metabolism, and excretion; Reproductive toxicity; Birth defects; Injection; Dioxins; Other contaminating compounds; Monkey; Mouse

See Pages 60 and 61.

Kurl, R.N., Choudhary, K.C., and Villee, C.A. 1986. Characterization and control of cytosolic binding proteins for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the rat lung. Pharmacology. 33:181-189

Keywords: Mechanism of action; Respiratory toxicity; Other toxic effects; Injection; In Vitro; Dioxins; Rat

The authors isolated and determined the properties of the Ah receptor from rat lung.

Lamb, J.C., Harris, M.W., McKinney, J.D., and Birnbaum, L.S. 1986. Effects of thyroid hormones on the induction of cleft palate by 2,3,7,8-tetrachlorodibenzo-p-dioxin(TCDD) in C57BL/6N mice. Toxicol. Appl. Pharmacol. 84:115-124

Keywords: Mechanism of action; Birth defects; Oral; Dioxins; Mouse

See Page 61.

Lambrecht, R.W., Bement, W.J., Sinclair, P.R., Sinclair, J.F., and Bonkovsky, H.L. 1986. Uroporphyrin (URO) accumulation in cultured chick embryo liver cells (CELC) treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:41

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; Porphyria cutanea tarda; In Vitro; Dioxins; Bird; Abstract

This abstract summarizes studies of the mechanism by which TCDD causes accumulation of uroporphyrin in chick embryo liver cells. Based on their results, the authors conclude that uroporphyrin accumulation is a consequence of the induction of cytochrome P-448.

Lang, T., Van, D.D., and Bach, T.T. 1986. Primary carcinoma of the liver (PLC) and potential exposure to Agent Orange: A case control study. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 178.

Keywords: Cancer; Epidemiological study; Hepatotoxicity; Environmental exposure; Phenoxy herbicide formulations; Human; Abstract

Leece, B., Denomme, M.A., Li, M.A., Towner, R., Kamps, C., Mason, G., and Safe, S. 1986. The effects of altered rat hepatic receptor levels on the enzyme induction activities of toxic haloaromatics. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:312

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; Unspecified route of exposure; Dioxins; Rat; Abstract

This abstract of a meeting presentation describes studies similar to those described in a full paper by Bannister et al. (1986a).

Lehnert, G., and Szadkowski, D. 1985. Zur Humankanzerogenitat von 2,3,7,8-TCDD-Unfallversicherungsrechtliche Beurteilung. [The carcinogenicity of 2,3,7,8-TCDD in humans - evaluation of liability]. Arbeitsmed. Sozialmed. Praventivmed. 20:225-232

Keywords: Cancer; Cardiovascular toxicity; Epidemiological study; Occupational exposure; Dioxins; Human

See Pages 34 and 39.

Li, W., Zhao, Y., and Chou, I.N. 1986. Cytoskeletal perturbation induced by herbicides 2,4-dichlorophenoxy-acetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Abstract of a paper presented at the 25th Annual Meeting of The Society of Toxicology. The Toxicologist. 6:276

Keywords: Mechanism of action; Other toxic effects; In Vitro; 2, 4-D; 2,4,5-T; Mammalian cells in culture; Abstract

This abstract describes studies in which 2,4-D and 2,4,5-T were added to cultures of mouse 3T3 cells. Both herbicides inhibited DNA synthesis and disrupted the organization of microfilaments and microtubules although 2,4,5-T stimulated the synthesis of cytoskeletal proteins. The significance of these findings for human health is unclear.

Lowrance, W.W. 1985. Dioxins: Some technical policy issues for the U.S. In Kamrin, M.A., and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 33-39.

Keywords: Miscellaneous study; Environmental exposure; Dioxins; Review article

In this conference presentation, the author reviews public policy regarding human exposure to chlorinated dibenzo-p-dioxins in the United States. Gaps in scientific knowledge and the response of federal and state governments to those issues are highlighted (no references).

Lu, C-J.H., Baggs, R.B., Redmond, D., Henry, E.C., Schecter, A., and Gasiewicz, T.A. 1986. Toxicity and evidence for metabolic alterations in 2,3,7,8-tetrachlorodibenzo-p-dioxin-treated guinea pigs fed by total parenteral nutrition. Toxicol. Appl.Pharmacol. 84:439-453

Keywords: Acute toxicity; Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; Injection; Dioxins; Guinea pig

In this study of the mechanism of the acute toxicity of TCDD, the authors fed TCDD-treated guinea pigs by total parenteral nutrition and compared them to ad libitum and pair fed controls. The results indicated that even though guinea pigs fed by total parentical nutrition did not display the "wasting syndrome" typical of acute TCDD poisoning, they still experienced the same mortality as animals with the "wasting syndrome" suggesting that wasting is not the direct cause of death.

Lundgren, L., Andries, M., Thompson, C., and Lucier, G.W. 1986. Dioxin treatment of rats results in increased in vitro induction of sister chromatid exchanges by B-naphthoflavone: An animal model for human exposure to halogenated aromatics. Toxicol. Appl. Pharmacol. 85:189-195

Keywords: Enzyme induction or inhibition; Genetic toxicity; Mechanism of action; Oral; Dioxins; Rat

See Pages 52 and 53.

Luster, M.I., Hong, L.H., Osborne, R., Blank, J.A., Clark, G., and Silver, M.T. 1986. 1-Amino-3,7,8-trichlorodibenzop-dioxin: A specific antagonist for TCDD-induced myelotoxicity. Biochem. Biophys. Res. Commun. 139:747-756

Keywords: Immunological effects; Mechanism of action; Hematologic effect; Oral; In Vitro; Dioxins; Mouse

See Page 75.

Lysy, H.H., McCay, J.A., and White, K.L. 1986. A structure activity relationship of dioxin suppression of complement activity and segregation with the Ah locus. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:171

Keywords: Immunological effects; Mechanism of action; Unspecified route of exposure; Dioxins; Mouse; Abstract

Madhukar, B.V., Bombick, D.W., Brewster, D.W., and Matsumura, F. 1986. Altered regulation of EGF-receptor by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in inbred strains of mice. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:311

Keywords: Hepatotoxicity; Mechanism of action; Other toxic effects; Unspecified route of exposure; Dioxins; Mouse; Abstract

This abstract describes studies that have been published previously in full (see Madhukar et al. 1984 and Madhukar et al. 1983 in Volumes VI and VIII of this review).

Manninen, A., Kangas, J., Klen, T., and Savolainen, H. 1986. Exposure of Finnish farm workers to phenoxy acid herbicides. Arch. Environ. Contam. Toxicol. 15:107-111

Keywords: Absorption, distribution, metabolism, and excretion; Miscellaneous study; Renal toxicity; Occupational exposure; Phenoxy herbicide formulations; Human

The authors measured exposure and urinary excretion of MCPA and dichlorprop (phenoxy herbicides) in farm workers engaged in the application of herbicides to farm fields. They conclude that the skin is the major exposure route and that elimination rate varies with dose. No health effects information is included.

Marlow, D.A. 1986. An exposure matrix for the NIOSH dioxin registry. Chemosphere. 15:1753-1764

Keywords: Epidemiological study; Miscellaneous study; Occupational exposure; Phenoxy herbicide formulations; Dioxins; Human

In this symposium presentation, the author describes methodology being used to assess the possible magnitude of exposure to chlorinated dibenzo-p-dioxins among workers included in the NIOSH Dioxin Registry. The exposure estimates are to be used for data analysis in a cohort epidemiology study of workers from 14 U.S. plants where there was a high probability of dioxin exposure.

Marquis, J.K. 1986. Herbicides. Contemporary Issues in Pesticide Toxicology and Pharmacology: Concepts in Toxicology. S Karger, A.G (Basel), Vol. 2. Pp. 87-96.

Keywords: Chronic toxicity; Neuro/behavioral effects; Environmental exposure; Occupational exposure; 2,4-D; Review article

This book chapter briefly reviews the types and uses of herbicides. There is a one-page review of the neurotoxicity of 2,4-D (23 references).

Mason, G., and Safe, S. 1986a. Synthesis, biologic and toxic effects of the major 2,3,7,8-tetrachlorodibenzo-p-dioxin metabolites in the rat. Toxicology. 41:153-159

Keywords: Acute toxicity; Enzyme induction or inhibition; Other toxic effects; Mechanism of action; Injection; Dioxins; Rat

The authors synthesized the two major mammalian metabolites of TCDD and administered them to rats. The results strongly suggest that none of the biological effects of TCDD can be attributed to these metabolites.

Mason, G., and Safe, S. 1986b. The biologic and toxic effects of 2,3,7,8-TCDD metabolites. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:43

Keywords: Acute toxicity; Mechanism of action; Unspecified route of exposure; Dioxins; Rat; Abstract

This abstract describes studies that are published as a full paper elsewhere (see Mason and Safe 1986a).

Mason, G., Farrell, K., Keys, B., Piskorska-Pliszczynska, J., Safe L., and Safe, S. 1986a. Polychlorinated dibenzo-p-dioxins: Quantitative in vitro and in vivo structure-activity relationships. Toxicology. 41:21-31

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Other toxic effects; Injection; In Vitro; Dioxins; Rat

The authors performed an extensive structure-activity analysis of 14 chlorinated dibenzo-p-dioxins and found excellent correllations between in vitro AHH induction and in vivo potency to induce hepatic mixed function oxidase enzymes, thymic atrophy, and body weight loss in rats.

Mason, G., Keys, B., Farrell, K., and Safe, S. 1986b. Polychlorinated dibenzo-p-dioxins: Quantitative structure-activity relationships. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:309

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Other toxic effects; In Vitro; Dioxins; Mammalian cells in culture; Abstract

This abstract describes studies that have been published as a full article (see Mason et al. 1986a).

Matsumura, F. 1985. The mechanism of action of dioxin. In Kamrin, M.A., and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 261-265.

Keywords: Mechanism of action; Dioxins; Review article

This conference presentation is a review of scientific information on the mechanism of action of polychlorinated dibenzo-p-dioxins with special emphasis on receptor interactions (15 references).

Mattsson, J.L., Johnson, K.A., and Albee, R.R. 1986a. Lack of neuropathologic consequences of repeated dermal exposure to 2,4-dichlorophenoxyacetic acid in rats. Fundam. Appl. Toxicol. 6:175-181

Keywords: Neuro/behavioral effects; Renal toxicity; Other skin effects; Dermal; 2,4-D; Rat

See Pages 79 and 81.

Mattsson, J.L., Albee, R.R., Johnson, K.A., and Quast, J.F. 1986b. Neurotoxicolgic examination of rats dermally exposed to 2,4-D amine for three weeks. Neurobehav. Toxicol. Teratol. 8:255-263

Keywords: Neuro/behavioral effects; Subchronic toxicity; Other skin effects; Dermal; 2,4-D; Rat

See Page 79.

McConnell, E.E. 1985. The clinicopathologic changes in various species of animals caused by dibenzo-p-dioxins. In Kamrin, M.A. and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 225-230.

Keywords: Miscellaneous study; Mechanism of action; Dioxins; Review article

In this conference presentation, the author reviews the characteristic pathology of animals treated with polychlorinated aromatic hydrocarbons including dibenzo-p-dioxins. Interspecies differences in site and degree of toxic response are discussed (29 references).

Mebus, C.A., and Piper, W.N. 1986. Depression of rat testicular 17-hydroxylase and 17,20-lyase after administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:42

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Reproductive toxicity; Oral; Dioxins; Rat; Abstract

See Page 109.

Merlo, F. 1985. Adverse health effects in human population exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) in Seveso: An update. In Kamrin, M.A. and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 241-260.

Keywords: Chloracne; Cancer; Epidemiological study; Hepatotoxicity; Reproductive toxicity; Environmental exposure; Dioxins; Human; Review article

See Pages 12 and 36.

Merlo, F., Puntoni, R., and Santi, L. 1986. The Seveso episode: The validity of epidemiological inquiries in relation with the definition of population at risk. Chemosphere. 15:1777-1786

Keywords: Chloracne; Cancer; Epidemiological study; Miscellaneous study; Environmental exposure; Dioxins; Human; Commentary or opinion

The author contends that the results of completed and proposed epidemiologic studies in the vicinity of the ICMESA plant in Seveso, Italy are invalid because of inappropriate means of defining exposure. He proposes that geographic areas of high, medium, and low contamination be defined on the basis of distribution of chloracne cases, acute skin lesions, and animal mortality rates.

Mocarelli, P., Marocchi, A., Brambila, P., Gerthoux, P., Young, D., and Mantel, N. 1986. Clinical laboratory manifestations of exposure to dioxin in children: A six-year study of the effects of an environmental disaster near Seveso, Italy. JAMA. 256:2687-2695

Keywords: Epidemiological study; Hepatotoxicity; Other toxic effects; Environmental exposure; Dioxins; Human

This study of serum clinical chemistry parameters in children from the vicinity of the ICMESA plant in Seveso, Italy has been described and reviewed in Volume V of this review (see Mocarelli et al. 1984a,b in Clement 1985).

Mohammad, F.K., and St. Omer, V.E.V. 1985. Developing rat brain monoamine levels following in utero exposure to a mixture of 2,4-dichlorophenoxyacetic and 2,4,5-trichlorophenoxyacetic acids. Toxicol. Lett. 29:215-223

Keywords: Neuro/behavioral effects; Birth defects; Oral; 2,4-D; 2,4,5-T; Rat

See Pages 65 and 67.

Mohammad, F.K., and St. Omer, V.E.V. 1986. Behavioral and developmental effects in rats following in utero exposure to 2,4-D/2,4,5-T mixture. Neurobehav. Toxicol. Teratol. 8:551-560

Keywords: Neuro/behavioral effects; Reproductive toxicity; Birth defects; Oral; 2,4-D; 2,4,5-T; Phenoxy herbicide formulations; Rat

See Pages 66 and 67.

Molloy, C.J., Gallo, M.A., and Laskin, J.D. 1986. Epidermal hyperplasia and alterations in keratinization in the hairless mouse induced by TCDD. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:42

Keywords: Chloracne; Cancer; Other skin effects; Mechanism of action; Dermal; Dioxins; Mouse; Abstract

This is an abstract of studies of the effect of dermally applied TCDD in hairless (hr/hr) mice and their haired (hr/+) littermates. In contrast to the findings of Poland et al. (1986), these authors find skin thickening and protein changes in both haired and hairless mice, independent of hr locus.

See Page 109.

Moore, R.W., Parsons, J.A., Bookstaff, R.C., and Peterson, R.E. 1986. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the plasma concentrations of pituitary hormones. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:309

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Reproductive toxicity; Oral; Dioxins; Rat; Abstract

See Page 109.

Morikawa, K., Morita, M., Fujita, M., and Tanaka, M. 1986. Study on tumor promoting activities of dioxins by generation of oxygen radicals from polymorphonuclear leukocytes. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 62.

Keywords: Cancer; Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture; Abstract

In this abstract of a symposium presentation, the authors describe studies of the effect of TCDD and other chlorinated dibenzo-p-dioxins on generation of oxygen radicals from cultured polymorphonuclear leukocytes and conclude that unlike phorbol esters, TCDD does not stimulate oxygen radical formation suggesting that TCDD and other PCDDs promote carcinogenesis by a different mechanism.

See Page 111.

Morris, P.D., Koepsell, T.D., Daling, J.R., Taylor, J.W., Lyon J.L., Swanson, G.M., Child, M., and Weiss, N.S. 1986. Toxic substance exposure and multiple myeloma: A case-control study. JNCI. 76:987-994

See Pages 5, 27, and 39.

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human

Morrison, A.B. 1985. Dioxins in Canada - Deciding the public health risk. In Kamrin, M.A. and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 39-48.

Keywords: Cancer; Miscellaneous study; Environmental exposure; Dioxins; Review article

In this paper, presented at a conference, the author describes the scope of environmental contamination by polychlorinated dibenzo-p-dioxins in Canada, the response of the Canadian government to the problem, and aspects of human health risk assessment for dioxins (14 references).

Mukerjee, D., Stara, J.F., and Schaum, J.L. 1986. Rationale for assessment of risk from exposure to 2,3,7,8-TCDD. Chemosphere. 15:1805-1813

Keywords: Cancer; Environmental exposure; Dioxins Human; Review article

This symposium presentation describes a human health risk assessment for exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin conducted by the U.S. Environmental Protection Agency. This assessment was incorporated into the Health Assessment Document for Polychlorinated Dibenzo-p-dioxins (USEPA 1986) (35 references).

Mustonen, R., Kangas, J., Vuojolahti, P., and Linnainmaa, K. 1986. Effects of phenoxyacetic acids on the induction of chromosome aberrations in vitro and in vivo. Mutagenesis. 1:241-245

Keywords: Epidemiological study; Genetic toxicity; Occupational exposure; In Vitro; 2,4-D; Human

See Page 49.

Muzi, J., Gorski, J.R., and Rozman, K. 1986. Oxygen consumption, carbon dioxide production and the respiratory quotient in TCDD-treated rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:311

Keywords: Acute toxicity; Mechanism of action; Lethality; Injection; Dioxins; Rat; Abstract

This is an abstract of a study in which the authors measured oxygen consumption and carbon dioxide production in rats given acutely toxic doses of TCDD. The authors concluded on the basis of the results that TCDD-treated rats do not adopt their energy metabolism to decreased food intakes.

Nau, H., Bass, R., and Neubert, D. 1986. Transfer of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) via placenta and milk, and postnatal toxicity in the mouse. Arch. Toxicol. 59:36-40

Keywords: Absorption, distribution, metabolism, and excretion; Birth defects; Reproductive toxicity; Oral; Dioxins; Mouse

See Pages 59 and 60.

Needham, L.L., Patterson, D.G., Isaacs, S., Maggio, V., Alexander, L.R., Smith, S.J., Ross, W., and Pirkle, J.L. 1986. Distribution of dioxins and furans in various human adipose tissues taken at autopsy. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 141.

Keywords: Tissue levels; Environmental exposure; Dioxins; Human; Abstract

In this abstract of a symposium presentation the authors describe a study to evaluate whether adipose tissues from different anatomic sites in the same individual give similar results when analyzed for chlorinated dibenzo-p-dioxins and dibenzofurans. The authors concluded that anatomic site was not a variable that needed to be controlled for in assessing body burden.

Neuhold, L.A., Gonzalez, F.J., Jaiswal, A.K., and Nebert, D.W. 1986. Dioxin-inducible enhancer region upstream from the mouse P450 gene and interaction with a heterologous SV40 promoter. DNA. 5:403-411

Keywords: Mechanism of action; Other toxic effects; In Vitro; Dioxins; Mammalian cells in culture

See Page 106.

Nguyen, C., Nguyen, T.X., Tran, T.H., Nguyen, K.T., and Do, B.D. 1983a. [Study of the gravidity of females in 3 districts of North Vietnam.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 81-88

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human

See Page 57.

Nguyen, C., Nguyen, T.X., Nguyen, L.T., and Do, B.D. 1983b. [Investigation of congenital malformations in the My Van District.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 88-92

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Human

See Page 58.

Nguyen, D.K. 1983. [Several biological parameters of the population of a region contaminated by toxic chemicals.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 111-116

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human

See Page 56.

Nguyen, T.N.P., and Le, T.D.H. 1983a. The effects of toxic chemicals on gravidity: An epidemiological study conducted in two sites in South Vietnam. Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. 3:67-70

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human

See Page 57.

Nguyen, T.N.P., and Le, D.H. 1983b. [Gross abnormalities and congenital malformations at an obstetrical-gynecological clinic in Ho Chi Minh City.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 103-111

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human

See Page 57.

Nguyen, T.N.P., Bui, S.H., and Schecter, A. 1986a. [Dioxin levels in adipose tissues of hospitalized women living in the south of Vietnam in 1984-1985 with a brief review of their clinical histories.] Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 89

Keywords: Tissue levels; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Human; Abstract

This abstract of a symposium presentation describes studies of levels of TCDD in adipose tissue samples taken from patients at an obstetrical hospital in Ho Chi Minh City in 1984 and 1985. No results are included in this abstract.

See Page 57.

Nguyen, T.N.P., Pham, V.T., and Phan, K.P. 1986b. A case-control study of hydatidiform moles and birth defects observed in women from herbicide sprayed areas in the south of Vietnam. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 171.

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human; Abstract

See Page 57.

Nguyen, T.X. 1986. Reproductive ages from the Institute for the Protection of Mothers and Newborns from various areas in the north of Vietnam. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 173.

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human; Abstract

See Page 57.

Nguyenthi, N.P., Nguyen, C.K., Pham, V.T., Chau, H.T., Nguyen T.T.V., and Dang, T.Y. 1986. Incidence of reproductive anomalies in herbicide-sprayed and nonherbicide-sprayed villages in the south of Vietnam (1952-1982). Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 170.

Keywords: Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human; Abstract

Olson, J.R. 1986a. Metabolism and disposition of 2,3,7,8-tetrachlorodibenzo-p-dioxin in guinea pigs. Toxicol. Appl. Pharmacol. 85:263-273

Keywords: Absorption, distribution, metabolism, and excretion; Injection; Dioxins; Guinea pig

See Pages 84 and 85.

Olson, J.R. 1986b. Fate of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) in guinea pigs. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:310

Keywords: Acute toxicity; Absorption, distribution, metabolism, and excretion; Injection; Dioxins; Guinea pig; Abstract

This abstract describes a study of the metabolism of 2,3,7,8-TCDD in guinea pigs. This study was described in detail in Wroblewski and Olson 1985 (see Volume VIII of this review, Clement 1986).

See Pages 84 and 85.

Palca, J. 1986. CDC study still at square one. Nature. 320:476

Keywords: Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human; Commentary or opinion

In this news article, the author describes the reasons behind the delay in conducting a major epidemiologic study among veterans who were exposed to Agent Orange in Vietnam.

Patterson, D.G., Holler, J.S., Smith, S.J., Liddle, J.A., Sampson E.J., and Needham, L.L. 1986a. Human adipose data for 2,3,7,8-tetrachlorodibenzo-p-dioxin in certain U.S. samples. Chemosphere. 15:2055-2060

Keywords: Tissue levels; Environmental exposure; Dioxins; Human

See Pages 91 and 92.

Patterson, D.G., Hoffman, R.E., Needham, L.L., Roberts, D.W., Bagby J.R., Pirkle, J.L., Falk, H., Sampson, E.J., and Houk, V.N. 1986b. 2,3,7,8-Tetrachlorodibenzo-p-dioxin levels in adipose tissue of exposed and control persons in Missouri. JAMA. 256:2683-2686

Keywords: Epidemiological study; Tissue levels; Environmental exposure; Dioxins; Human

See Page 93.

Patterson, D.G., Hoffman, R.E., Needham, L.L., Bagby, J.R., Roberts D.W., Pirkle, J.L., Falk, H., Sampson, E.J., and Houk, V.N. 1986c. Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in adipose tissue of exposed and control persons in Missouri. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. 143

Keywords: Epidemiological study; Tissue levels; Environmental exposure; Dioxins; Human; Abstract

See Pages 93, 95, and 96.

Patterson, D.G., Needham, L.L., Pirkle, J.L., Sampson, E.J., Roberts, D.W., Andrews, J., and Garrett, W. 1986d. Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in paired human serum and adipose tissue. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 142.

Keywords: Tissue levels; Environmental exposure; Dioxins; Human; Abstract

This abstract of a symposium presentation describes a study that has been published as a full paper (see Patterson et al. 1986b).

Paustenbach, D.J., and Murray, F.J. 1986. A critical examination of assessments of the health risks associated with 2,3,7,8-TCDD in soil. Chemosphere. 15:1867-1874

Keywords: Cancer; Human; Dioxins; Environmental exposure; Review article; Commentary or opinion

In this symposium presentation the authors criticize the quantitative risk assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin conducted by the U.S. Centers for Disease Control (see Kimbrough et al. 1984 in Volume VIII of this review). The authors contend that unrealistic exposure assumptions give rise to greatly inflated cancer risk estimates (17 references).

Paustenbach, D.J., Shu, H.P., and Murray, F.J. 1986. An examination of critical assumptions in health risk assessments of 2,3,7,8-tetrachlorodibenzo-p-dioxin contaminated soil. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:282

Keywords: Cancer; Miscellaneous study; Environmental exposure; Dioxins; Review article; Commentary or opinion; Abstract

This is an abstract of a meeting presentation in which the authors examine assumptions that are critical to the estimation of health risks among humans exposed to TCDD through contact with contaminated soil. The authors suggest that assumptions used by federal regulatory agencies are overly conservative and overestimate risk.

Pearce, N.E., Smith, A.H., Howard, J.K., Sheppard, R.A., Giles H.J., and Teague, C.A. 1986. Non-Hodgkin's lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: A case-control study. Br. J. Ind. Med. 43:75-83

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human

A preprint of this paper was reviewed in detail in Volume VII of this review (Clement 1986).

Pearn, J.H. 1986. Herbicides and congenital malformations: A review for the paediatrician. Paediatr. J. 21:237-242

Keywords: Birth defects; Epidemiological study; Phenoxy herbicide formulations; Dioxins; Human; Review article

The author summarizes the data supporting the teratogenicity of 2,4,5-T and 2,4-D in rodents and the potent teratogenicity and fetotoxicity of TCDD in animals. He then reviews the epidemiological evidence for teratogenic effects following the exposure of pregnant women to these herbicides or their contaminant; he concludes that there is no such convincing evidence, with no discussion of the limitations of the existing studies.

Pham, H.P., Luong, T.T., and Nguyen, K.D. 1983. [A preliminary report on primary liver cancer and exposure to Agent Orange.] Proceeding of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Conséquences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 24-29

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human

See Page 38.

Pham, H.P., Luong, T.T., and Nguyen, K.D. 1986. Preliminary observations on the clinical histories, PCDD/F adipose tissue levels and 2,3,7,8-TCDD equivalents in potentially dioxin exposed patients living in the south of Viet Nam from Cho Ray Hospital. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 88.

Keywords: Cancer; Absorption, distribution, metabolism, and excretion; Other toxic effects; Environmental exposure; Phenoxy herbicide formulations; Human; Abstract

Poellinger, L., Lund, J., Soderkvist, P., and Gustafsson, J. 1986a. The receptor for 2,3,7,8-TCDD: Structure possible functions and relationship to endocrine receptors - An overview. Chemosphere. 15:1649-1656

Keywords: Mechanism of action; Hepatotoxicity; Dioxins; Review article

The authors review the accumulated evidence on the structure and physicochemical properties of the TCDD receptor and compare this receptor to the steroid hormone receptor, concluding that despite the similarities there are several important differences between them.

Poellinger, L., Wilhelmsson, A., Lund, J., and Gustaffsson, J-A. 1986b. Biochemical characterization of the rat liver receptor for 2,3,7,8-TCDD - A comparison to the rat liver glucocorticoid receptor. Chemosphere. 15:1681-1686

Keywords: Mechanism of action; Dioxins; Review article

In this brief review, the author summarizes research on the physical and physiological properties of steroid hormone receptors and compares those properties to those of the Ah receptor. Similarities include molecular size, shape, isodielectric point, and the ability to bind to DNA. Important differences exist, however, and the ligands for the two receptors do not compete with each other for their respective receptors (49 references).

Poellinger, L., Wilhelmsson, A., Cuthill, S., Lund, J., Gillner, M., and Gustafsson, J. 1986c. Structure and function of the dioxin receptor. A DNA-binding protein similar to steroid hormone receptors. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 55.

Keywords: Mechanism of action; Dioxins; Rat; Review article; Abstract

Poiger, H., and Schlatter, C. 1986. Pharmacokinetics of 2,3,7,8-TCDD in man. Chemosphere. 15:1489-1494

Keywords: Absorption, distribution, metabolism, and excretion; Oral; Dioxins; Human

See Pages 84, 86, and 96.

Poland, A., Glover, E., Ebetino, F.H., and Kende, A.S. 1986. Photoaffinity labeling of the Ah receptor. J. Biol. Chem. 261:6352-6365

Keywords: Hepatotoxicity; Mechanism of action; Other toxic effects; In Vitro; Dioxins; Mouse

The authors used photoaffinity labeling to isolate and purify the Ah receptor from mouse liver cytosol. These studies suggested that the receptor is a dimer composed of two noncovalently linked subunits of 95 and 70 kDa.

Pollak, J.K. 1986. Storm in a cup of 2,4,5-T. Med. J. Aust. 144:612

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human; Commentary or opinion

In this letter to the editor the author, a scientific witness in the proceedings before the Australian Royal Commission, comments on the editorial by Armstrong (1986) and provides examples of incorrect treatment of scientific witnesses in the proceedings.

Pollei, S., Mettler, F.A., Kelsey, C.A., Walters, M.R., and White, R.E. 1986. Follow-up chest radiographs in Vietnam Veterans: Are they useful? Radiology. 161:101-102

Keywords: Epidemiological study; Respiratory toxicity; Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Human

See Page 100.

Potter, C.L., Menahan, L.A., and Peterson, R.E. 1986a. Relationship of alterations in energy metabolism to hypophagia in rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fundam. Appl. Toxicol. 6:89-97

Keywords: Acute toxicity; Mechanism of action; Oral; Dioxins; Rat

In an investigation of the mechanism of acute lethality in rats, the authors provide experimental evidence that TCDD causes a decrease in caloric intake without affecting the efficiency of energy utilization.

See Page 110.

Potter, C.L., Moore, R.W., Inhorn, S.L., Hagen, T.C., and Peterson R.E. 1986b. Thyroid status and thermogenesis in rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 84:45-55

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Oral; Dioxins; Rat

See Page 110.

Puhvel, S.M., Sakamoto, M., and Reisner, R.M. 1986. Localization of TCDD in hairless mouse skin. Chemosphere. 15:2065-2067

Keywords: Absorption, distribution, metabolism, and excretion; Other skin effects; Injection; Dioxins; Mouse

The authors studied the disposition of TCDD in skin of mice after systemic administration in order to determine whether chloracne and other skin responses are direct or indirect effects. They considered their results to be inconclusive.

Puntoni, R., Merlo, F., Fini, A., Meazza, L., and Santi, L. 1986. Soft tissue sarcomas in Seveso. Lancet. August 30, 1986. P. 525.

Keywords: Cancer; Epidemiological study; Environmental exposure; Dioxin; Human

See Pages 36, and 39.

Quattrochi, L.C., Okino, S.T., Pendurthi, U.R., and Tukey, R.H. 1985. Cloning and isolation of human cytochrome P-450 cDNAs homologous to dioxin-inducible rabbit mRNAs encoding P-450 4 and P-450 6. DNA. 4:395-400

Keywords: Enzyme induction or inhibition; Mechanism of action; In Vitro; Dioxins; Human

Quilley, C.P., and Rifkind, A.B. 1986. Prostaglandin release by the chick embryo heart is increased by 2,3,7,8-tetrachlorodibenzo-p-dioxin and by other cytochrome P-448 inducers. Biochem. Biophys. Res. Commun. 136:582-589

Keywords: Acute toxicity; Cardiovascular toxicity; Enzyme induction or inhibition; Mechanism of action; Injection; Dioxins; Other species

Injection of TCDD, related chlorinated aromatic hydrocarbons, and AHH inducers into chicken eggs caused an increase in prostaglandin release at doses below those that induced AHH activity in the embryo heart. The significance of these findings for human health is unclear.

Rappe, C., Nygren, M., Lindstrom, G., and Hansson, M. 1986. Dioxins and dibenzofurans in biological samples of European origin. Chemosphere. 15:1635-1639

Keywords: Tissue levels; Environmental exposure; Dioxins; Human

See Page 110.

Rickenbacher, U.J., and McKinney, J.D. 1986. Thyroid status and reaction of thyroxine metabolizing enzymes in TCDD treated rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:308

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; Other toxic effects; Unspecified route of exposure; In Vitro; Dioxins; Rat; Abstract

Roberts, E.A., Golas, C.L., and Okey, A.B. 1986. Ah receptor mediating induction of aryl hydrocarbon hydroxylase: Detection in human lung by binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Cancer Res. 46:3739-3743

Keywords: Acute toxicity; Mechanism of action; Enzyme induction or inhibition; In Vitro; Dioxins; Human

The results of this study showing low and variable levels of Ah receptor in lung tissues from 53 human subjects were discussed in Volume VII of this review (see Okey et al. 1985 in Clement 1986).

Rodwell, D.E., Wilson, R.D., Nemec, M.D., Tasker, E.J., and Adam, G. 1986. A dietary two-generation reproduction study in Fischer 344 rats with 2,4-dichlorophenoxyacetic acid. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:33

Keywords: Reproductive toxicity; Subchronic toxicity; Oral; 2,4-D; Rat; Abstract

See Page 65.

Romkes, M., Piskorska-Plisczynska, J., and Safe, S. 1986a. Effects of 2,3,7,8-TCDD on the estrogen receptor in immature female Long Evans rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:42

Keywords: Mechanism of action; Reproductive toxicity; Unspecified route of exposure; Dioxins; Rat; Abstract

See Page 109.

Romkes, M., Piskorska-Pliszcynska, J., and Safe, S. 1986b. Role of the Ah receptor in mediating the down regulation of uterine and hepatic estrogen receptor levels in rats. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 57.

Keywords: Mechanism of action; Reproductive toxicity; Unspecified route of exposure; Dioxins; Rat; Abstract

See Page 109.

Roth, W., Bank, P.A., and Aust, S.D. 1986. A study of thyroid status after a nonanorexigenic dose of TCDD. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:41

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; Other toxic effects; Unspecified route of exposure; Dioxins; Rat; Abstract

See Page 110.

Rozman, K., and Greim, H. 1986. Metabolism of palmitic acid in TCDD-treated rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:207

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Injection; Dioxins; Rat; Abstract

This is an abstract of a study in which the authors show that rats treated with TCDD excrete more radiolabel from 14C-palmitic acid than do pair-fed controls suggesting that increased fat utilization may contribute to the "wasting syndrome" induced by lethal doses of TCDD.

Rozman, K., Pereira, D., and Iatropoulos, M.J. 1986. Histopathology of liver and interscapular brown adipose tissue (IBAT) in TCDD-treated rats adapted to two ambient temperatures. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:207

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; Other toxic effects; Injection; Dioxins; Rat; Abstract

This is an abstract of a study of the morphology of liver and interscapular brown adipose tissue (IBAT) in rats treated with nearly lethal doses of TCDD. Extensive changes were seen in both tissues with marked depletion of IBAT. Cold-adaptation accelerated the time course of changes in both tissues.

Russell, D.H., Weisenburger, W.P., Jones, M.K., and Sipes, I.G., 1986. Profound modifications of circadian rhythms of serum prolactin (PRL) and corticosterone in response to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and receptor down regulation. Abstract of paper presented at the Joint Meeting of the American Society for Pharmacology and Experimental Therapeutics and the Society of Toxicology. The Pharmacologist. 28:179

Keywords: Acute toxicity; Mechanism of action; Other toxic effects; Injection; Dioxins; Rat; Abstract

This abstract describes companion studies to that of Jones, M.K. et al. (1986) of the effects of TCDD on serum prolactin levels. In addition to decreasing serum prolactin levels, TCDD disrupts the normal circadian rhythm of this parameter and changes in other biochemical parameters appear to be the result of these alterations.

Ryan, J.J. 1986. Variation of dioxins and furans in human tissues. Chemosphere. 15:1585-1593

Keywords: Tissue levels; Environmental exposure; Dioxins; Human

See Pages 90, 91, and 96.

Safe, S., Fujita, T., Romkes, M., Piskorska-Pliszczynska, J., Homonko, K., and Denomme, M.A. 1986a. Properties of the 2,3,7,8-TCDD receptor - A QSAR approach. Chemosphere. 15:1657-1663

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; In Vitro; Dioxins; Other contaminating compounds; Guinea pig; Hamster; Mouse; Rat

The authors measured receptor-binding EC50 values of a series of 7-substitiuted-2,3-dichlorodibenzo-p-dioxin analogues in hepatic cytosol from rats, mice, guinea pigs, and hamsters and used multiparameter linear regression analyses to relate these to physicochemical properties. Although significant differences were found among the species these differences were not sufficient to account for interspecies differences in sensitivity to the toxic effects of TCDD.

Safe, S., Mason, G., Keys, B., Farrell, K., Zmudzka, B., Sawyer, T., Piskorska-Pliszozynska, J., Safe, L., Romkes, M., and Bandiera, S. 1986b. Polychlorinated dibenzo-p-dioxins and dibenzofurans: Correlation between in vitro and in vivo structure-activity relationships (SARs). Chemosphere. 15:1725-1731

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Other toxic effects; In Vitro; Injection; Dioxins; Other contaminating compounds; Mammalian cells in culture; Rat

The authors describe the results of quantitative structure-activity relationship studies among chlorinated dibenzo-p-dioxins and dibenzofurans.

Safe, S., Fujita, T., Homonko, K., Romkes, M., Piskorska-Pliszczynska, J., and Denomme, M.A. 1986c. Binding of substituted dibenzo-p-dioxins and dibenzofurans to the rat cytosolic 2,3,7,8-TCDD receptor protein - A QSAR approach. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. Vol. 6. P. 309.

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Other toxic effects; In Vitro; Dioxins; Other contaminating compounds; Mammalian cells in culture; Abstract

This abstract describes studies that have been published as a full article (see Safe et al. 1986)

Safe, S., Romkes, M., Mason, G., Piskorska-Pliszczynska, J., and Fujita, T. 1986d. Binding of substituted aryl hydrocarbons to the Ah receptor - A QSAR Analysis. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 66.

Keywords: Hepatotoxicity; Mechanism of action; Other toxic effects; In Vitro; Dioxins; Rat; Abstract

This abstract of a symposium presentation describes the results of structure-activity studies of receptor binding of a series of 2-substituted chlorinated dibenzo-p-dioxins. This is an extension of work described elsewhere by Mason et al. 1986a,b and Safe et al. 1986a,b.

Safe, S.H. 1986. Comparative toxicology and mechanism of action of polychlorinated dibenzo-p-dioxins and dibenzofurans. Ann. Rev. Pharmacol. Toxicol. 26:371-99

Keywords: Mechanism of action; Enzyme induction or inhibition; Dioxins; Review article

The author reviews studies of enzyme induction and receptor binding and discusses structure activity relationships among the chlorinated dibenzo-p-dioxins and dibenzofurans. In addition to geometry, substituent lipophilicity and electronegativity as well as steric hinderance appear to play an important role in determining relative activities of various congenus (149 references).

Sampson, E.J., Patterson, D.G., Alley, C.C., Isaacs, S., Bagby J.R., Hoffman, R.E., and Needham, L.L. 1986. Polychlorinated dibenzo-p-dioxins and dibenzofuran levels in persons with high levels and normal levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 153.

Keywords: Epidemiological study; Tissue levels; Environmental exposure; Dioxins; Human; Abstract

This is an abstract of a symposium presentation in which the authors describe a proposed study to determine whether tissue levels of chlorinated dibenzofurans are correllated with those of chlorinated dibenzo-p-dioxins (PCDDs) using individuals with relatively high body burdens of PCDDs. No results are presented in this abstract.

Saracci, R. 1986. Storm in a cup of 2,4,5-T. Med. J. Aust. 144:611

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human; Commentary or opinion

In this letter to the editor, the author, an official with the International Agency for Research on Cancer (IARC), comments on the findings of the Austalian Royal Commission regarding epidemiologic evidence for an association between soft tissue sarcoma and lymphoma and exposure to 2,4,-D, 2,4,5-T, and TCDD. The author indicates that IARC considers the studies of Hardell et al. to provide "limited evidence" of such an association.

Schecter, A., and Gasiewicz, T. 1986. Human breast milk levels of PCDDs and PCDFs: Their significance with respect to current risk assessments. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 199.

Keywords: Tissue levels; Environmental exposure; Dioxins; Phenoxy herbicide formulations; Human; Abstract; Review article

The authors of this abstract of a symposium presentation review the available data on levels of TCDD in breast milk and, using conventional unit risk estimates for cancer, estimate relative cancer risks among breast-fed infants in the U.S., Sweden, and Vietnam.

Schecter, A.J., Ryan, J.J., and Constable, J.D. 1986a. Chlorinated dibenzo-p-dioxin and dibenzofuran levels in human adipose tissue and milk samples from the north and south of Vietnam. Chemosphere. 15:1613-1620

Keywords: Tissue levels; Environmental exposure; Dioxins; Phenoxy herbicide formulations; Human

See Page 94.

Schecter, A., Eisen, H., and Eichelberger, H. 1986b. Functional and structural characterization by transmission and scanning electron microscopy of mouse Hepatotoxicity Al hepatoma cells in vitro after 2,3,7,8-TCDD treatment. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 64.

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; In Vitro; Dioxins; Mammalian cells in culture; Abstract

This abstract of a symposium presentation describes the results of studies that have been published in full previously (see Schecter et al. 1985a in Clement 1986).

Schecter, A., Gross, M., and Constable, J. 1986c. The use of adipose tissue biopsies to define populations with elevated body burden of 2,3,7,8-TCDD after potential exposure to Agent Orange or related compounds. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 147.

Keywords: Tissue levels; Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Dioxins; Human; Review article; Abstract

In this abstract of a symposium presentation the authors review the results of studies of adipose tissue levels of chlorinated dibenzo-p-dioxins in humans and address the question as to whether such measurements provide useful exposure indices for epidemiological studies.

Schecter, A., Ryan, J.J., and Constable, J. 1986d. Polychlorinated dibenzo-p-dioxin and polychlorinated dibenzofuran levels in human breast milk from Vietnam compared with cows milk and human breast milk from the North American continent. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 151.

In this abstract, the authors summarize studies of the effects of a series of chlorinated aromatic hydrocarbons including TCDD on rats with particular emphasis on lipid peroxidation. The authors conclude that lipid peroxidation obeys the same structure-activity relationship as AHH induction.

Sharp, D.S., and Eskenazi, B. 1986. Delayed health hazards of pesticide exposure. Ann. Rev. Public Health. 7:441-471

Keywords: Cancer; Epidemiological study; Neuro/behavioral effects; Reproductive toxicity; Birth defects; Environmental exposure; Occupational exposure; Dioxins; Phenoxy herbicide formulations; Human; Review article

This is a comprehensive review of epidemiolgic evidence for associations between pesticide exposure and cancer, reproductive hazards, and neurological toxicity. Sudies of phenoxy herbicide and/or chlorinated dibenzo-p-dioxin exposures are reviewed extensively (178 references).

Shireman, R.B., and Wei, C. 1986a. Uptake of 2,3,7,8-tetrachlorodibenzo-p-dioxin from plasma lipoproteins by cultured human fibroblasts. Chem. Biol. Interact. 58:1-12

Keywords: Mechanism of action; Absorption, distribution, metabolism, and excretion; In Vitro; Dioxins; Mammalian cells in culture

The authors studied the effect of serum lipid composition on the uptake of TCDD by human skin fibroblasts cultured in blood plasma. The results suggest mediation by a low density lipoprotein receptor and the authors suggest that physiological rather than solvent vehicles should be used for experimental studies of TCDD.

Shireman, R.B., and Wei, C.I. 1986b. Uptake of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) from plasma lipoproteins by cultured human fibroblasts. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:308

Keywords: Mechanism of action; Absorption, distribution, metabolism, and excretion; In Vitro; Dioxins; Human; Mammalian cells in culture; Abstract

This meeting abstract describes a study that was also published as a full paper (see Shireman and Wei 1986a).

Sielken, R.L. 1986. Statistical evaluations reflecting the skewness in the distribution of TCDD levels in human adipose tissue. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 197.

Keywords: Tissue levels; Environmental exposure; Dioxins; Human; Commentary or opinion; Abstract

The author of this abstract of a symposium presentation uses data on levels of TCDD in human adipose tissues to estimate the shape of the distribution of background levels. He suggests that the distribution curve is skewed with a long right-hand tail.

Sielken, R.L., Carlborg, F.W., Paustenbach, D.J., Shu H.P., and Murray, F.J. 1986. Alternative approaches to mathematically analyzing the bioassay data for 2,3,7,8-TCDD. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:282

Keywords: Cancer; Environmental exposure; Dioxins; Review article; Commentary or opinion; Abstract

This is an abstract of a meeting presentation in which the authors criticize models used by federal regulatory agencies to estimate cancer risks among humans exposed to TCDD. The authors propose alternative methods.

Silbergeld, E.K., and Max, S.R. 1986. Neuromuscular targets for the action of 2,3,7,8-TCDD. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 60.

Keywords: Acute toxicity; Mechanism of action; Neuro/behavioral effects; Unspecified route of exposure; Dioxins; Rat; Abstract

This abstract summarizes studies of the effect of acutely lethal doses of TCDD on neuromuscular tissues in rats. The results suggest that the "wasting syndrome" preferentially attacks muscle tissue and that the mechanism of this effect is different from disuse atrophy or denervation.

Silkworth, J.B., and Antrim, L. 1986. Ah receptor mediated suppression of the antibody response in mice is dependent on the Ah genotype of lymphoid tissue. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:16

Keywords: Immunological effects; Mechanism of action; Injection; Other contami- nating compounds; Mouse; Abstract

See Page 75.

Silkworth, J.B., Tumasonis, C., Briggs, R.G., Narang, A.S., Narang R.S., Rej, R., Stein, V., McMartin, D.N., and Kaminsky, L.S. 1986. The effects of Love Canal soil extracts on maternal health and fetal development in rats. Fundam. Appl. Toxicol. 7:471-485

Keywords: Reproductive toxicity; Birth defects; Oral; Dioxins; Other contaminating compounds; Rat

Silkworth et al. (1986) studied the effects on the maternal and fetal development of rats of solvent extracts of soil from the Love Canal area, Niagara Falls, N.Y. These were complex mixtures containing TCDD, so the studies provide no information specifically about the effects of TCDD.

Singh, S.V., and Awasthi, Y.C. 1986. Inhibition of human glutathione S-transferases by 2,4-dichlorophenoxyacetate (2,4-D) and 2,4,5-trichlorophenoxyacetate (2,4,5-T). Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:149

Keywords: Enzyme induction or inhibition; Hepatotoxicity; Mechanism of action; In Vitro; 2,4-D; 2,4,5-T; Human; Abstract

This abstract describes studies that have been published previously as a full paper (see Singh and Awasthi 1985 in Clement 1986).

Smith, A.H., and Pearce, N.E. 1986. Update on soft tissue sarcoma and phenoxyherbicides in New Zealand. Chemosphere. 15:1795-1798

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human; Review article

This paper is a symposium presentation in which the authors describe the results of case-control epidemiology studies of the association of soft-tissue sarcoma with phenoxy herbicide and chlorinated phenol exposure in New Zealand. These studies have been discussed in earlier volumes of this review (see Smith et al. 1984, 1983, and 1982a in Clement 1985 and 1986).

Smuckler, E.A. 1985. Biological effects of dioxins and other halogenated polycyclics. In Kamrin, M.A. and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 215-223.

Keywords: Miscellaneous study; Environmental exposure; Dioxins; Review article

In this conference presentation, the author reviews the information on the health effects of polychlorinated dibenzo-p-dioxins emphasizing the inconclusiveness of the human epidemiologic data base and the apparent conflict between animal and human data. The author also notes the intense public interest in the issue (32 references).

Sobel,, W. Bond, G.G., Skowronski, B.J., Brownson, P.J., and Cook, R.R. 1986a. A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. Paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, Fukuoka, Japan, September 16-19, 1986. 5 pages

Keywords: Cancer; Epidemiological study; Occupational exposure; Dioxins; Human

Sobel, W., Bond, G.G., Skowronski, B.J., Brownson, P.J., and Cook R.R., 1986b. A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 184.

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Dioxins; Human; Abstract

This is the abstract of the paper presented by Sobel et al. at the 6th International Dioxin Symposium (Sobel et al. 1986a).

See Pages 33 and 34.

Soderkvist, P., Poellinger, L., and Gustafsson, J. 1986. Carcinogen-binding proteins in the rat ventral prostate: specific and nonspecific high-affinity binding sites for benzo(a)pyrene, 3-methylcholanthrene, and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Cancer Res. 46:651-657

Keywords: Acute toxicity; Mechanism of action; Cancer; Enzyme induction or inhibition; In Vitro; Dioxins; Rat

The authors isolated a protein from rat ventral prostate that binds TCDD and polynuclear aromatic hydrocarbons with high affinity and shows many of the properties of the Ah receptor isolated from other tissues. This receptor is shown to be similar to prostatic secretory protein which binds androgens.

Spitsbergen, J.M., Schat, K.A., Kleeman, J.M., and Peterson, R.E. 1986. Interactions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) with immune responses of rainbow trout. Vet. Immunol. Immunopathol. 12:263-280

Keywords: Acute toxicity; Immunological effects; Injection; Dioxins; Fish

The authors studied the effect of TCDD on immune function in yearling rainbow trout. Trout were generally resistant to the immunosuppressive effects of TCDD except that the lymphoprioliferative response to pokeweed mitogen was suppressed at doses near the LD50.

Stanley, J.S., Boggess, K.E., Onstot, J., and Sack, T.M. 1986. PCDDs and PCDFs in human adipose tissue from the EPA FY82 NHATS repository. Chemosphere. 15:1605-1612

Keywords: Tissue levels; Environmental exposure; Dioxins; Human

See Pages 92, 93, and 96.

Stehr, P.A., Stein, G., Falk, H., Sampson, E., Smith, S.J., Steinberg, K., Webb, K., Ayers, S., Schramm, W., Donnell, H.D., and Gedney, W.B. 1986. A pilot epidemiologic study of possible health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin contaminations in Missouri. Arch. Environ. Health. 41:16-22

Keywords: Enzyme induction or inhibition; Epidemiological study; Hematologic effect; Hepatotoxicity; Immunological effects; Neuro/behavioral effects; Other skin effects; Environmental exposure; Dioxins; Human

This pilot study of potential adverse health effects among individuals putatively exposed to dioxin-contaminated soil in Missouri has been published previously (see Webb et al. 1984 and Knutsen 1984 in Volume V of this review Clement 1985). Interestingly, neither of these earlier publications are cited in this paper.

Stehr-Green, P.A., Hoffman, R.E., Webb, K.B., Evans, R.G., Knutsen, A.P., Schramm, W.F., Staake, J.L., Gibson, B.B., and Steinberg, K.K. 1986. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 182.

Keywords: Epidemiological study; Hepatotoxicity; Immunological effects; Environmental exposure; Dioxins; Human; Abstract

This is an abstract of a symposium presentation in which the authors describe the results of the Quail Run cohort epidemiologic study which has been published as a full paper (see Hoffman et al. 1986b).

Steinberg, K.K., MacNeil, M.L., Karon, J.M., Stehr, P.A., Neese J.W., and Needham, L.L. 1985. Assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure using a modified D-glucaric acid assay. J. Toxicol. Environ. Health. 16:743-752

Keywords: Enzyme induction or inhibition; Epidemiological study; Environmental exposure; Dioxins; Human

See Page 99.

Stellman, S.D., and Stellman, J.M. 1986. Estimation of exposure to Agent Orange and other defoliants among American troops in Vietnam: A methodological approach. Am. J. Ind. Med. 9:305-321

Keywords: Miscellaneous study; Occupational exposure; Phenoxy herbicide formulations; Human

The authors developed algorithms for estimating exposure of military personnel in Vietnam to Agent Orange and related herbicides using HERBS tapes and questionnaires. Exposure indices were computed for a self-selected trial cohort of 478 veterans. The results indicated that there was poor correllation between semi-objective indices of exposure and the veteran's assessment as to whether or not he was exposed. No health effects information was included.

Sterling, T.D., and Arundel, A. 1986a. Review of recent Vietnamese studies on the carcinogenic and teratogenic effects of phenoxy herbicide exposure. Int. J. Health Serv. 16:265-278

Keywords: Cancer; Epidemiological study; Reproductive toxicity; Birth defects; Environmental exposure; Phenoxy herbicide formulations; Human; Review article

The authors summarize and review studies of reproductive outcome and cancer incidence in Vietnamese populations. These studies were presented at the conference on herbicides in warfare in Ho Chi Minh City, Vietnam in 1983, and they are reviewed in this volume of the review (27 references).

Sterling, T.D., and Arundel, A.V. 1986b. Health effects of phenoxy herbicides. Scand. J. Work Environ. Health. 12:161-173

Keywords: Cancer; Epidemiological study; Reproductive toxicity; Birth defects; Phenoxy herbicide formulations; Human; Review article

Suskind, R.R. 1985. The health effects of 2,4,5-T and its toxic contaminants. In Kamrin, M.A. and Rodgers, P.W. Dioxins in the Environment. 1985. Hemisphere Publishing Corp., Washington, D.C. Pp. 231-239.

Keywords: Epidemiological study; Cancer; Chloracne; Hepatotoxicity; Neuro/behavioral effects; Reproductive toxicity; Other toxic effects; Occupational exposure; Dioxins; Phenoxy herbicide formulations; Human; Review article

In this paper, presented at a conference, the author reviews the history of occupational exposure to polychlorinated dibenzo-p-dioxins and phenoxy herbicides at the Monsanto chemical manufacturing facility at Nitro, West Virginia. Findings of epidemiologic investigations among populations of exposed workers are discussed (6 references).

Suskind, R.R., Pershing, L.K., and Krueger, G.G. 1986. The study of absorption and metabolism of 2,3,7,8-TCDD in human skin using the human/rat skin flap in the nude athymic rat. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 168.

Keywords: Absorption, distribution, metabolism, and excretion; Other skin effects; In Vitro; Dioxins; Human; Abstract

This abstract describes studies whose primary focus was to test a new in vitro system for studying the absorption of chemicals through the skin. In this system, absorption of TCDD through rat skin was greater than through human skin.

Sweeney, G.D. 1986. Porphyria cutanea tarda, or the uroporphyrinogen decarboxylase deficiency diseases. Clin. Biochem. 19:3-15

Keywords: Mechanism of action; Porphyria cutanea tarda; Dioxins; Review article

This is a comprehensive review of disorders in porphyrin metabolism with emphasis on the condition known as porphyria cutanea tarda (PCD). Some researchers have implicated TCDD as an etiologic agent in PCD; although this is disputed by others. This detailed review describes difficulties in the diagnosis and treatment of the disease and points out the complexity of establishing its mechanism and etiology (115 references).

Tarkowski, S., and Yrjanheikki, E. 1986. Polychlorinated dibenzo-p-dioxins and dibenzofurans in human milk - Reasons for concern. Chemosphere. 15:1641-1648

Keywords: Tissue levels; Environmental exposure; Dioxins; Human; Review article

See Page 95.

Thalken, C.E., Young, A.L., and Cockerham, L.G. 1986. A long-term study of ecosystems contamination with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 90.

Keywords: Absorption, distribution, metabolism, and excretion; Reproductive toxicity; Other toxic effects; Miscellaneous study; Environmental exposure; Phenoxy herbicide formulations; Other species

Animal and bird species exposed to TCDD at Eglin Air Force Base, Florida were examined to determine if exposure had any serious ecological consequences. The authors report that exposure of 50 generations of the beachmouse to soil contaminated with between 0.5 and 1.5 ppb TCDD has had minimal effect on the health and reproduction of the species.

Thomas, A.S. 1986. Storm in a cup of 2,4,5-T. Med. J. Aust. 144:611

Keywords: Cancer; Epidemiological study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human; Commentary or opinion

This brief letter to the editor, stimulated by an earlier editorial by Armstrong (1986), recalls heavy use of 2,4,5-T to eradicate blackberry plants in Victoria, Australia from 1952 on. The author expresses his opinion that there has been no increase in cancer as a result.

Tomaszewski, K., Harrington, F., Greenwell, A., Rahn, C., Moore, J., Birnbaum, L., and Melnick, R. 1986. Interactive effects of di(2-ethylhexyl)phthalate (DEHP) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on lipid metabolism in F344 rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:44

Keywords: Acute toxicity; Hepatotoxicity; Mechanism of action; Other toxic effects; Oral; Dioxins; Rat; Abstract

This is an abstract of a study of the interaction of TCDD and di(2-ethylhexyl)phthalate (DEHP) in rats. Both of these chemicals affect serum lipid levels and lipid metabolism in the liver, but these studes suggest that they do so by independent mechanisms.

Ton, D.L. 1986. Possible teratogenic effects of dioxin among the first generation and the concordance between the rate of birth defects and reproductive abnormalities with the degree of potential paternal exposure to Agent Orange in Vietnam. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 169.

Keywords: Reproductive toxicity; Birth defects; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human; Abstract

Ton, D.L., Do, D.V., Ton, T.T. 1983. [Mutagenic effects of the herbicide Agent Orange on progeny.] Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. Vol. 3. Pp. 92-98

Keywords: Epidemiological study; Birth defects; Occupational exposure; Environmental exposure; Phenoxy herbicide formu- lations; Human

Toth, K., and Sugar, J. 1983. Study of the delayed carcinogenic potency of the herbicide 2,4,5-trichlorophenoxyethanol (TCPE) containing 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and of pure TCDD in Swiss mice and of the mutagenic potency of TCPE in the Ames assay. Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. 3:178-190

Keywords: Cancer; Mechanism of action; Genetic toxicity Oral; In Vitro; Dioxins; Mouse

Toyoshima, E., Mayer, R.F., and Max, S.R. 1985. Effects of 2,4-dichlorophenoxyacetic acid (2,4-D) on the contractile properties of reinnervated rat skeletal muscle. Experim. Neurol. 90:601-610

Keywords: Neuro/behavioral effects; Mechanism of action; Subchronic toxicity; Injection; 2,4-D; Rat

See Page 79.

Tschirley, F.H. 1986. Dioxin. Sci. Am. 254:29-35

Keywords: Acute toxicity; Cancer; Epidemiological study; Reproductive toxicity; Dioxins; Review article

The author reviews, for the lay reader, the state of knowledge regarding the human health consequences of environmental contamination with chlorinated dibenzo-p-dioxins. He concludes that the issue does not deserve the scientific attention that it has received (no references).

Tsyrlov, I.B., Chasovnikova, O.B., Grishanova, A.Y., and Lyakhovich V.V. 1986. Reappraisal of the liver benzpyrene hydroxylase synthesized de novo after treatment of rats with 2,3,7,8-tetrachlorodibenzo-p-dioxin and 3-methylcholanthrene. Febs. Lett. 198:225-228

Keywords: Acute toxicity; Enzyme induction or inhibition; Mechanism of action; Injection; Dioxins; Rat

The authors studied the properties of the benzpyrene hyroxylase induced by TCDD in the livers of treated rats and provide evidence that the increase is due to activation of existing enzymes rather than de novo synthesis of new cytochrome P-448.

Tucker, A.N., Vore, S.J., and Luster, M.I. 1986. Suppression of B cell differentiation by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Mol. Pharmacol. 29:372-377

Keywords: Acute toxicity; Immunological effects; Mechanism of action; Oral; In Vitro; Dioxins; Mouse; Mammalian cells in culture

See Page 74.

U.S. Environmental Protection Agency (USEPA). 1985. Health Effects Assessment Document for Polychlorinated Dibenzo-p-dioxins. USEPA Report Number EPA-600/8-84-014F. August, 1985. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, USEPA, Cincinnati, OH.

Keywords: Cancer Reproductive toxicity; Birth defects; Genetic toxicity; Environmental exposure; Dioxins; Review article

The objective of this document is to provide a scientific basis for the determination of safe levels of human exposure to chlorinated dibenzo-p-dioxins in water and in air as a result of environmental contamination. The agency concludes that these compounds have the potential to cause cancer in humans exposed via either route and the risks due to such exposure are estimated. (Approximately 700 references)

Umbreit, T.H., Hesse, E.J., and Gallo, M.A. 1986. Comparative toxicity of TCDD contaminated soils from Times Beach, Missouri, and Newark, New Jersey. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:317

Keywords: Acute toxicity; Hepatotoxicity; Absorption, distribution, metabolism, and excretion; Environmental exposure; Oral; Dioxins; Other contaminating compounds; Guinea pig; Abstract

The acute oral toxicity to guinea pigs of soils contaminated with TCDD and other chlorinated dibenzo-p-dioxins from Newark, NJ and Times Beach, MO were compared. Times Beach soil had a lower LD50 and caused more liver damage than did Newark soil. Reasons for the difference are not discussed in this abstract.

Van Tiggelen, C.J.M. 1983. Australian Vietnam Veterans and Agent Orange. Proceedings of the International Symposium on the Use of Herbicides and Defoliants in Warfare: Long-Term Effects on Man and the Environment. Ho Chi Minh City, January 13-20, 1983. Comite' National d'Investigation des Consequences de la Guerre Chimique des E.U.A. au Vietnam, Hanoi. 2:40-42

Keywords: Miscellaneous study; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Dioxins; Review article

In this symposium presentation, the author describes the response of the Australian Parliament to the question of potential adverse health consequences in Australian veterans as a result of exposure to herbicides in Vietnam.

Vecchi, A., Sironi, M., Sfreddo-Gallotta, E., Graziani, A., and Cantoni L. 1986. Effect of inducers of P-450 cytochrome isoenzymes on TCDD immunosuppressive activity. Chemosphere. 15:1707-1714

Keywords: Immunological effects; Mechanism of action; Injection; Dioxins; Mouse

See Page 74.

Veterans Administration. 1986. Advisory Committee on Health-Related Effects of Herbicides: Transcript of Proceedings. June 12, 1986. Veterans Administration, Washington, D.C. Pp. 1-242.

Keywords: Epidemiological study; Cancer; Other toxic effects; Occupational exposure; Environmental exposure; Phenoxy herbicide formulations; Human; Review article; Commentary or opinion

This transcript of the proceedings of the meeting of the VA Advisory Committee on the Health-Related Effects of Herbicides contains discussions of the Vietnam Experience Twin Study, The Ranch Hand Study, the CDC Epidemiology Study, and the Massachusetts Vietnam Veterans Health Survey.

Wacker, R., Poiger, H., and Schlatter, C. 1986. Pharmacokinetics and metabolism of 1,2,3,7,8-pentachlorodibenzo-p-dioxin in the rat. Chemosphere. 15:1473-1476.

Keywords: Absorption, distribution, metabolism, and excretion; Oral; Other contaminating compounds; Rat

See Pages 84 and 88.

Wallace, W.H., Hryhorczuk, D., and Zugerman, C. 1986. Persistent chloracne in pentachlorophenol workers. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 167.

Keywords: Chloracne; Occupational exposure; Dioxins; Human; Abstract

This is an abstract of a symposium presentation of four case reports of chloracne among employees of a plant in Sauget, Illinois who were exposed to chlorinated dibenzo-p-dioxins during the manufacture of pentachlorophenol. The cases are said to be illustrative of severe, persistent chloracne as a result of brief exposure to higher chlorinated dioxins.

Webb, K.B., Ayres, S.M., Jayma Mikes, A.B., and Evans, R.G. 1986. The diagnosis of dioxin-associated illness. Am. J. Prev. Med. 2:103-108

Keywords: Chloracne; Cancer; Hepatotoxicity; Porphyria cutanea tarda; Neuro/behavioral effects; Other toxic effects; Environmental exposure; Occupational exposure; Dioxins; Human; Review article

This review article is directed at physicians and discusses health effects to be looked for in individuals who may have been exposed to TCDD (25 references).

Weber, L.W.D., and Rozman, K. 1986. Glucose metabolism in TCDD-treated rats. Abstract of a paper presented at the 25th Annual Meeting of the Society of Toxicology. The Toxicologist. 6:311

Keywords: Acute toxicity; Absorption, distribution, metabolism, and excretion; Mechanism of action; Injection; Dioxins; Rat; Abstract

This is an abstract of a study of the mechanism of the acute lethality of TCDD in rats. A near-lethal dose of TCDD caused a 50% decrease in the rate of metabolism of 14C-glucose within the first eight hours after treatment.

Weerasinghe, N.C.A., Schecter, A.J., Pan, J.C., Lapp, R.L., Giblin, D.E., Meehan, J.L., Hardell, L., and Gross, M.L. 1986. Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) in adipose tissue of U.S. Vietnam veterans seeking medical assistance. Chemosphere. 15:1787-1794

Keywords: Tissue levels; Occupational exposure; Phenoxy herbicide formulations; Dioxins; Human

Adipose tissue samples from 13 Vietnam veterans, who claimed to have been exposed to Agent Orange in Vietnam and who sought medical assistance for health effects that they ascribed to that exposure, were analyzed for TCDD. The levels were not different from a control group and were consistent with U.S. background levels.

West Virginia Health Department. 1986. West Virginia Vietnam-Era Veterans Mortality Study: West Virginia Residents (1968-1983). January 1986. West Virginia Health Department, West Virginia. P. 30 pages.

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human;

See Pages 5 and 14.

White, K.L., Lysy, H.H., McCay, J.A., and Anderson, A.C. 1986. Modulation of serum complement levels following exposure to polychlorinated dibenzo-p-dioxins. Toxicol. Appl. Pharmacol. 84:209-219

Keywords: Acute toxicity; Immunological effects; Subchronic toxicity; Oral; Dioxins; Other contaminating compounds; Mouse

See Page 74.

Whitlock, J.P. 1986. The regulation of cytochrome P-450 gene expression. Ann. Rev. Pharmacol. Toxicol. 26:333-69

Keywords: Enzyme induction or inhibition; Mechanism of action; Dioxins; Review article

See Page 106.

Wiklund, K. 1986. Soft tissue sarcoma risk in Swedish agricultural and forestry workers. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 186.

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human; Abstract

The cohort epidemiology study described in this abstract of a symposium presentation is published in full as a report of the Karolinska Institute (Wiklund and Holm, 1986).

See Page 25.

Wiklund, K., and Holm, L.E. 1986. Soft tissue sarcoma risk in Swedish agricultural and forestry workers. Cancer Risks Among Agricultural Workers in Sweden. 1986. Dept. of Cancer Epidemiology, Radiumhemmet, Karolinska Hospital, Stockholm, Sweden. P. 19 pages.

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human

Wilhelmsson, A., Wikstrom, A.C., and Poellinger, L. 1986. Polyanionic-binding properties of the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Biol. Chem. 261:13456-13463

Wolfe, W.W., Michalek, J.E., Miner, J.C., and Peterson, M.R. 1986. [An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides - Mortality update 1986.] Report to the Surgeon General, United States Air Force. December 26, 1986. Epidemiology Division, USAF School of Aerospace Medicine, Brooks Air Force Base, TX. P. 7

Keywords: Cancer; Epidemiological study; Other toxic effects; Environmental exposure; Occupational exposure; Phenoxy herbicide formulations; Human

See Page 19.

Wong, T.K., Sloop, T., and Lucier, G.W. 1986. Nondetectable concentrations of human placental Ah receptors are associated with potent induction of microsomal benzo[a]pyrene hydroxylase in individuals exposed to polychlorinated biphenyls, quaterphenyls, and dibenzofurans. Toxicol. Appl. Pharmacol. 85:60-68

Keywords: Enzyme induction or inhibition; Mechanism of action; Reproductive toxicity; Environmental exposure; Other contaminating compounds; Human

See Page 109.

Woods, J., Polissar, L., Severson, R., Heuser, L., and Kulander, B. 1986a. Soft tissue sarcoma and non-Hodgkins lymphoma in relation to phenoxy herbicide and chlorophenol exposure in western Washington State, USA. Abstract of a paper presented at the 6th International Symposium on Chlorinated Dioxins and Related Compounds, September 16-19, 1986, Fukuoka, Japan. P. 78.

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human; Abstract

This is an abstract of a symposium presentation in which the author describes an epidemiologic study of soft-tissue sarcoma and non-Hodgkins lymphoma in western Washington. A full paper describing this study is reviewed in detail in this critical review (see Woods et al. 1986c).

See Pages 22 and 39.

Woods, J.S., Polissar, L., Severson, R.K., and Heuser, L.S. 1987c. Soft tissue sarcoma and non-Hodgkins lymphoma in relation to phenoxy herbicide and chlorinated phenol exposure in western Washington. JNCI (In Press). P. 44 pages.

Keywords: Epidemiological study; Cancer; Occupational exposure; Phenoxy herbicide formulations; Human

Woods, J.S., Pollissar, L., Severson, R.K., Heuser, L.S., and Kulander, B.G. 1986b. Soft tissue sarcoma and non-Hodgkins lymphoma in relation to phenoxy herbicide and chlorinated phenol exposure in western Washington. 1986 Ann. Meeting of the Soc. for Epidemiologic Research.

Keywords: Cancer; Epidemiological study; Occupational exposure; Phenoxy herbicide formulations; Human; Abstract

This is an abstract of a meeting presentation in which the authors describe the preliminary results of a case-control epidemiologic study of soft-tissue sarcoma and non-Hodgkins lymphoma in western Washington. This study has subsequently become available as a full-length paper (see Woods et al. 1987c).

See Pages 22 and 39.

Yanders, A.F. 1986. The Missouri dioxin episode. Chemosphere. 15:1571-1576

Keywords: Miscellaneous study; Environmental exposure; Dioxins; Human; Review article

The author reviews the history of chlorinated dioxin contamination in Missouri and describes the political, legal, scientific, and technical problems that interfered with the development of a timely and efficient remedial response.

Yeary, R.A. 1986. Urinary excetion of 2,4-D in commercial lawn specialists. Appl. Ind. Hyg. 119-121

Keywords: Mechanism of action; Miscellaneous study; Occupational exposure; 2,4-D; Human

Concentrations of 2,4-D in urine were determined for 45 commercial lawn care specialists who had sprayed herbicide formulations containing 2,4-D for at least three weeks prior to monitoring. Assumptions based on previous studies of absorption and excretion were used to estimate total daily dose. No health effects information is included.

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