Item ID Number 04924 ☐ **Not Scanned**

Author

Corporate Author Clement Associates, Inc.

Report/Article Title Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins: Volume VII, Analysis of Recent Literature on Health Effects; and Volume VIII, Annotated Bibliography of Recent Literature on Health Effects

Journal/Book Title

Year 1986

Month/Day October

Color ☑

Number of Images 147

Descripton Notes VA Contract No.: V101(93)P-953

Veterans Administration

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

Volume VII
Analysis of Recent Literature on Health Effects
and
Volume VIII
Annotated Bibliography of Recent Literature on Health Effects

Department of
Medicine and Surgery

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

Analysis of Literature on Health Effects Published in 1985

Volume VII

Prepared for Contracting Officer's Technical Representative:

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

Submitted by:

Clement Associates, Inc.
1850 K Street, N.W.
Suite 450
Washington, D.C. 20006

May 1, 1986

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402

TABLE OF CONTENTS

I.	Introduction	1
II.	Summary and Conclusions	3
III.	Health Effects of Phenoxy Herbicides and Their Impurities	8
	A. Cancer	8
	B. Genetic Toxicity	39
	C. Teratogenicity and Reproductive Toxicity	45
	D. Immunotoxicity	54
	E. Neurobehavioral Toxicity	59
	F. Metabolism	64
	G. Other Effects	71
IV.	Relevance of Basic Research on TCDD Toxicity	77
V.	Health Effects of Other Herbicidal Active Ingredients	86
	A. Picloram	86
	B. Cacodylic Acid	88

I. INTRODUCTION

This report consists of a bibliography and critical review of scientific literature that became available during 1985 on the health effects of herbicides (including their impurities) that were used as defoliants in the Vietnam conflict. This update comprises Volumes VII and VIII of an ongoing series of publications entitled, "Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins." Volumes I and II were prepared by JRB Associates and were published by the Veterans Administration in October 1981. These volumes are referred to as JRB (1981) in the remainder of this report. Volumes III and IV, covering literature published from 1981 through 1983 were prepared by Clement Associates, Inc. and were published by the Veterans Administration in the summer of 1984. Volumes V and VI, also prepared by Clement Associates, Inc., covered literature that became available during 1984; they were published in the summer of 1985. In this report ICF-Clement, Inc., has identified and reviewed the relevant literature that became available during 1985.

Included in this review is literature (including unpublished but publicly available documents) relevant to the potential human health effects of the phenoxy herbicide formulation commonly referred to as Agent Orange, as well as other formulations of the herbicidal active ingredients

2,4-D, 2,4,5-T, and their esters; the herbicidal active ingredients picloram and cacodylic acid; formulations containing these active ingredients; and polychlorinated dibenzo-p-dioxins (primarily 2,3,7,8-tetrachlorodibenzo-p-dioxin, henceforth referred to as TCDD) which are known to be contaminating impurities of some phenoxy herbicide formulations. The scope of this review does not include literature describing the chemistry, chemical analysis, environmental fate, or non-mammalian toxicology of these compounds.

II. SUMMARY AND CONCLUSIONS

Approximately 250 documents relevant to the health effects of phenoxy herbicides, their chlorinated dioxin impurities, and the herbicides picloram and cacodylic acid became available during 1985. Thus, the rate of publication has remained relatively constant over the past several years. Close analysis reveals, however, that an increasing percentage of the published information (over 50% in 1985) consists of review articles and abstracts. This is due, in part, to the proliferation of scientific meetings and symposia devoted to chlorinated dibenzodioxins and related chlorinated aromatic hydrocarbons. Often the same studies are described at two or more symposia and may be published first as abstracts and later as full papers in the proceedings of the symposia over a period of several years. Also, the distinction between primary and secondary literature resources has tended to blur in recent years. For example, a symposium presentation may consist primarily of a review of previously published data, yet incorporate the results of two recent experiments in the author's laboratory that were unpublished at the time of the symposium. Those new data may subsequently be published along with the results of additional experiments in another "primary" source. The net effect of these trends is to make the literature on the health effects of herbicides, and particularly chlori-

nated dioxins, appear to be more substantial than it actually is and may also complicate the use and interpretation of this literature.

Despite the problems related to the proliferation of secondary literature in the field, it should be pointed out that some exceptionally comprehensive reviews and analyses of the state of scientific knowledge of phenoxy herbicides and associated dioxins were published during 1985. Deserving special mention are the Scientific Criteria Document on the Health Effects of Chlorinated Dibenzodioxins and Dibenzofurans prepared by the Ontario Provincial Government (Birmingham et al. 1985), Banbury Report 18: Biological Mechanisms of Dioxin Action published by the Cold Spring Harbor Laboratory, the Proceedings of the 4th International Symposium on Chlorinated Dioxins and Related Compounds published in Volume 14 of Chemosphere, a review of the toxicological and environmental effects of picloram (Mullison 1985), and the Environmental Health Criteria Document on 2,4-D prepared by the World Health Organization (WHO 1984). Because of normal delays in publication all of these sources are already slightly out of date, but they are excellent starting points for scientists needing a historical background on the scientific investigation of the health effects of these compounds.

Of the primary literature published in 1985 approximately three-quarters of the references described studies in experimental animals, and the vast majority of these were studies of the effects of TCDD. Only one study of the effects of 2,4,5-T

was published in 1985. This is probably a reflection of the removal of this herbicide from the commercial market. Only 12 publications described studies of the effects of 2,4-D, picloram, or cacodylic acid. Most of the studies of TCDD were designed to elucidate the mechanisms of action of this compound at cellular and sub-cellular levels. A few generalizations regarding the human health implications of these studies have been advanced, but much more research is needed before scientific information on mechanisms of action can be used to evaluate human health effects of this and related compounds.

Of the studies of human populations exposed to phenoxy herbicides and/or chlorinated dioxins, approximately half are epidemiologic studies, and the remainder are case studies or studies of the effects of TCDD on human tissues or cells in vitro. Several of the epidemiologic studies are publications of studies reviewed in earlier volumes of this review, i.e., Falk et al. 1985, Ideo et al. 1985, Lawrence et al. 1985, Stehr et al. 1984, and Wolfe et al. 1985a. The remaining epidemiologic studies consist primarily of studies of cancer incidence among Vietnam veterans who may have been exposed to Agent Orange or among populations with potential occupational exposure to phenoxy herbicides or chlorinated dioxins either during manufacturing or during use in agriculture. A major difference from previous years is that few full-length papers were published in 1985 describ-

ing studies of health effects among the population exposed to chlorinated dioxins as a result of the ICMESA accident at Seveso, Italy, or among populations of workers exposed to chlorinated dioxins during the manufacture of phenoxy herbicides and chlorinated phenols in the United States.

Studies of cancer incidence or mortality among human populations with potential exposure to phenoxy herbicides or chlorinated dioxins were essentially negative. Although two studies suggested increased risks of soft-tissue sarcoma and several studies suggested increased risk of malignant lymphoma in populations with potential exposure to phenoxy herbicides and/or chlorinated dibenzodioxins, the apparent associations failed to stand-up to attempts to correlate the exposures to herbicide exposure per se.

Most studies of other health effects of phenoxy herbicides and chlorinated dibenzodioxins that were published in 1985 tended to confirm earlier studies and shed light on the mechanisms by which these compounds act. A major portion of the literature was taken up by studies of the action of TCDD at the cellular, sub-cellular, and molecular levels. Of greatest consequence to human health is the increased evidence that susceptibility of individual organisms to many of the toxic effects of TCDD is under genetic control and therefore, there is a great deal of inter- and intra-species variability in responsiveness to the effects of these compounds.

REFERENCES

Birmingham, B., et al. 1985. Chlorinated dioxins and dibenzofurans in Ontario: Analyzing and controlling the risks. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 2 pages (abstract)

Falk, H., Stehr, P.A., Stein, G.F., Sampson, E.J., Donnell, H.D., Jr., Schromm, W.F., Webb, K., and Gedney, W.B. 1984. A pilot epidemiologic study of health effects due to 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) contamination in Missouri. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 447-460

Ideo, G., Bellati, G., Bellobuono, A., and Bissanti, L. 1985. Urinary D-glucaric acid excretion in the Seveso area, polluted by tetrachlorodibenzo-p-dioxin (TCDD): Five years of experience. Environ. Health Perspect. 60:151-157

Lawrence, C.E., Reilly, A.A., Quickenton, P., Greenwald, P., Page, W.F., and Kuntz, A.J. 1985. Mortality patterns of New York State Vietnam veterans. Am. J. Public Health 75:277-279

Mullison, W.R. 1985. A toxicological and environmental review of picloram. Proc. West. Soc. Weed Sci. 38:21-92

Stehr, P.A., Stein, G.F., and Webb, K. 1984. An epidemiologic study of community exposures to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Presented at the 5th National Conference on Management of Uncontrolled Hazardous Waste Sites, November 7-9, Washington, D.C. Pp. 287-289

Wolfe, W.H., Lathrop, G.D., Albanese, R.A., and Moynahan, P.M. 1985a. An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides and associated dioxins. Chemosphere 14:707-716

World Health Organization (WHO). 1984. 2,4-Dichlorophenoxyacetic acid (2,4-D). Environ. Health Criteria 29:1-151

III. HEALTH EFFECTS OF PHENOXY HERBICIDES AND THEIR IMPURITIES

A. Cancer

1. Studies of Exposed Human Subjects

The results of several studies of cancer in human populations that may have been exposed to phenoxy herbicides or to chlorinated dibenzodioxins became available during 1985. Two of these were studies of cancer among veterans who may have been exposed to Agent Orange in Vietnam. Two were of workers potentially exposed to phenoxy herbicides and/or chlorinated dibenzodioxins during the manufacture of phenoxy herbicides or related chlorinated aromatic hydrocarbons. Five studies are of agricultural workers who may have been exposed to phenoxy herbicides. Most of these studies were stimulated by early findings in Sweden of an apparent association between exposure to phenoxy herbicides and the incidence of soft-tissue sarcomas and lymphomas (particularly non-Hodgkins lymphoma). Additionally, some of these studies were stimulated by findings of excess incidences of lymphomas and colon cancers in farmers.

The preliminary results of a case-comparison analysis of soft-tissue sarcomas that is being conducted by the Veterans Administration were presented orally at the 5th International Symposium on Chlorinated Dioxins and Related Compounds (Shepard et al. 1985). Using the patient treatment file from the VA's 172 hospitals, the authors identified

418 cases which had been coded as soft-tissue sarcoma (ICD 171) between 1969 and 1982. The pathology reports of these cases were reviewed by a pathologist. Of these, 204 cases were eliminated from the study because of missing pathology or service records or because of probable misdiagnosis of the neoplasm. The remaining 214 cases were individuals who probably had soft-tissue sarcomas and for whom military records were available and sufficiently complete to determine Vietnam service status. Of these 214 cases, 78 (36.5%) had served in Vietnam. For comparison purposes a random sample of 13,446 veterans was selected from the VA patient treatment file for the same years. Of these, 5,530 (41.1%) had served in Vietnam. Since the proportion of veterans with Vietnam service was similar in the two groups, the authors concluded that there was no significant association of soft-tissue sarcoma with military service in Vietnam. The authors pointed out the preliminary nature of this study and indicated that additional studies are in progress including a histopathological review of actual tissue samples from the cases in this study and a second case-control study involving approximately 400 cases of soft-tissue sarcoma diagnosed at the Armed Forces Institute of Pathology.

In addition to the limitations described by the authors of this study, it is important to recognize that, because of the way the cases were selected, the latent period between exposure during service in Vietnam and diagnosis of soft-tissue sarcoma, if the two were associated, would lie in the range

of 6 to 19 years. This latent period is relatively short compared to those of 20 years or more characteristic of many known carcinogens. Also, as has been the case with all studies of Vietnam veterans to date, service in Vietnam is used as an index of exposure to phenoxy herbicides. In fact, a number of individuals with little or no actual exposure to phenoxy herbicides could be included in a study of this design.

A mortality study was conducted by the Massachusetts Department of Public Health (MDPH) to compare causes of death among Vietnam veterans with causes of death among veterans who did not serve in Vietnam and to those among non-veterans (Kogan and Clapp 1985). This study was a records-linkage study using computerized data bases compiled by the Commonwealth of Massachusetts. All deaths among white males in Massachusetts between the years 1972 and 1983 were identified using a data base compiled by MDPH from death certificates. Causes of death were taken from death certificates and entered as codes based on the ninth revision of the International Classification of Diseases (ICD). This data base was then linked to a data base consisting of veterans who had been awarded bonuses by the Commonwealth of Massachusetts. In order to qualify for this bonus, a veteran had to have lived in Massachusetts for a minimum of 6 months immediately prior to induction, have served for at least 6 months between July 1, 1958, and

April 1, 1973, have been honorably discharged, and have applied for the bonus. Veterans who served in Vietnam were awarded a $300.00 bonus whereas veterans who did not serve in Vietnam received a $200.00 bonus.

By matching social security numbers, it was possible to identify among all white males who died between 1972 and 1983 those who received a $300.00 bonus (Vietnam veterans), those who received a $200.00 bonus (non-Vietnam veterans), and those who received no bonus (non-veterans). The number of deaths by specific cause among Vietnam veterans was compared to an expected number derived from calculations of cause-specific proportionate mortality within 10-year age groups in the combined non-Vietnam veteran and non-veteran cohorts. This resulted in a standardized proportional mortality rate (SPMR).

For those causes of death for which the SPMR indicated statistically significant differences among groups, deaths among Vietnam veterans were compared to those in the other groups by calculating standardized mortality odds-ratios (SMOR). The SMOR is derived by calculating the ratio of deaths due to specific causes to the deaths due to a single cause unrelated to exposure. In this study the unrelated cause chosen was all circulatory diseases except rheumatic heart disease.

The results of this study indicated that relative mortality rates due both to cancer of connective or other

soft-tissues (ICD 171) and to "estimated suicides" were significantly higher in Vietnam veterans than in either non-Vietnam veterans or non-veterans. Also, relative mortality rates due to cancer of the kidney, to all external causes, and to recorded suicides were significantly higher in Vietnam veterans than in non-veterans.

There were nine deaths attributed to cancer of the connective or other soft-tissues among Vietnam veterans, compared to 1.02 "expected" deaths due to this cause calculated on the basis of non-Vietnam veterans or 1.90 "expected" deaths calculated on the basis of non-veterans. For these nine cases the average length of time between year of induction and year of death was 11.3 years, and the average length of time between year of discharge and year of death was 8.6 years.

The validity of a record-linkage study such as this one depends on the completeness and the accuracy of the records that are used. Reliance on death certificates for cause of death is subject to error. The authors cited studies indicating that the accuracy of causes of death listed on death certificates is approximately 90%, but it is probably lower for certain specific causes of death, including connective and soft-tissue neoplasms. Of more concern, however, is the specificity of the veterans' bonus records. Any Vietnam veteran who did not live in Massachusetts for at least 6 months before induction, who served for

less than 6 months during the designated period, who was less than honorably discharged, or who failed to apply for the bonus would have been classified as a non-veteran. On the other hand, veterans who may have had little or no potential exposure to Agent Orange and/or combat may have been classified as Vietnam veterans.

Verification of service in Vietnam using service records was not attempted by the authors of this study. The diagnosed cases of STS were not reviewed by pathologists. No information was available on the age of the veterans at the time of service. Therefore, age-specific mortality rates could not be calculated for the veterans. Also, no information was available about potential confounding variables such as smoking behavior, alcohol consumption, dietary habits, socioeconomic status, or non-military occupational exposures.

Because of these limitations, the findings of this study cannot be considered to be definitive. It is of interest to compare the results of this study with the results of a very similar study conducted in New York State at about the same time (see Lawrence et al. 1985 and Lawrence 1984 as discussed in Clement 1985). These authors found no significant differences between Vietnam and non-Vietnam veterans for causes of death including soft-tissue sarcomas. They did find that Vietnam veterans and non-Vietnam veterans had significantly higher mortality due to external causes and suicide than did non-veterans. Consideration of these

studies together point out the difficulties that are inherent in interpreting the body of epidemiologic evidence that is available relevant to the possible association between cancer of the soft-tissues and connective tissues and exposure to phenoxy herbicides and their contaminating impurities.

A retrospective cohort epidemiological study of cancer incidence among employees of phenoxy herbicide manufacturing facilities in Denmark was conducted by Lynge (1985). The stated purpose of this study was to investigate the potential carcinogenic effects of phenoxy herbicide exposure that had been suggested by studies in Sweden. A total of 4,459 persons (3,390 men and 1,069 women) contributing nearly 18,000 person-years at risk were identified from company records as having been employed in phenoxy herbicide manufacture in Denmark between 1947 and 1982. Employment histories were supplemented by data from a public pension plan that was begun in 1964. The vital status of these individuals was determined using the Central Population Register, and cancer incidence in the cohort was ascertained using the Danish Cancer Registry. The incidence of cancer in the cohort was compared to expected incidence in the entire Danish population based on incidence rates for the Danish population for six 5-year age groups and 5-year periods from 1943 to 1980.

The results of this study indicated that the incidence of all neoplasms in the cohort was comparable to that in

the overall Danish population for both sexes. The only statistically significant finding was an excess incidence of soft-tissue sarcoma (5 vs. 1.84 expected, relative risk = 2.72) among men. Cancers of the esophagus and stomach were also elevated in men, but these increased incidences were not statistically significant. When a subcohort, consisting of individuals who had worked in the actual manufacturing or packaging of herbicides, was analyzed, a significant excess of lung cancer was observed among the men (11 vs. 5.33 expected, relative risk = 2.06). The numbers of soft-tissue sarcomas (1), esophageal cancers (1), and stomach cancers (2), although all higher than expected, were too small to permit meaningful statistical analysis.

The data in this study were also analyzed to allow for a 10-year latency period between first employment and the registration of cancer. Again the number of total cancers in the cohort was comparable to that expected on the basis of the total Danish population. Four of the five soft-tissue sarcomas in men were within the group with at least a 10-year latency, and the relative risk for this cancer was 3.67 among men in this group. Among individuals who worked in manufacture or packaging, and with minimum 10-year latency, there was an excess incidence of rectal cancer in males (4 vs 0.98 expected, relative risk = 4.08) and of cancer of the cervix uteri in women (4 vs. 0.85 expected, relative risk = 4.71).

Because of the potential significance of the soft-tissue sarcoma cases in this study, the author reviewed these five cases in detail. As indicated above, one of the cases was registered at the cancer registry within 10 years of entering employment at the herbicide manufacturing facility. Only one of the five had worked in the actual manufacture or packaging of herbicides. Two of the five had been employed for 3 months and one for half a month. For these and other reasons, the author concluded that the evidence for a cause-and-effect relationship between employment in herbicide manufacture and soft-tissue sarcoma was equivocal.

The author also addressed the hypothesis that soft-tissue sarcoma might be related to exposure to TCDD, an unwanted by-product in the manufacture of trichlorophenols. In Denmark most of the phenoxy herbicides that had been manufactured were 2,4-D and 4-chloro-2-methylphenoxy acetic acid (MCPA) and were unlikely to be contaminated with TCDD. Very little 2,4,5-T has been manufactured in Denmark.

Other aspects of this study serve to complicate its interpretation. Cancer incidence was determined using coded data in the Danish Cancer Registry. The coding was based on the 7th revision of the International Classification of Diseases. Previous studies have shown that this approach may result in a significant degree of misclassification of soft-tissue sarcomas. Furthermore, this study was not

controlled for some potentially important confounding variables including smoking behavior and socioeconomic class. One interesting aspect of this study was that there was no "healthy worker effect." In other words, cancer incidences in the occupational cohort were comparable to those in the general population. Usually, occupational cohorts have a lower cancer incidence than the general population.

In sum, this study shows a significantly increased risk of "soft-tissue sarcoma" among men employed in phenoxy herbicide manufacturing plants in Denmark. However, because this incidence was seen in individuals with little or no exposure to the manufacturing process itself and because of other limitations in the design and conduct of the study, it provides little support for a cause-and-effect relationship between exposure to phenoxy herbicides and soft-tissue sarcoma.

The results of a mortality study among chemical workers who may have been exposed to chlorinated dioxins including TCDD were presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds (Cook et al. 1985). A cohort of 2,189 men who had worked in chemical processes where they might have been exposed to chlorinated dioxins at the Dow Chemical plant in Midland, Michigan, was identified. The vital status as of December 31, 1979, was ascertained for all but six men. There was a total of 298 deaths in this group. Standardized mortality ratios

were calculated by cause of death, with United States white males as the comparison population. In addition, the cohort was divided into five exposure categories on the basis of "estimated cumulative exposure to chlorinated dibenzodioxins," and trends in mortality rates with exposure were analyzed. There were no statistically significant findings that would suggest an increased risk for any specific cause of death among the cohort, nor were any trends observed with increasing exposure. The authors emphasized that the study had great power to detect increased incidence of death due to total malignant neoplasms and cardiovascular disease. The available report of this study does not contain sufficient detail regarding selection of the cohort, ascertainment of cause of death, ascertainment of exposure, and definition of exposure categories to allow independent evaluation of the author's conclusions.

A series of case-control studies of soft-tissue sarcoma conducted in New Zealand (Smith et al. 1982, 1983, 1984 as reviewed in Clement 1984 and 1985) showed no significant association between soft-tissue sarcoma and exposure to phenoxy herbicides during application. In 1985, these workers reported on new cancer registry-based studies designed to investigate possible associations between agricultural occupations and malignant lymphoma and multiple myeloma. Potential exposure to phenoxy herbicides was also examined in the second of these studies.

In the first study, Pearce et al. (1985a) identified all male patients registered between 1977-1981 in the New Zealand Cancer Registry with cancers in ICD codes 200-203 (non-Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma) and who were at least 20 years old at the time of registration. Controls were selected from males registered at age 20 or older for all other types of cancer except soft-tissue sarcoma. Controls were matched to cases by age and year of registry. Information regarding occupation and socioeconomic status for both cases and controls was derived from coded data in the Cancer Registry regarding current or most recent occupation. Age-standardized mortality and incidence rates for each of the three types of cancer were calculated from data for the years 1955-1979 compiled by the New Zealand National Health Statistics Center. A total of 734 cases and 2,936 controls were identified for this study.

Cases were significantly more likely to be employed in agriculture and forestry than were controls (odds ratio = 1.25). The excess in this category was accounted for almost entirely by individuals who were less than 65 years old at the time of registration. The association was particularly strong for multiple myeloma and non-Hodgkin's lymphoma. When farming occupations were broken down into more specific categories, e.g., working in orchards or with livestock, no individual category stood out.

The authors indicated that the results of this study were limited in their implications. The occupational data were crude, and their accuracy was questionable. Since current or most recent occupation served as the basis for occupational classification, men who had worked in agricultural occupations early in life but switched to nonagricultural occupations would be classified in the nonagricultural classification and vice versa. The authors concluded that more specific occupational information might be expected to increase the odds ratio. They also indicated that the results of these studies paralleled similar results of studies in the United States and the United Kingdom.

In order to study the role of herbicides and other occupational factors in the etiology of non-Hodgkin's lymphomas, Pearce et al. (1985b) conducted a case-control study using 83 cases of histologically confirmed non-Hodgkin's lymphoma in New Zealand males. These individuals were between 20 and 70 years of age and were selected from all cases registered in the New Zealand Cancer Registry between 1977 and 1981. The authors selected 168 "other cancer" controls who were matched to cases by age and year of registry. Another 228 general controls (not age-matched) were selected randomly from the 1982 New Zealand electoral rolls. All the cases and "other cancer" controls or their next of kin were interviewed by an individual who was not aware of the form of cancer that the subject of the interview had. The interviews

consisted of specific questions regarding employment history and chemical exposures.

In this study, cases were slightly more likely to have been farmers and to have been exposed to agricultural sprays, including herbicides, than were controls but these differences were not statistically significant. There was also no trend toward increasing risk of non-Hodgkin's lymphoma with increased duration of exposure or with latency since first exposure. The authors did find a statistically significant excess of individuals among the cases who reported a history of employment in slaughter houses (especially tannery department workers) or who worked at installing fences. Both of these employment categories involved potential exposures to chlorinated phenols. However, when slaughter house employees and fence workers were categorized on the basis of probable exposure to chlorinated phenols, there was no significant difference between cases and controls in terms of exposure.

Taken together, these studies fail to support the hypothesis of an association between exposure to phenoxy herbicides and an increased risk of non-Hodgkin's lymphoma. However, limitations in ascertainment of exposure limit the ability of these studies to establish definitely the absence of such an association.

Balarajan and Acheson (1984) described a case-control study of soft-tissue sarcoma in men in England and Wales

designed to reveal whether farmers and related workers had a greater risk for this form of cancer than did men employed in other occupations. It was assumed that farm workers would have experienced greater exposure to phenoxy herbicides. Cases of soft-tissue sarcoma were identified from the National Cancer Registry for England and Wales. The registry also contains coded information indicating the occupation of the cases at the time of registration. Occupational information was available for 70% of the soft-tissue sarcoma cases in the registry and 60% of the other malignant neoplasms.

A total of 1961 cases of malignant neoplasms of connective tissue and other soft tissue (ICD 171, 8th revision) in men 45 years and over for whom occupational information was available were selected as the cases in this study. These cases were registered between 1968 and 1976. Each case was matched with a control by age and region of residence. The controls were selected from men who were registered with any cancer other than that encompassed by ICD 171 and for whom occupational information was available. The specific occupational units selected by the authors as having potential phenoxy herbicide exposure were farmers, farm managers, and market gardeners; agricultural workers; agricultural machinery drivers; gardeners and groundsmen; and foresters and farmers. Relative risks were calculated for each of the five defined occupations and for the group as a whole by matched pair analyses.

The relative risk of soft-tissue sarcoma among farmers and related workers as a whole was 1.15, which was not statistically significant. However, the relative risk of soft-tissue sarcoma was significantly increased (1.7) in the category--farmers, farm managers, and market gardeners. The biological significance of this finding is unclear as there is no reason to expect that farmers, farm managers, or market gardeners are more likely to be exposed to a carcinogen than are men employed in any of the other occupational classifications included in this study. The authors further analyzed the data by eliminating cases and controls who were over the age of 75 when registered on the assumption that these individuals were less likely to have been exposed to phenoxy herbicides. This analysis resulted in a nonsignificant relative risk of 1.44 for soft-tissue sarcoma among farmers, farm managers, or market gardeners.

This study is limited in its ability to test a hypothesis regarding the association between soft-tissue sarcoma and exposure to phenoxy herbicides. The authors had no direct information regarding herbicide exposure of either cases or controls. The presumption of exposure was based on occupation at the time of cancer registration. Individuals with potential herbicide exposure as agricultural workers who left agricultural occupations before diagnosis of cancer would have been misclassified as nonexposed. Additional potential sources of confounding or bias are the high percent-

age of cases in the registry for which no occupational information is available and the lack of histological verification of tumor diagnoses.

Schumacher (1985) described the results of a case-control epidemiologic study of non-Hodgkin's lymphoma (NHL) in Utah. Using the Utah State Cancer Registry, the author identified 228 white males with a diagnosis of NHL who died during the years 1967-1982 and for whom death certificates containing occupational information could be obtained. Only individuals who were between 35 and 75 years of age at the time of diagnosis were included in the study. A control group was selected from the same cancer registry; it consisted of 261 deceased white males who were diagnosed as having colon cancer. This group was selected so that the number of individuals in each 10-year age group and the years of diagnosis of cancer were similar to the cases. For the purpose of occupational classification, individuals whose death certificate listed their "usual occupation" as farming, dairy farming, ranching, sheep herding, poultry farming, or "educational agricultural occupations" were considered to be farmers. All other occupations were classified as nonfarming occupations.

When all cases were compared to the controls without matching for age at diagnosis or for year of diagnosis, the odds-ratio for NHL in farmers vs. non-farmers was 1.5. When matched by both age at diagnosis and year of diagnosis

the odds-ratio was 1.3. Neither of these was statistically significant. However, when the data were stratified by year of diagnosis, the author found statistically significant odds-ratios for NHL of 6.6 for those whose diagnosis were made from 1952-1966 and 3.1 for those whose diagnosis were made from 1966-1971. Also, when stratified by age at the time of diagnosis, a statistically significant increase in risk was observed for those who were 45 to 65 years old at the time of diagnosis. The excess NHL was accounted for by lymphocytic lymphoma as opposed to histiocytic lymphoma.

This study is discussed here only because of earlier reports by Hardell et al. (1981) of an increased risk of malignant lymphoma among individuals exposed to phenoxy herbicides and chlorophenols and by Burmeister et al. (1983) of increased rates of NHL in farmers in Iowa counties where there was high herbicide usage. No attempt was made in the present study to ascertain herbicide exposure among either the cases or the controls. Therefore, this study cannot be considered to be direct evidence for an association between herbicide exposure and non-Hodgkin's lymphoma.

In a brief report, Hoar et al. (1985) described a case-control epidemiological study of colon cancer in Kansas. Fifty-seven (57) cases of pathologically confirmed colon cancer were sampled from among all colon cancer cases diagnosed in Kansas during 1976-1982. For comparison purposes, a control group of 948 individuals was selected at random

from Medicare files and Kansas mortality files. Occupational information and exposure to herbicides was determined by interview.

There was an increased risk of colon cancer associated with employment on a farm (odds-ratio = 1.6) but the increase was not statistically significant. The risks for colon cancer were similar in farmers who used herbicides and farmers who did not use herbicides, and there was no increase in risk with increasing years of herbicide use. The odds-ratio for colon cancer was slightly higher in farmers who used phenoxy herbicides but this increase was not statistically significant. The authors concluded that their findings were consistent with those of Hardell (1981, see Clement 1984) showing no association between colon cancer and exposure to phenoxy herbicides.

The brevity of this report precludes meaningful critical evaluation of the study. No information is given on how the cases were selected. The methods used in selecting the cases and controls and how they were matched are not specified. There is no information on how the interviews were conducted and what questions were asked. Participation rates and possible sources of confounding are not discussed. In addition to these limitations in reporting, the study lacked the power to detect a small but biologically important increased risk of colon cancer.

Two abstracts of symposia presentations described studies of levels of polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF) in adipose tissue samples taken from patients with soft-tissue sarcoma or malignant lymphoma. The patients were patients identified in earlier case-control studies conducted by Hardell and coworkers in Sweden that indicated that individuals with soft-tissue sarcoma or malignant lymphoma were significantly more likely to have been exposed to phenoxy herbicides and/or chlorophenols. Because PCDD, and perhaps PCDF, are contaminants of phenoxy herbicides and chlorophenols it was thought that the presence of elevated levels of these compounds in adipose tissues might serve as a confirmatory index of recalled exposure to phenoxy herbicides and/or chlorophenols.

In one study, adipose tissues from 13 patients with soft-tissue sarcoma and a reported history of exposure to phenoxy herbicides or chlorophenols were analyzed for PCDD and PCDF and compared to adipose tissue levels determined for 18 control subjects who did not report a history of exposure (Nygren et al. 1985). There were no significant differences between the cancer group and controls in levels or patterns of isomer distribution. The authors reported that the levels of 2,3,4,7,8-pentachlorodibenzofuran were higher in exposed than in non-exposed individuals. The authors also reported that analyses of adipose tissues

from two healthy subjects who had been heavily exposed to either PCDD or PCDF in the past showed significantly elevated levels of PCDD and PCDF suggesting that the approach is valid for monitoring past exposure to these compounds.

The second abstract describes a study in which tissue samples from seven cancer patients (soft-tissue sarcoma or malignant lymphoma) with a history of exposure to phenoxy herbicides or chlorophenols were analyzed and compared to the results of similar analyses of tissues from 18 "unexposed" controls (Hardell et al. 1985). The authors reported that PCDDs and PCDFs were present in the adipose tissues of all the patients and controls, but that the levels of some unspecified isomers were significantly higher in adipose tissues from the "exposed" patients.

Because these reports are only abstracts and lack detail regarding experimental methods it is difficult to ascertain how these studies differ. The authors are the same and the number of "unexposed" controls in each study is the same. What is unclear is how the "exposed" patients were selected and why the numbers differ between the two studies. Based on the limited information available it appears that both studies failed to show striking and characteristic differences between "exposed" and "unexposed" subjects. However, Hardell's own analysis of the epidemiology studies that showed an association between soft-tissue sarcomas or malignant lymphomas, and exposure to phenoxy

herbicides or chlorophenols suggested that the degree of contamination of the formulations with PCDD and PCDF was not a determining factor in the association. Therefore, these studies shed little light on the bases of the apparent association between these cancers and phenoxy herbicide or chlorophenol exposure as seen in the case-control studies conducted in Sweden.

2. Studies in Animals

Newell et al. (1984) investigated the relationship of the incidence of small-intestinal adenocarcinoma (SIA) in sheep to the use of various herbicides in New Zealand. This study was undertaken because New Zealand has the highest rates of SIA in sheep and of colon cancer in humans of any country in the world, and there is relatively heavy use of herbicides in New Zealand agriculture. The abdominal contents of 20,678 female sheep between 5.5 and 7.5 years of age were examined grossly at slaughter in all 15 of New Zealand's export slaughter houses between 1980 and 1982. SIA incidence (cases per thousand animals) was broken down by breed of sheep, topography and environment of the farms on which they were raised, and exposure to herbicides. Use of herbicides was determined by questionnaires provided to the farmers who brought the sheep to slaughter. The questionnaires asked about the pattern of herbicide use and the specific chemicals used over the lifetime of each mob of sheep. On the basis of answers to these questions

sheep were classified as "unexposed," "sprayed," and "recently sprayed" in reference to the interval between herbicide application and when sheep were allowed to graze in the sprayed area.

Analysis of tumor incidence rates indicated that there was a significantly higher rate of SIA in "recently sprayed" sheep compared to "sprayed" sheep. Also sheep exposed to phenoxy herbicides, picolinic acid herbicides (picloram), and combined phenoxy-picolinic acid herbicides had significantly higher incidences of SIA, and this increase was related to the frequency of herbicide exposure. In these comparisons, there was no subdivision of the cohort according to breed or environment. Breakdown of exposures between herbicides known to be contaminated with TCDD and herbicides not so contaminated showed no differences.

Several shortcomings complicate the interpretation of the results of this study. First, like all retrospective studies, the accuracy of recall regarding herbicide use in the last 7 years is questionable. If SIA in sheep has a relatively long latency, as do most cancers, then exposures early in life are probably more important in its etiology than more recent exposures. The relative rarity of SIA in sheep resulted in there being only 125 cases of SIA in the total population examined. When these are broken down into subcategories based on breed, environment, and herbicide exposure many of the categories contain fewer

than 10 tumors. The biological significance of statistical comparisons based on these small numbers is not clear. Finally, the "independent variables" in this study may not be totally independent. Certain types of herbicides may be used more frequently on mountain pastures than pastures in the plain, and certain breeds of sheep may be more likely to be raised in certain environments. Therefore, herbicide use may parallel genetic or other environmental factors.

The relevance of the findings of this study for human health is unclear. The authors state that "in several respects the small intestine in sheep resembles the colon in man" and that the rate of human colon cancer in New Zealand is relatively high. On the other hand, a case-control study conducted by Hardell (1981, see Clement 1984) in Sweden indicated no association between phenoxy herbicide exposure and colon cancer in humans.

3. <u>In Vitro Studies</u>

Abernethy et al. (1985) investigated the activity of TCDD in the C3H/10T1/2 mouse embryo fibroblast system for detection of cell transformation, a predictor of carcinogenicity. The system can distinguish between substances that can induce morphological transformations by themselves or that act as inducers or promoters. Demonstrating the sensitivity of the system with appropriate positive controls, Abernethy et al. found that 24-hour treatment with 10 concentrations of TCDD between 0.06 and 5,000 nM did not induce

an excess of transformed foci, either alone or when followed by 6 weeks of promoting exposure to 0.25 μg/ml 12-O-tetradecanoyl phorbol-13-acetate (TPA). When TCDD was tested as a potential promoter following initial treatment with the direct-acting mutagen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) at a concentration of 0.5 μg/ml, TCDD concentrations of 0.04-1.2 pM did not induce an increase in the incidence of transformed foci. For six concentrations of TCDD between 4 and 4,000 pM, however, the frequencies of transformed foci were very significantly increased and showed a monotonic increase (17-37%) with the exception of the next highest concentration, 1,200 pM, which only produced a frequency of 18%. The promoting potency of TCDD demonstrated in this set of experiments is 100-10,000 fold higher than that of the classical promoter TPA. The lack of initiating activity in this study speaks against TCDD's having direct genotoxic activity that is manifested as cell transformation in this assay. However, the finding that TCDD is a potent promoter in this assay suggests that TCDD may act as a promoter of carcinogenesis through mechanisms that act at the cellular level of organization.

Additional information regarding the potential mechanism of action of TCDD at the cellular level has become available from studies of the effects of TCDD on epithelial cells in culture. Puhvel et al. (1985a) showed that TCDD caused an increase in the amount of keratin, an increase in the

number of cornified cell envelopes, and an increase in epidermal transglutaminase activity (a marker of terminal differentiation) in primary cultures of epidermal keratinocytes from neonatal mice. The response was greater in cells derived from hairless mice. These results are consistant with those of Knutson and Poland (1984) who studied the effects of TCDD on XB cells, a cell line derived from mouse teratoma. TCDD caused increased thymidine incorporation and keratinization in these cells. Greenlee et al. (1985a) studied the effects of TCDD on normal human epidermal cells cultured on a feeder layer of mouse 3T3 fibroblasts. In this test system, the epidermal cells form a stratified culture with a basal layer and several layers of cells in various stages of terminal differentiation. TCDD caused a concentration-dependent decrease in the number of undifferentiated basal cells and an increase in differentiating and terminally differentiated cells. Rice and Cline (1984) demonstrated that TCDD caused a disordered stratification of cells when they treated fully confluent cultures of a human epidermal squamous carcinoma cell line. TCDD also caused an increase in keratinization and spontaneous envelope formation in the presence of hydrocortisone.

Together these studies indicate that TCDD affects cell proliferation and differentiation in cell lines derived from murine and human cancers as well as from normal epithelial cells. These findings are of primary relevance to the

skin lesions, i.e., chloracne and hyperkeratinization, caused by TCDD in humans. However, these findings may also be relevant to the issue of the mechanism by which TCDD may cause an increase in cancer in experimental animals. One theory of cancer promotion is that the promoting agent stimulates proliferation and commitment of cells to differentiation and thus increases the probability of malignant transformation of initiated cells. Within this theoretical framework, the in vitro studies described here can be considered as supporting the role of TCDD as a promoter of a carcinogenic response.

Summary

Two human epidemiology studies published during 1985 reported a statistically significant excess risk of soft-tissue sarcoma (STS). One study of men in Massachusetts suggested an increased risk of STS among Vietnam veterans and another study suggested a possible increased risk of STS among workers in phenoxy herbicide manufacturing facilities. However, the former study was seriously flawed and, in the latter study, closer analysis of STS cases revealed relatively little potential exposure to phenoxy herbicides. Likewise, several studies which showed an increased risk of malignant lymphoma in agricultural workers failed to associate this risk with phenoxy herbicides or their contaminating dioxins. The human studies published this year, along

with studies from previous years, tend to suggest that increased risks of STS and malignant lymphoma may be associated with agricultural occupations, but more rigorous studies have failed to connect these possible increased risks specifically to phenoxy herbicide or dioxin exposure. The issue remains unresolved because of the practical difficulty of identifying and quantifying exposure and because of the inability to form a sufficiently large cohort of individuals who were first exposed to these compounds more than 20 years ago.

Studies of the action of TCDD at the cellular level indicate that this and related compounds interact with the genetic material of the cell to initiate numerous complex responses. In epithelial cells one of these responses is proliferation and increased commitment to terminal differentiation. Since this response is similar to that caused by classical carcinogenic "promoters" it is possible that some of the carcinogenic response seen in experimental animals treated with TCDD is due to promotion of initiated cells. A potential human health consequence of this hypothesis is that TCDD exposure might be associated with increased incidence of cancer at numerous sites through promotion of cancer initiated by other agents.

REFERENCES

Abernethy, D., Greenlee, W., Huband, J., and Boreiko, C. 1985. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) promotes the transformation of C3H/10T1/2 cells. Carcinogenesis 6:651-653

Balarajan, R., and Acheson, E. 1984. Soft-tissue sarcomas in agriculture and forestry workers. J. Epidemiol. Community Health 38:113-116

Burmeister, L.F., Everett, G.D., and Van Lier, S.F. 1983. Selected cancer mortality and farm practices in Iowa. Am. J. Epidemiol. 118:72-77

Cook, R.R., Bond, G.G., Olson, R.A., and Ott, M.G. 1985. Mortality experience of chemical workers exposed to chlorinated dioxins. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

Greenlee, W.F., Dold, K.M., and Osborne, R. 1985a. Actions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on human epidermal keratinocytes in culture. In Vitro Cell. & Develop. Biol. 21:509-512

Hardell, L., Eriksson, M., Lenner, P., and Lundgren, E. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. Br. J. Cancer 43:169-176

Hardell, L., Domellof, L., Nygren, M., Hansson, M., and Rappe, C. 1985. Levels of polychlorinated dibenzodioxins and dibenzofurans in adipose tissue of patients with soft-tissue sarcoma or malignant lymphoma exposed to phenoxy acids and of unexposed controls. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

Hoar, S.K., Blair, A., Holmes, F.F., Boysen, C., and Robel, R.J. 1985. Herbicides and colon cancer. Lancet 1:1277-1278

Knutson, J.C., and Poland, A. 1984. XB cells: An in vitro model for the differentiation and proliferation response to 2,3,7,8-TCDD. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 381-389

Kogan, M.D. and Clapp, R.W. 1985. Mortality among Vietnam veterans in Massachusetts, 1972-1983. Massachusetts Office of Commissioner of Veterans Services, Agent Orange Program, Massachusetts (January 18, 1985) 29 pages

Lawrence, C.E. 1984. New York State proportional mortality study. Oral presentation to the Veterans Administration Advisory Committee on Health-Related Effects of Herbicides. December 11, 1984, Washington, D.C.

Lawrence, C.E., Reilly, A.A., Quickenton, P., Greenwald, P., Page, W.F., and Kuntz, A.J. 1985. Mortality patterns of New York State Vietnam veterans. Am. J. Public Health 75:277-279

Lynge, E. 1985. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br. J. Cancer 52:259-270

Newell, K.W., Ross, A.D., and Renner, R.M. 1984. Phenoxy and picolinic acid herbicides and small-intestinal adenocarcinoma in sheep. Lancet 1:1301-1305

Nygren, M., Hansson, M., Rappe, C., Dommellof, L., and Hardell, L. 1985. Analysis of polychlorinated dibenzo-p-dioxins and dibenzofurans in adipose tissue from soft-tissue sarcoma patients and controls. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

Pearce, N.E., Smith, A.H., and Fisher, D.O. 1985a. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. Am. J. Epidemiol. 121:225-237

Pearce, N.E., Smith, A.H., Howard, J.K. Sheppard, R.A., Giles, H.J., and Teague, C.A. 1985b. Case-control study of non-Hodgkin's lymphoma, and exposure to phenoxy herbicides, chlorophenols, fencing work and meat works employment. Br. J. Ind. Med. 29 pages (in press)

Puhvel, S.M., Reisner, R.M., and Ertl, D.C. 1985a. Effect of TCDD on murine epidermal keratinocytes in vitro. Chemosphere 14:971-973

Rice, R.H., and Cline, P.R. 1984. Response of malignant epidermal keratinocytes to 2,3,7,8-TCDD. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 373-380

Schumacher, M.C. 1985. Farming occupations and mortality from non-Hodgkin's lymphoma in Utah. J. Occup. Med. 27:580-584

Shepard, B.M., Kang, H.K., Enzinger, F., and Weatherbee, L. 1985. Soft-tissue sarcoma and military service in Vietnam: A case comparison analysis of hospitalized veterans. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

Smith, A.H., Fisher, D.O., Pearce, N., and Teague, C.A. 1982. Do agricultural chemicals cause soft-tissue sarcoma? Initial findings of a case-control study in New Zealand. Community Health Studies 6:114-119

Smith, A.H., Fisher, D.O., Giles, H.J., and Pearce, N. 1983. The New Zealand soft-tissue sarcoma case-control study: Interview findings concerning phenoxyacetic acid exposure. Chemosphere 12:565-571

Smith, A.H., Pearce, N.E., Fisher, D.O., Giles, H.J., Teague, C.A., and Howard, J.K. 1984. Soft-tissue sarcoma and exposure to phenoxyherbicides and chlorophenols in New Zealand. JNCI 73:1111-1117

B. Genetic Toxicity

Kaye et al. (1985) studied cytogenetic end points in 10 men who reported that they had been exposed to Agent Orange during their service in Vietnam 10 to 16 years earlier. Their karyotypes were analyzed, and the frequencies of chromosome breaks and sister chromatid exchanges (SCEs) in their peripheral lymphocytes were determined. These subjects were self-referred; two because they were concerned about the possibility of reproductive problems, but the remaining eight because their spouses had experienced at least one pregnancy that ended in miscarriage or a congenitally defective child. Nine of their spouses and four of their children (not stated whether normal or not) were used as control groups. When the statistical tests were performed, the individuals were not matched by family; such matching might have provided some rationale for this otherwise inappropriate selection of controls.

All of the men were reported to have normal karyotypes and frequencies of SCEs (average per chromosome $\pm$ SEM, 0.187 ± 0.013) that were essentially equal to those of the wives (0.200 ± 0.017) and children (0.188 ± 0.011). Their frequencies of chromosome breaks (average per cell $\pm$ SD, 0.120 ± 0.057) were found to be significantly higher than those of the wives (0.053 ± 0.037) or children (0.035 ± 0.034). However, these comparisons are not strictly valid (matched for sex, age, etc.) for testing the effect of exposure

to Agent Orange on the frequency of chromosome breaks. The fact that 8 of the 10 men had frequencies of chromosome breaks (0.08-0.20 breaks/cell) that were outside the range usually observed in this laboratory (0.00-0.06 breaks/cell) is more suggestive of a real elevation in these men. Bias introduced by the fashion in which the sample was selected, however, means that this elevation cannot be attributed to exposure to Agent Orange with any certainty, but might for instance be a characteristic of all fathers of problem pregnancies. As in other case studies of health effects in veterans reporting past exposure to Agent Orange, the sample was self-selected, and the fact and intensity of exposure to Agent Orange are unverifiable.

No new studies of the genotoxicity of 2,4,5-T in whole animal or in vitro systems have been published in the period covered by this survey of the literature.

Turkula and Jalal (1985) reported a study of the effect of 2,4-D in inducing SCEs in human cells. Aliquots of a 24-hour culture of human peripheral lymphocytes (source unspecified) were treated with 0, 50, 100, or 250 μg/ml 2,4-D in 0.1 ml DMSO concurrently with 10 μg/ml 5-bromodeoxyuridine. After 72 hours the cells were harvested, stained with Gurr-improved Giemsa, and 50 well-spread cells per treatment group were scored for SCEs. Analysis of variance followed by Duncan's t-test for multiple comparisons was performed on the data. The average number of SCEs per

cell in the low-dose group (9.8) was reported to be significantly ($p<0.05$) greater than that of the control group (7.02), while the increases in the 100- and 250-μg/ml groups (8.32 and 8.36) were not statistically significant. The degree of cytotoxicity produced by the tested concentrations of 2,4-D was not reported. A single sample of blood from the highly heterogeneous human population is insufficient to characterize the response of human cells in vitro. Although these results are similar to those reported previously by Korte and Jalal (1982, see Clement 1984), a satisfactory explanation for the deviation from a dose-response relationship has not been given. The magnitude of the increase at 50 μg/ml 2,4-D, although reported to be statistically significant, was only modest.

Meyne et al. (1985) reported a set of thorough experiments on the potential of TCDD to induce cytogenetic effects in "responsive" and "non-responsive" mice. Groups of 7- to 9-week-old male mice of two strains (C57Bl/6J with high-affinity TCDD receptors, and DBA/2J with low-affinity TCDD receptors) were given single intraperitoneal doses of 0, 50, 100, or 150 μg/kg TCDD in corn oil. At various times after TCDD treatment, bone marrow was collected from the femurs and prepared for microscopic scoring for three end points: chromosomal aberrations at 8, 12, and 24 hours, with 100 cells per animal scored in 3-25 mice per strain-time-dose group; micronuclei at 24 and 48 hours, with 500

polychromatic erythrocytes scored in 3-10 mice per group; and SCEs at 16 hours, with 25 cells scored in 6 mice per group. One month after treatment, tissue sections from the livers of C57Bl/6J mice from all four treatment groups and control and high-dose DBA/2J mice were subjected to histopathologic examination.

For none of the three cytogenetic end points was there any suggestion of a positive response to the acute dosage of TCDD in either strain after any treatment interval at any dose level. In contrast, the positive control substance, cyclophosphamide, produced distinct positive responses for each strain-end point-time interval combination. The histopathologic examination of the hepatic tissue, however, revealed lesions (primarily necrotic foci with acute inflammatory response) increasing in prevalence and severity with dose in the C57Bl/6J mice and to a less marked degree in the high-dose DBA/2J mice. Although these findings demonstrate that acute hepatotoxic doses of TCDD do not induce cytogenetic damage in the bone marrow of mice, they do not exclude the possibility that TCDD could cause cytogenetic damage in other tissues, e.g., the liver itself. As Meyne et al. pointed out, to the extent that results may be extrapolated from mouse to man, these results should provide a cautionary note that monitoring chromosomal damage in peripheral lymphocytes of humans potentially exposed to TCDD may not be sufficient to screen for such damage in other tissues.

Toth et al. (1984) tested 2,4,5-trichlorophenoxyethanol (TCPE) contaminated with 0.1 ppm TCDD in the Ames test and in an SCE assay in Chinese hamster cells (clone 451). TCPE was negative in the Ames assay, but produced a dose-related increase in SCEs, with a three-fold increase over background at a concentration of 100 µg/ml. (The SCE response was substantially reduced by addition of S-9 mixture from an Aroclor 1254-pretreated male Swiss mouse.) A single concentration of TCDD alone, 0.1 ng/ml (corresponding to the amount of TCDD contaminating the 100 µg/ml treatment of TCPE), was tested in the SCE assay and produced a frequency of SCEs (5.78±2.55) equivalent to that seen in the controls (5.93±2.05). This isolated finding implies that TCDD (alone) was not responsible for the elevated frequency of SCEs seen in the Chinese hamster cells treated with the TCDD-contaminated TCPE.

REFERENCES

Kaye, C.I., Rao, S., Simpson, S.J., Rosenthal, F.S., and Cohen, M.M. 1985. Evaluation of chromosomal damage in males exposed to Agent Orange and their families. J. Craniofacial Genetics & Developmental Biol. Suppl. 1:259-265

Korte, C., and Jalal, S.M. 1982. 2,4-D induced clastogenicity and elevated rates of sister chromatid exchanges in cultured human lymphocytes. J. Hered. 73:224-226

Meyne, J., Allison, D.C., Bose, K., Jordan, S.W., Ridolpho, P.F., and Smith, J. 1985. Hepatotoxic doses of dioxin do not damage mouse bone marrow chromosomes. Mutat. Res. 157:63-69

Toth, K., Olah, E., Somfai-Relle, S., and Sugar, J. 1984. Effect of herbicide 2,4,5-trichlorophenoxyethanol (TCPE) containing dioxin on mutation and induction of sister chromatid exchanges. Carcinogenesis 5:1725-1728

Turkula, T.E., and Jalal, S.M. 1985. Increased rates of sister chromatid exchanges induced by the herbicide 2,4-D. J. Hered. 76:213-214

C. Teratogenicity and Reproductive Toxicity

1. Studies of Exposed Human Populations

No new studies on the effects of Agent Orange or its individual components on human reproduction have become available in the period under review. Constable and Hatch (1985) did, however, author a review of nine unpublished studies on the reproductive effects of herbicide spraying on Vietnamese populations. These studies have been alluded to previously (Hatch 1984, Volume VI of this review), but the fact that detailed versions of the studies have not been made available makes critical review impossible. Furthermore, the conditions in wartime and post-war Vietnam were such that baseline data for comparison and reliable exposure information have been virtually impossible to reconstruct, as discussed with respect to Kunstadter (1982, Volume II). Constable and Hatch noted these problems, as well as possible difficulties in interpretation due to selection biases and confounding variables, but they found that studies of North Vietnamese veterans versus unexposed North Vietnamese men suggested that an increase in congenital defects, especially anencephaly and orofacial defects, was associated with potential herbicide exposure. Constable and Hatch also concluded that in spite of many deficiencies, several studies of South Vietnamese populations suggested an association of hydatidiform mole (molar pregnancy) with herbicide exposure.

2. Studies in Animals

Pratt and coworkers (Pratt et al. 1984, Pratt 1985) have investigated the mechanism by which TCDD induces cleft palate in the mouse. Treatment of C57Bl/6J mice, a strain sensitive to TCDD toxicity, with a single subcutaneous injection of 100 μg/kg TCDD on days 2, 5, or 6 of gestation produced fetal resorption (100%, 95%, or 60%, respectively). With a single treatment between days 8 and 13, fetal resorption was minimal and cleft palates were observed, with maximum incidence (greater than 95%) when treatment was on day 10. The distribution of TCDD in mothers and fetuses of this strain was compared to its distribution in the insensitive AKR/J strain by injecting a single dose of 100 μg/kg TCDD including 50 μCi of ^{3}H-labeled TCDD on day 11 of gestation. After 6 hours, the amount of TCDD bound to tissue (maternal liver, placenta, and embryo) was significantly higher in the C57Bl/6J mice than in the AKR/J mice, whereas levels of TCDD in maternal serum were lower in the C56Bl/6J mice. Autoradiography 48 hours after this treatment showed that TCDD in the embryo was concentrated primarily in the palatal epithelium, brain, limb buds, and liver. Sucrose density gradient profiles of secondary palatal shelves isolated from 13-day embryos of both strains and incubated with ^{3}H-labeled TCDD showed that there was specific binding of TCDD to receptors in the C57Bl/6J tissue, but not in the AKR/J tissue. The secondary palate was

found to be the embryonic tissue with the highest level of TCDD receptors. (Relative levels in the kidney were not reported.) Morphological examination of treated and untreated C57Bl/6J fetuses revealed that the palatal tissues grew, elevated, and made contact in the same manner in both, but did not fuse on day 14 in the treated fetuses. Fusion apparently failed to occur because of a lack of degeneration of the epithelium, i.e., programmed cell death was responsible for fusion in the normal development of the palate and TCDD disrupted this developmental pattern. The finding that TCDD binds specifically to the palatal tissue of fetuses from a susceptible strain suggests that cleft palate is induced by a direct mechanism of action of TCDD within the affected tissue; this mechanism is mediated by the receptor which is likely to be the product of the Ah locus.

Weber et al. (1985) conducted a series of experiments on the relative teratogenic potencies of TCDD and TCDF, and interactions between these compounds, in C57Bl/6N mice. This strain carries the Ah gene for the cytosolic receptor that binds with high affinity to these substances and the strain is susceptible to the induction of teratogenic effects by them. Groups of 7 to 11 pregnant females were treated by gavage on day 10 of gestation with TCDD (12, 17, or 22 μg/kg), TCDF (300, 600, or 900 μg/kg), a combination of the two (12 μg/kg TCDD, plus 300 or 600 μg/kg TCDF),

or the corn oil vehicle. The females were sacrificed on day 18, and their fetuses were examined specifically for cleft palate and kidney damage (hydronephrosis). Aside from the teratologic end point in question and increases in the maternal liver-to-body-weight ratio, these doses of both substances alone or in combination did not produce maternal or fetal toxicity.

None of the control fetuses had cleft palate. For both TCDD and TCDF, there was a clear dose-response relationship in the proportions of fetuses per litter with cleft palate (9%, 44%, and 78% for the increasing TCDD doses, and 8%, 56%, and 89% for the TCDF doses). A probit model with the same slope but separate intercept terms fitted these data well, suggesting that these two substances cause cleft palate by the same mechanism, although TCDD is approximately 30 times more potent than TCDF. The combination of 300 or 600 μg/kg TCDF with the lowest dose of TCDD resulted in proportions of affected fetuses that were more than the sum of the effects of the two chemicals individually and, in fact, appeared to be multiplicative (79% and 100%, respectively). This relative additivity and possible synergism supports the idea of a similar mechanism of action.

The fetal kidney was more sensitive than the palate to the teratogenic effects of these substances. All of the treated groups showed a significant increase in renal damage, but the degree was not dose-related. This suggests

that for the doses used the effect may have reached saturation. For this reason, the reported data do not permit testing of the additivity hypothesis on a second teratogenic end point, although they are consistent with this hypothesis.

In a parallel experiment, members of the same research group tested the teratogenic potency of two polychlorinated biphenyl (PCB) isomers in C57Bl/6N mice alone and in combination with TCDD (Birnbaum et al. 1985). One PCB isomer (2,3,3',4,4',5-hexachlorobiphenyl, abbreviated as 345-HCB) is similar to TCDD in the type of toxicity it produces, binding to the Ah receptor and inducing cytochrome P-448; it also induces cytochrome P-450. The other isomer (2,2', 4,4',5,5'-hexachlorobiphenyl, abbreviated as 245-HCB) does not bind strongly to the Ah receptor or cause TCDD-like toxicity and induces only P-450.

The first set of pregnant females (18 to 21 per group) were treated by gavage on day 11 of gestation with 12 μg/kg TCDD alone, 40 or 80 mg/kg 345-HCB alone, or a combination of 12 μg/kg TCDD and 40 or 80 mg/kg of 345-HCB. Another set of animals (10 to 13 per group) were treated daily by gavage on days 10, 11, 12, and 13 of gestation with 3 μg/kg TCDD alone, 10 or 20 mg/kg 345-HCB alone, or 3 μg/kg TCDD plus 10 or 20 mg/kg of 345-HCB. A final set of animals (10 to 14 per group) was treated daily on days 10 through 13 with 3 μg/kg TCDD alone, 25 or 50 mg/kg 245-HCB alone, or 3 μg/kg TCDD plus 25 or 50 mg/kg 245-HCB. Untreated

controls were run, but were not concurrent for the last two experiments. All animals were sacrificed on day 18, and the fetuses were examined for cleft palate and renal damage.

Increased maternal liver-to-body-weight ratios were seen in all treated groups. The combined treatments in all three experiments produced liver-to-body-weight ratios higher than the treatments with the individual substances, suggesting an additive mechanism for the induction of this effect. An increase in placental weight was associated with TCDD treatment in all three experiments. Treatment with 245-HCB produced a reduction in fetal weight. Otherwise, the doses used did not produce maternal or fetal toxicity, but did generate the teratogenic end points of interest, cleft palate and renal damage.

Neither of the HCBs alone produced any cleft palates. The proportions of fetuses with cleft palate seen per litter treated with TCDD and 25 or 50 mg/kg 245-HCB (8% and 5%, respectively) were similar to that seen with TCDD alone (8%). 345-HCB, however, when given in combination with TCDD in single or repeated treatment produced a marked increase in the proportion of affected fetuses over those treated with TCDD alone (60% and 65%, versus 36% for TCDD alone on day 11; 20% and 43%, versus 4% for TCDD alone on days 10-13). This incidence of cleft palate was not further increased by adding 245-HCB to the combined 345-HCB + TCDD treatment.

The number of fetuses with renal damage and the severity of the lesions were also scored. 245-HCB alone did not produce this effect and did not change TCDD's pattern of effect when given in combination with it. 345-HCB did produce renal lesions in a dose-related fashion, but these were of a less severe nature than those produced by TCDD. In combination with TCDD, 345-HCB did not increase the severity of the effect seen with TCDD alone.

The experiments of Birnbaum et al. (1985) and Weber et al. (1985) demonstrate that certain PCB isomers can augment the teratogenic effects of TCDD. Furthermore, they support the hypothesis that such enhancement occurs for substances that share other properties with TCDD: induction of P-448, binding to the Ah receptor, and similar structural conformation. These similarities suggest that TCDD and these substances share a common mechanism of teratogenicity in the mouse, resulting in additivity of effect when potencies are converted into TCDD equivalents. This mechanism may directly involve binding to the Ah receptors. Discrepancies in binding affinity and teratogenic potency, however, suggest that these less potent chemicals, when present in much higher concentrations than TCDD, might compete with TCDD for binding to the Ah receptor, freeing TCDD to follow another pathway that leads to teratogenicity. These studies are of great significance in illustrating that the risks posed by TCDD cannot be evaluated in isola-

tion. They suggest that the concepts of "thresholds" and "safe levels" for exposure to TCDD require reevaluation if other related chemicals that may occur together with TCDD at low concentrations in the environment may have a joint effect on susceptible organisms.

REFERENCES

Birnbaum, L.S., Weber, H., Harris, M.W., Lamb, J.C., and McKinney, J.D. 1985. Toxic interaction of specific polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin: Increased incidence of cleft palate in mice. Toxicol. Appl. Pharmacol. 77:292-302

Pratt, R.M. 1985. Receptor-dependent mechanisms of glucocorticoid and dioxin-induced cleft palate. Environ. Health Perspect. 61:35-40

Pratt, R.M., Grove, R.I., Kim, C.S., Dencker, L., and Diewert, V.M. 1984. Mechanism of TCDD-induced cleft palate in the mouse. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 61-71

Weber, H., Harris, M.W., Haseman, J.K., and Birnbaum, L.S. 1985. Teratogenic potency of TCDD, TCDF and TCDD-TCDF combinations in C57BL/6N mice. Toxicol. Letters 26:159-167

D. Immunotoxicity

No reports of studies of immune function in humans exposed to phenoxy herbicides or chlorinated dioxins appeared in the literature during 1985. Two comprehensive reviews of available studies on the immunosuppressive effects of TCDD in experimental animals were published in the Banbury Report 18 (Clark et al. 1984, Vos 1984). The Vos review also summarizes the results of studies of human populations exposed to chlorinated dibenzodioxins or chlorinated dibenzofurans. These reviews indicate that TCDD causes thymic atrophy in a wide variety of species and that thymic atrophy is accompanied by dose-related suppression of cell-mediated and humoral immunity, although the precise nature of these effects and the mechanism by which they occur are not clear.

A few studies of the effects of TCDD on immune function in experimental animals were published during 1985. Luster et al. (1984-1985) examined the effect of acute doses of TCDD on bone marrow function in mice. Administration of a single oral dose of TCDD in corn oil to mice caused a significant decrease in bone marrow hematopoiesis as indicated by the number of granulocyte-macrophage progenitor cells and erythrocyte precursor cells in bone marrow five days after treatment. In genetically "responsive" mice (BCF strain), the lowest effect level was 1.0 μg/kg and the no-observed-effect level was 0.2 μg/kg. In genetically "nonresponsive" mice (DBA/2 strain), a weak response was

seen at 10 μg/kg and 5 μg/kg was a no-observed-effect level. Addition of TCDD to cultures of bone marrow cells resulted in a concentration-dependent decrease in total cellularity and the formation of granulocyte-macrophage progenitor and erythrocyte precursor cells. Again, bone marrow from BCF mice was more sensitive than marrow for DBA/2 mice. Further experiments using cultured bone marrow cells indicated that TCDD directly inhibited DNA synthesis, and that sensitivity to this effect segregates with the Ah-gene locus. Receptor studies indicated the presence of a TCDD receptor in bone marrow cells and that sensitivity to suppression of differentiation of bone marrow progenitor cells was correlated with affinity of the receptor for the test substance. The authors pointed out that this effect in vivo occurred at a lower dose than that causing thymic atrophy in sensitive mouse strains. The study reveals a new target system and effect for the action of TCDD. This acute myelotoxicity of TCDD in mice appears to be mediated through binding of TCDD to the TCDD receptor and may be related to the suppression of humoral immunity in adult animals.

Vecchi et al. (1985a) examined humoral immunity in genetically "responsive" mice treated with TCDD and TCDF (2,3,7,8-tetrachlorodibenzofuran) either singly or in combination. Single intraperitoneal injections of 1 μg/kg TCDD or 100 μg/kg TCDF alone had no significant effect on thymus weight but caused comparable decreases in the number of

plaque-forming cells (PFC) in the spleen in response to a challenge by sheep red blood cells (SRBC) in immunized mice. These doses also caused comparable increases in AHH activity in hepatic microsomes. Administration of 1 μg/kg TCDD and 100 μg/kg TCDF simultaneously to mice had predictable additive effects on both immunosuppression and AHH induction. However, administration of 1 μg/kg TCDD and 10 μg/kg TCDF had antagonistic effects. In other words, this combination resulted in reduced immune suppression and enzyme induction compared to 1 μg/kg of TCDD alone. The authors suggested that this might be a result of TCDF competing for receptors with TCDD thus lessening the effect of TCDD on immune function and AHH induction at levels at which the TCDF alone has no such effect.

In an abstract of a symposium presentation, the same research group described further studies of interactions of TCDD with compounds known to induce cytochrome P-450 monooxygenase activity (Vecchi et al. 1985b). In this study, 3-methylcholanthrene (3MC) and beta-naphthoflavone (beta-NF) administered simultaneously with TCDD caused an increased suppression of the PFC response to SRBC compared to TCDD alone. 3MC and beta-NF were also immunosuppressive by themselves. Phenobarbital, on the other hand, was not effective either alone or in combination with TCDD. The authors concluded that TCDD immunotoxicity is modified by cytochrome P-450 inducers that bind to the Ah receptor,

but not by cytochrome P-450 inducers that do not bind to the receptor.

In summary, the available studies indicate that, in experimental animals, TCDD is a potent suppressor of both cell-mediated and humoral immunity, and these effects may be secondary to effects on bone marrow and the thymus. Although, the precise nature and mechanism of these effects is not clear, it appears that some if not all of the immunosuppressive effects are mediated through binding to a receptor and that these effects are probably under genetic control. The few available studies of immune function in humans possibly exposed to TCDD are inconclusive. Because of potential genetic variability in responsiveness as well as difficulties in determining exposure, it is unlikely that appropriate human studies can be designed to establish conclusively the presence or absence of effects of TCDD on the immune system.

REFERENCES

Clark, D.A., Gauldie, J., and Sweeney, G. 1984. Dose response, time-course and mechanism for suppression of cytotoxic T cell generation by 2,3,7,8-tetrachlorodibenzo-p-dioxin. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 421-434

Luster, M.I., Tucker, A.N., Hong, L., Boorman, G.A., and Patterson, R. 1984. In vivo and in vitro effects of TCDD on stem cell and B cell differentiation. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 411-419

Luster, M.I., Hong, L.H., Boorman, G.A., Clark, G., Hayes, H.T., Greenlee, W.F., Dold, K., and Tucker, A.N. 1985. Acute myelotoxic responses in mice exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol. Appl. Pharmacol. 81:156-165

Vecchi, A., Graziani, A., Sironi, M., Fiume, D.D., Sfreddo-Gallotta, E., Saletti, M.C., and Cantoni, L. 1985a. Simultaneous administration of TCDD and TCDF at different ratios induces different effects. Chemosphere 14:957-951

Vecchi, A., Sironi, M., Sfreddo-Gallotta, E., Graziani, A., and Cantoni, L. 1985b. Effect of cytochrome P450/448 inducers on TCDD immunosuppression. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985). 1 page (abstract)

Vos, J.G. 1984. Dioxin-induced thymic atrophy and suppression of thymus-dependent immunity. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 401-410

E. Neurotoxicity

In a brief abstract of a presentation at a meeting, Dyro (1985) described a study in which nerve conduction velocities were measured in 15 Vietnam veterans who had probably been exposed to Agent Orange while in Vietnam and who claimed onset of symptoms of sensory neuropathy many years after exposure. All had complained of paresthesias of the extremities of several months duration. The author reported that all but one of the patients had nerve conduction velocities and latencies well within normal limits and not different from those of an unspecified control group. The one individual with bilateral peroneal neuropathy had a history of excessive alcohol intake. The author concluded that the paresthesias in these patients were not explained by peripheral neuropathy. The lack of specific details regarding the selection of subjects, the nature of their exposure, and the measurement methods used in this study preclude independent evaluation of the results. It is of interest to note that the absence of changes in nerve conduction velocities and latencies is consistent with the findings of Fleck (1985) described below.

Neuropathy, possibly related to exposure to phenoxy herbicides in Vietnam, was described in a single case report by Fleck (1985). The patient was examined in 1981 and 1982. Although motor and sensory nerve conduction velocities and latencies were normal and reflexes were normal, explora-

tion of muscle function revealed fibrillations, polyphasic potentials, and general instability which, the author concluded, indicated a long standing terminal axonopathy not involving the larger axons. A ninhydrin sweat test also revealed spotty deficits in sweating which the author attributed to loss of sympathetic innervation.

The patient reported that he had been exposed to Agent Orange by direct exposure to spray and by ingestion of contaminated water and food in Vietnam in 1967. He reported that he developed chloracne at the time of exposure and that this recurred after discharge. He also described a number of generalized symptoms some of which suggested neurological effects such as numbness, paresthesia, weakness, fasciculations, etc. He also reported a series of seizures possibly secondary to an operation for subdural hematomas in 1968. The author indicated that the patient was not a diabetic, alcoholic, or drug abuser.

As with all case reports, there is little scientific basis to support a cause-and-effect relationship between the diagnosed neuropathy and the self-reported exposure. The neuropathy seen in this individual was not like the neuropathy seen in experimental animals exposed to high levels of 2,4-D in that there was no evidence of involvement of the large axons. The author speculated that earlier damage to the large axons may have been repaired. The author also speculated that the loss of sympathetic innerva-

tion of the extremities might be secondary to chloracne. All conclusions based on this report must be classified as speculative.

Toyoshima et al. (1985) studied the effects of 2,4-D on the nervous system of rats. In one study young adult male rats were treated six days per week for three weeks with intraperitoneal injections of 100 mg/kg 2,4-D. In another experiment, adult male rats were given 80 mg/kg 2,4-D three days per week for 12 weeks. The rats in both experiments were examined daily for signs of altered motor (gait) or sensory (toe spreading reflex) nerve function. The authors also measured nerve conduction velocity in motor and sensory nerves and distal motor latency. In neither experiment were there any significant differences between treated and control animals in the objective parameters studied. The authors observed that transient myotonia was observed in the rats receiving 100 mg/kg 2,4-D. The authors concluded that 2,4-D did not cause peripheral neuropathy in rats and that this supported the findings of Dyro (1985) discussed above. The authors also pointed out, however, that there may be interspecies differences in susceptibility to neurological effects of 2,4-D and that mytonia does appear to be a consequence of relatively large doses of 2,4-D.

Bernard et al. (1985) studied the effect of 2,4-D on acetylcholinesterase levels in rat muscle. A single

intraperitoneal injection of 200 mg/kg of 2,4-D caused a significant decrease in acetylcholinesterase levels in the diaphram, white quadriceps, and red quadriceps muscles within three hours. The decrease was maximal at 15-24 hours after treatment and acetylcholinesterase levels returned to control values by 48 hours. These decreases in acetylcholinesterase levels were accompanied by an increased distal motor latency, but no changes in motor or mixed conduction velocities were observed. Spontaneous locomotion activity decreased markedly within four hours and recovered by 48 hours. Myotonia was observed with similar time courses in rats receiving 100 and 200 mg/kg 2,4-D. The authors concluded that 2,4-D at acutely toxic doses probably causes neuromuscular toxicity by interference with postjunctional processes at the neuromuscular junction leading to muscle necrosis.

REFERENCES

Bernard, P.A., Toyoshima, E., Eccles, C.U., Mayer, R.F., Johnson, K.P., and Max, S.R. 1985. 2,4-Dichlorophenoxyacetic acid (2,4-D) reduces acetylcholinesterase activity in rat muscle. Exp. Neurol. 87:544-556

Dyro, F.M. 1985. Conduction velocities and Agent Orange exposure. Electroencephalogr. Clin. Neurophysiol. 60:112

Fleck, H. 1985. An Agent Orange: Case history. Milit. Med. 150:103-104

Toyoshima, E., Mayer, R.F., Max, S.R., and Eccles, C. 1985. 2,4-Dichlorophenoxyacetic acid (2,4-D) does not cause polyneuropathy in the rat. J. Neurol. Sci. 70:225-229

F. Metabolism

It has long been recognized that there are large interspecies differences in sensitivity to the acute toxic effects and perhaps some of the longer term effects of TCDD. The oral LD_{50} of TCDD is over 1,000 times higher in hamsters than the oral LD_{50} in guinea pigs. One possible explanation for this interspecies variability is differences in the disposition, i.e., absorption, metabolism, and distribution of TCDD among species. If one species metabolizes and eliminates a toxic substance more quickly than another, it would be expected to be less sensitive to the toxic effects of that compound. To date, information on the disposition of TCDD in various mammalian species indicates that interspecies differences in metabolism and elimination do not correlate with interspecies differences in acute toxicity (Neal et al. 1984). Most mammalian species metabolize TCDD slowly, and TCDD administered orally is largely excreted unchanged in the feces.

One recent finding of interest is that TCDD promotes its own metabolism, presumably as a result of the induction of AHH activity in hepatic microsomes (Olson and Wroblewski 1985, Poiger and Buser 1984, Poiger and Schlatter 1985a). Wroblewski and Olson (1985) showed that pretreatment of rats with TCDD caused a three-fold increase in the rate of TCDD metabolism by cultured hepatocytes, whereas TCDD had no effect on its own metabolism in guinea pigs. This

may explain, in part, the greater sensitivity of guinea pigs to the toxic effects of TCDD. Since the induction of AHH activity is mediated by the Ah receptor, there would be expected to be important intra and interspecies differences in the induction of TCDD metabolism. One important question is the basal level and inducibility of AHH activity and, therefore, of TCDD metabolism in humans. Preliminary results suggest that there is a wide variation among individuals in the amount of Ah receptor present in human tissues (Nagayama et al. 1985, Roberts et al. 1985, Okey et al. 1985). This variability may explain the apparent differences between exposed and nonexposed human populations in body burdens of TCDD and related chlorinated aromatic hydrocarbons (Hardell et al. 1985, Nygren et al. 1985, Schecter and Ryan 1985, Schecter et al. 1985d).

In an oral presentation at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Poiger and Schlatter (1985b) described a study in which a human volunteer ingested a single oral dose of 1.14 ng/kg of tritium-labeled TCDD in corn oil. Feces and urine were collected for 35 days and adipose tissue biopsies were taken 10 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. No detectable radioactivity was found in the urine through 35 days. Adipose tissue samples contained radioactivity

equivalent to 3.0 and 2.8 parts per trillion TCDD after 10 and 69 days, respectively. Using these data, the authors calculated a half-life of 4.95 years for elimination of TCDD from the human body. This is much longer than the half-lives for TCDD reported in most 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, the results from only one subject provide a weak basis for generalization in light of probable large intraspecies variability.

Frank et al. (1985) studied the absorption and excretion of 2,4-D in humans involved in the application of this phenoxy herbicide to conifer forests during 1981 and 1982. The study population consisted of seven individuals including four workers who mixed and loaded aircraft with the 2,4-D formulation, two workers who went aloft in balloons to direct the aerial application, and one of the authors who volunteered to be directly sprayed by an aircraft during an application run. Except for the volunteer, the workers wore protective clothing and respiratory protection at all times while working with the herbicides and all workers took showers within one hour after each spray session. Twenty-four hour urine samples were collected from all

subjects beginning several days prior to the first spraying and continuing for 10-15 days after spraying operations were completed. In addition, surface samples were collected from aircraft, workplace, and living quarters surfaces using cotton swabs wetted with methanol. Urine and swab samples were analyzed for 2,4-D. Also the respirator filters from one worker were analyzed for 2,4-D.

The results of this study indicated that the peak daily excretion of 2,4-D in the six workers ranged from 0.30 to 22.2 μg/kg body weight. The volunteer who was directly exposed to the spray absorbed 0.44% of the calculated dose as indicated by urinalysis. One finding of note was that body burdens of 2,4-D did not decrease in a linear first-order fashion after cessation of exposure. Analysis of swab samples, however, revealed extensive contamination of work surfaces and living quarters with 2,4-D. The authors concluded that, when appropriate protective measures are taken, total exposures to 2,4-D are well below doses that might be expected to cause acute toxic effects and that 2,4-D is rapidly eliminated in the urine.

Schulze et al. (1985) studied the metabolism of the butyl ester of 2,4-D in male rats in order to determine whether the metabolic fate of this ester, which was often used in formulations of 2,4-D, including Agent Orange, was similar to that for the free acid. A single dose of 100 mg/kg of 2,4-D butyl ester was administered by subcutaneous injection

ous injection and urine and feces were collected for 96 hours. They found that 95% of the administered dose was excreted as 2,4-D free acid in the urine within 48 hours of administration. Less than 2% of the dose appeared as a metabolite. These results are similar to findings about the disposition of 2,4-D and support the conclusion that esters of 2,4-D do not differ from the parent acid in their biological properties.

REFERENCES

Frank, R., Campbell, R.A., and Sirons, G.J. 1985. Forestry workers involved in aerial application of 2,4-dichlorophenoxyacetic acid (2,4-D): Exposure and urinary excretion. Arch. Environ. Contam. Toxicol. 14:427-435

Hardell, L., Domellof, L., Nygren, M., Hansson, M., and Rappe, C. 1985. Levels of polychlorinated dibenzodioxins and dibenzofurans in adipose tissue of patients with soft-tissue sarcoma or malignant lymphoma exposed to phenoxy acids and of unexposed controls. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

Neal, R., Gasiewicz, T., Geiger, L., Olson, J., and Sawahata, T. 1984. Metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian species. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 49-60

Nygren, M., Hansson, M., Rappe, C., Dommellof, L., and Hardell, L. 1985. Analysis of polychlorinated dibenzo-p-dioxins and dibenzofurans in adipose tissue from soft-tissue sarcoma patients and controls. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

Olson, J.R., and Wroblewski, V.J. 1985. Metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in isolated hepatocytes from guinea pigs and rats. Chemosphere 14:979-982

Poiger, H., and Buser, H.-R. 1984. The metabolism of TCDD in the dog and rat. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 39-47

Poiger, H., and Schlatter, C. 1985a. Influence of phenobarbital and TCDD on the hepatic metabolism of TCDD in the dog. Experientia 41:376-378

Poiger, H., and Schlatter, C. 1985b. Pharmacokinetics of 2,3,7,8-TCDD in man. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

Schecter, A., and Ryan, J.J. 1985. Dioxin and furan levels in human adipose tissue from exposed and control populations. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

Schecter, A., Tiernan, T., Schaffner, F., Taylor, M., Gitlitz, G., VanNess, G.F., Garrett, J.H., and Wagel, D.J. 1985d. Patient fat biopsies for chemical analysis and liver biopsies for ultrastructural characterization after exposure to polychlorinated dioxins, furans, and PCBs. Environ. Health Perspect. 60:241-254

Schulze, G.E., Blake, J.W., and Dougherty, J.A. 1985. The metabolic fate of 2,4-dichlorophenoxyacetic acid-n-butyl ester in the Wistar rat. Arch. Toxicol. 57:231-236

Wroblewski, V.J., and Olson, J.R. 1985. Hepatic metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the rat and guinea pig. Toxicol. Appl. Pharmacol. 81:231-240

G. Other Toxic Effects

Moses and Prioleau (1985) published the results of a histologic examination of skin samples taken from a subcohort of workers at the Monsanto plant in Nitro, West Virginia. Skin biopsies were taken from the lateral malar area of the face from 79 workers during examination as part of a comprehensive evaluation of the health status of workers at the plant in 1981. The methods and results of the comprehensive study were published in 1984 and were reviewed in Volume V of this review (see Moses et al. 1984 in Clement 1985).

The purpose of the study reported by Moses and Prioleau (1985) was to determine whether persistent histologic markers of chloracne exist and whether these markers could be used to evaluate past exposure to chemicals that cause chloracne. Two specimens were not suitable for evaluation, so the actual study population consisted of 77 white males who had a mean of 28 years of employment with the company. Thirty-seven of the participants had clinically evident residual chloracne, 18 reported a history of chloracne but had no current indication of the condition, while 22 reported that they had never had chloracne. Tissues were examined by a dermatopathologist who was unaware of the status of each subject.

A comparison of findings among the three groups revealed that follicular infundibular dilatation and/or comedones

and cysts were more prevalent in workers with current chloracne than in either workers with a history of chloracne or workers who never had chloracne. There was no difference in the prevalence of these conditions between workers with a history of chloracne and workers who had never had chloracne. No other findings were related to chloracne status. The authors concluded that skin biopsy was not useful or diagnostic in individuals with past exposure to TCDD that was insufficient to produce persistent chloracne.

This study is subject to the same criticisms as the larger study of which it was a part. Participants in this study were a self-selected cohort of a larger self-selected cohort and those with residual chloracne or a past history of chloracne were more likely to volunteer for skin biopsy than were workers with no history of chloracne, raising the possibility of participation bias. Furthermore, the authors' conclusion depends heavily on the assumption that the workers' recall of past chloracne or the absence of chloracne is accurate. This study, like the larger study, lacked a control group of individuals who were not exposed to TCDD. Based on the workers' recall of exposure, it is likely that the group who reported no history of chloracne included some individuals who were "heavily" exposed to TCDD.

Schecter et al. (1984, 1985a, and d) described morphological changes in liver cells in three human patients who

gave indication of liver involvement after being exposed to soot from a PCB-filled transformer fire and explosion in the New York State Office Building in Binghamton, New York. All three patients were selected on the basis of complaints of fatigue and persistent moderate elevation of serum enzyme levels indicative of liver damage. Liver biopsies were performed two years after exposure. Examination of liver tissue at the light microscopic level revealed no outstanding abnormalities, although two of the three patients had fat droplets. Electron microscopic examination, however, revealed numerous mitochondrial abnormalities. The most characteristic finding was swollen mitochondria with the cristae lined up parallel to the long axis. There were also occasional crystalline structures within the mitochondria. For comparison purposes, male rats were given two doses of 80 μg TCDD/kg a week apart. Electron microscopic examination of liver tissues from these animals revealed similar enlarged mitochondria with cristae parallel to the long axis but no crystalline structures. The authors concluded that the mitochondrial changes which they saw could serve as a biological marker for exposure to dioxins and related compounds in humans.

It is important to recognize that this report is essentially a case-report, that there is no control group, and no pre-exposure liver biopsies were available for comparison purposes. Although elevated levels of polychlorinated

dibenzofurans and polychlorinated dibenzo-p-dioxins were present in adipose tissue samples from these three patients, a cause-and-effect relationship between the liver and morphological changes and exposure to these compounds has not been proved. Also, the soot to which these workers were exposed was a very complex mixture containing PCBs, chlorinated benzenes, and chlorinated naphthalenes and biphenylenes as well as dioxins and furans. In fact, 2,3,7,8-TCDD was a relatively minor constituent in this mix. If the mitochondrial changes seen are due to this exposure it may be that compounds other than TCDD play an important role in the etiology. At present these studies are an insufficient basis for recommending liver biopsies as a means of ascertaining potential exposure to chlorinated dibenzo-p-dioxins.

McMillin and Samples (1985) described a case of iritis in a worker who had rubbed his eye with an unwashed hand after moving a number of old metal containers of a 2,4-D herbicide preparation. The irritation was quite severe, marked by ciliary flush, vasodilitation of the large vessels of the iris, fine keratinic precipitates in the cornea, and cells and flare in the anterior chamber. The eye changes were accompanied by headache and generalized weakness. The signs and symptoms disappeared after 3 weeks. The author attributed the ocular effects in this incident to the herbicidal active ingredient. No information was given regarding the other components of the formulation that

was handled. Other "inactive" ingredients may have contributed to, or been solely responsible for, the toxic effects.

McMillin, R.B., and Samples, J.R. 1985. Iritis after herbicide exposure. Am. J. Ophthalmol. 99:726-727

Moses, M., Lilis, R., Crow, K.D., Thornton, J., Fischbein, A., Anderson, H.A., and Selikoff, I.J. 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: Comparison of findings with and without chloracne. Am. J. Ind. Med. 5:161-182

Moses, M., and Prioleau, P.G. 1985. Cutaneous histologic findings in chemical workers with and without chloracne with pase exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Am. Acad. Dermatol. 12:497-506

Schecter, A., Schaffner, F., Tiernan, T., and Taylor, M. 1984. Ultrastructural alterations of liver mitochondria in response to dioxins, furans, PCBs, and biphenylenes. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 177-190

Schecter, A., Gasiewicz, T.A., Eisen, H., and Schaffner, F. 1985a. Ultrastructural alterations in liver cells of humans, rats, and mouse hapatoma cells in response to 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds. Chemosphere 14:939-944

Schecter, A., Tiernan, T., Schaffner, F., Taylor, M., Gitlitz, G., VanNess, G.F., Garrett, J.H., and Wagel, D.J. 1985d. Patient fat biopsies for chemical analysis and liver biopsies for ultrastructural characterization after exposure to polychlorinated dioxins, furans and PCBs. Environ. Health Perspect. 60:241-254

IV. RELEVANCE OF BASIC RESEARCH ON TCDD TOXICITY

As indicated in the Summary and Conclusions section, an increasing proportion of the literature relevant to the health effects of phenoxy herbicides consists of reports of basic research in experimental animals or in cell or tissue cultures designed to elucidate the mechanisms of action of TCDD. The objective of many of these studies is to identify the cause of death after acute oral or parenteral doses of TCDD and to determine the reasons for interspecies differences in susceptibility to acute lethal doses of TCDD. The relevance of the results of these studies to elucidating the human health effects of exposure to TCDD at levels that do not cause overt acute toxic effects is not clear.

Among the studies included in the current bibliography, several were concerned with characterizing the genetic properties of the Ah and cytochrome P_1-450 loci. In hybrids of P_1-450 inducible and noninducible mouse cell lines, Dufresne and Doseau (1985) demonstrated that Ah activity is expressed in a dominant fashion. Jones et al. (1985) cloned the DNA sequence immediately preceding the cytochrome P_1-450 structural gene in mouse hepatoma cells. Passing subclones of this sequence with various deletions into normal cells and cells with abnormal TCDD-receptor complexes, they noted the responsiveness of the sequences in the presence

and absence of TCDD. Their findings indicate that there are three functional areas in the cloned sequence regulating the expression of cytochrome P_1-450: the usual promoter adjacent to the gene, a segment that binds with an inhibitory element, and, further away, a portion that binds with the TCDD-receptor complex to release inhibition, thus inducing expression of the enzyme. Researchers in Nebert's laboratory have cloned and sequenced the structural genes for TCDD-induced P-450 enzymes in mice (Gonzales et al. 1985) and humans (Jaiswal et al. 1985). Sequences so derived permit comparisons among the various members of the P-450 enzyme family and across species, giving evolutionary information and clues about how biological variability may result from differences in the primary DNA sequences. These cloned sequences were also used as probes by Hildebrand et al. to map the P_1-450 gene to chromosome 15 in humans (1985a), to chromosome 4 in hamsters (1985b), and to chromosome 9 in mice (1985c). Research on the molecular genetics of TCDD-responsive loci not only is answering immediate questions but is generating tools such as these clones that can be applied to future tasks, such as identifying susceptible individuals or investigating means of blocking detrimental enzyme induction.

A number of other studies over the last decade have begun to show how TCDD interacts with cellular and subcellular components of living organisms and how these interactions

are manifested in various organs and tissues in the whole organism. A detailed review of these studies and their implications is beyond the scope of this review. Interested readers are referred to Banbury Report 18: Biological Mechanisms of Dioxin Action, published by Cold Spring Harbor Laboratory in 1984, and to the Proceedings of the 4th International Symposium on Chlorinated Dioxins and Related Compounds, published in Chemosphere (Volume 14, 1985), for comprehensive reviews of these studies. Several studies of the mechanism of action of TCDD are discussed here, however, because they address the important question of how to extrapolate from results of animal experiments to predict health effects in humans.

A number of investigators have shown, using both in vitro and in vivo studies, that TCDD and structurally-related compounds bind to a high affinity receptor in the cells of a number of tissues in mammalian species (see Denison and Wilkinson 1985, Gasiewicz 1984, Roberts et al. 1985). The receptor is associated with the Ah gene locus in mice and is often referred to as the Ah receptor. Several investigators have shown that this receptor is similar in its physicochemical properties to steroid hormone receptors, but that it is not identical to these receptors (see Gustafsson et al. 1984, Poellinger et al. 1985a, Poellinger and Gullberg 1985, and Poland 1984). An endogenous ligand for this receptor has not been identified. The substrate-receptor

complex interacts with DNA in the nucleus leading to the expression of one or more structural genes that code for isozymes of cytochrome P-450, as indicated by increased synthesis of mRNA. There is also suggestive evidence that the substrate-receptor complex interacts with regulatory genes that control proliferation and differentiation mechanisms. A wealth of studies suggests that many of the responses to TCDD seen in experimental animals are mediated by the receptor and subsequent interaction of the TCDD-receptor complex with the genetic material of the cell. Included are chloracne and related skin effects, thymic atrophy, cell-mediated immune suppression, teratogenicity, enzyme induction, hepatic porphyria, and changes in lipid metabolism. However, some investigators have suggested that there may be more than one receptor for TCDD. One of these receptors may mediate enzyme induction (the Ah receptor) and the other may mediate the acute toxic effects of TCDD (McKinney et al. 1985a,b, Rifkind et al. 1984 and 1985).

Among various strains of mice, there are wide variations in the affinity of the receptor for TCDD. This receptor affinity appears to be under genetic control and correlates with susceptibility to many of the toxic effects of TCDD. Between species the picture is not so clear; however, many studies suggest that there is some correlation between receptor affinity and susceptibility across a number of species.

The demonstration of genetically-controlled variability in responsiveness to some of the effects of TCDD and related compounds in mice has raised the question as to whether there might be variable sensitivity in human populations. Nagayama et al. (1985a) established cultures of human lymphoblastoid cells from peripheral blood collected from healthy volunteers who were non-smokers and alcohol abstainers. They then measured aryl hydrocarbon hydroxylase (AHH) activity in these cells both after treatment with various AHH inducers, e.g., 3-methylcholanthrene and TCDD, and in the absence of inducers. AHH activity in uninduced cells from eight subjects ranged from 0.005-0.088 pmol/min/10^6 cells. Furthermore, there was large variability among individuals in the inducibility of this enzyme by various inducers. Among 25 female subjects, 13 had relative AHH-inducible activity of less than 3, i.e., treatment of cells with AHH-inducers caused less than a 3-fold increase in AHH activity. Eight subjects had relative inducibilities of greater than 6, with a high of 23. This range of variability is similar to the range of AHH-inducibilities seen in "responsive" and "non-responsive" mouse strains.

Roberts et al. (1985) assayed human cells and tissues for Ah receptor by measurement of specific binding of tritium-labeled TCDD after separation on sucrose density gradients. Examination of liver, lung, kidney, spleen, and thymus from four human fetuses revealed no detectable Ah receptor.

In a fifth human fetus the Ah receptor was detected in the lung but not the liver. Ah receptor was detected in two human squamous cell carcinoma lines in culture and in one hepatoma cell line.

Finally, the same authors assayed Ah receptors in 53 specimens of histologically normal lung tissue taken from patients during lobectomy for bronchogenic carcinoma (Okey et al. 1985). Only 10 of these 53 specimens had detectable Ah receptor. The concentration of receptor in these specimens ranged from 2.6-14.1 fmol/mg of cytosolic protein compared to 50-100 fmol/mg in mouse and rat tissues.

The results of the studies of Nagayama et al. (1985a) and Roberts et al. (1985) suggest that there is a great deal of variability among humans both in basal levels and in inducibility of the Ah receptor and that, on average, humans may have less receptor than rodent species. If responsiveness to the toxic effects of TCDD is dependent, in part, on the presence of this receptor, then we might expect to see "responsive" and "non-responsive" human populations. In general, humans might be less "responsive" than rodents to some of the toxic manifestations of TCDD exposure. Individual variability in responsiveness to the chloracnegenic effects of TCDD in exposed human populations has been suggested by the results of studies of chloracne among children in Seveso and among workers exposed to TCDD in industrial settings. Further, studies designed

to elucidate the specific role of the Ah receptor in TCDD toxicity may help provide a quantitative basis for extrapolation from animal studies to predict health effects in humans.

Denison, M.S., and Wilkinson, C.F. 1985. Identification of the Ah receptor in selected mammalian species and induction of aryl hydrocarbon hydroxylase. Eur. J. Biochem. 147:429-435

Gasiewicz, T.A. 1984. Evidence for a homologous nature of Ah receptors among various mammalian species. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 161-175

Gustafsson, J-A., Poellinger, L., Lund, J., Gillner, M., and Hansson, L-A. 1984. Physicochemical characteristics of the TCDD receptor. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 153-160

McKinney, J.D., Chae, K., Oatley, S.J., and Blake, C.C.F. 1985a. Molecular interactions of toxic chlorinated dibenzo-p-dioxins and dibenzofurans with thyroxine binding prealbumin. J. Med. Chem. 28:375-381

McKinney, J.D., Fawkes, J., Jordan, S., Chae, K., Oatley, S., Coleman, R.E., and Briner, W. 1985b. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) as a potent and persistent thyroxine agonist: A mechanistic model for toxicity based on molecular reactivity. Environ. Health Perspect. 61:41-53

Nagayama, J., Kiyohara, C., Masuda, Y., and Kuratsune, M. 1985a. Genetically mediated induction of aryl hydrocarbon hydroxylase activity in human lymphoblastoid cells by polychlorinated dibenzofuran isomers and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch. Toxicol. 56:230-235

Okey, A.B., Roberts, E.A., Golas, C.L., and Manchester, D.K. 1985. Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): Identification and characterization in human tissues. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

Poellinger, L., and Gullberg, D. 1985. Characterization of the hydrophobic properties of the receptor for

2,3,7,8-tetrachlorodibenzo-p-dioxin. Mol. Pharmacol. 27:271-276

Poellinger, L., Lund, J., and Gustafsson, J.A. 1985a. The rat liver receptor protein for 2,3,7,8-tetrachlorodibenzo-p-dioxin: A comparison with steroid hormone receptors. Chemosphere 14:963-966

Poland, A. 1984. Reflections on the mechanism of action of halogenated aromatic hydrocarbons. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 109-117

Rifkind, A.R., Hattori, Y., Levi, R., Hughes, M.J., Quilley, C., and Alonso, D.R. 1984. The chick embryo as a model for PCB and dioxin toxicity: Evidence of cardiotoxicity and increased prostaglandin synthesis. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 255-266

Rifkind, A.B., Sassa, S., Reyes, J., and Muschuck, H. 1985. Polychlorinated aromatic hydrocarbon lethality, mixed-function oxidase induction, and uroporphyrinogen decarboxylase inhibition in the chick embryo: Dissociation of dose-response relationships. Toxicol. Appl. Pharmacol. 78:268-279

Roberts, E.A., Shear, N.H., Okey, A.B., and Manchester, D.K. 1985. The Ah receptor and dioxin toxicity: From rodent to human tissues. Chemosphere 14:661-674

V. HEALTH EFFECTS OF OTHER HERBICIDAL ACTIVE INGREDIENTS

A. Picloram

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

John-Greene et al. (1985) evaluated the embryotoxic and teratogenic potency of picloram (potassium salt) in New Zealand white rabbits. Doses of 0, 40, 200, or 400 mg/kg bodyweight/day picloram acid equivalents were administered daily by oral gavage to groups of 25 inseminated dams on days 6 to 18 of gestation. The animals were observed daily for signs of toxicity and body weights were taken on days 8-16, 19, and 29 of gestation. Liver and kidneys were weighed at the time of sacrifice.

Animals were sacrificed on day 29 of gestation and examined for the position of fetuses in utero, the number of live and dead fetuses, the number of resorption sites, the number of corpora lutea, and the body weight, crown-rump length, and sex of each fetus. All fetuses were examined for gross external anomalies and for skeletal alterations. Half the fetuses (randomly selected) were examined by dissecting microscope for soft-tissue anomalies.

Pregnant rabbits given either 200 or 400 mg/kg picloram lost weight on the first 3 days of treatment but subsequently gained weight and their total weight gain during gestation was comparable to that in controls. Several animals died during the course of the study; causes of death were reported to be possible gavage errors or severe pneumonia, or were not discernible at autopsy.

The authors reported that no compound-related adverse effects (either embryotoxicity or tetatogenicity) were seen in the fetuses. The only indication of such effects was that the proportion of implantations resorbed (8, 11, 14, and 17% for the 0, 40, 200, and 400 mg/kg/day groups) and percent of litters with resorptions (39, 39, 42, and 45% for the 0, 40, 200, and 400 mg/kg/day groups) were both slightly increased with increasing dose. The number of implantation sites and number of live fetuses per dam (average of 8 in both cases), fetal body weight (average ranged from 36-38 g), and fetal crown-rump length (average ranged from 90-93 mm) were comparable in all groups. Malformations such as hemivertebrae, hypoplastic tail, and severe forelimb flexure were seen sporadically in both controls and dosed animals and did not appear to be compound-related. The only fetal alteration that differed significantly from control values ($p \leq 0.05$) was delayed ossification of the hyoid, which was less common in the two mid-dose groups. Delayed ossification of the sternebrae occurred in approximately 50% of the animals in all dose groups.

The study appeared to have been well conducted overall. A chi-square analysis indicated that the number of resorptions was significantly increased on a per fetus basis, but not on a per litter basis, which is the more appropriate basis for statistical testing. With this minor exception, the study supports the authors' conclusions that under the condition of this study, picloram (in the form of the potassium salt) was not embryotoxic or teratogenic to New Zealand white rabbits.

B. Cacodylic Acid

Cacodylic acid (dimethylarsinic acid) is a broad spectrum herbicide that was a major ingredient in Agent Blue. Only limited information is available on its toxicity. One weak study has suggested that cacodylic acid might have tumor-promoting activity. It has shown mutagenic activity in several eukaryotic test systems. A number of authors have reported that it is teratogenic, primarily causing skeletal anomalies. Clement (1984, 1985) and JRB (1981) have reviewed the limited information available on the toxicology of cacodylic acid. No new studies on the health effects of cacodylic acid were published during 1985.

REFERENCES

John-Greene, J.A., Ouellette, J.H., Jeffries, T.K., Johnson, K.A., and Rao, K.S. 1985. Teratological evaluation of picloram potassium salt in rabbits. Food Chem. Toxicol. 23:753-756

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

Annotated Bibliography of
Literature on Health Effects
Published in 1985

Volume VIII

Prepared for Contracting Officer's Technical Representative:

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

Submitted by:

Clement Associates, Inc.
1850 K Street, N.W.
Suite 450
Washington, D.C. 20006

May 1, 1986

REFERENCES

Abernethy, D.J., Greenlee, W.F., Huband, J.C., and Boreiko, C.J. 1985. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) promotes the transformation of C3H/10T1/2 cells. Carcinogenesis 6:651-653

KEYWORDS: Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Mouse, Cancer, In vitro study

Appel, K.E., Beck, H., Hildebrandt, A.G., and Lingk, W. 1985. Approaches to the health risk assessment of PCDD/PCDF. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This is an abstract of a symposium presentation in which the author discussed the rationale underlying the assessment of carcinogenic risk by the West German health agency in order to arrive at a tolerable dose for the daily intake of TCDD.

Aust, S.D. 1984. On the mechanism of anorexia and toxicity of TCDD and related compounds. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 309-318

KEYWORDS: Acute toxic effects, Hepatic effects, Mechanism of toxic action, Other toxic effect, Chlorinated dibenzo-p-dioxins, Review

Ayres, S.M., Webb, K.B., Evans, R.G., and Mikes, J. 1985. Is 2,3,7,8-TCDD (dioxin) a carcinogen for humans? Environ. Health Perspect. 62:329-335

KEYWORDS: Cancer, Environmental exposure, Occupational exposure, Chlorinated dibenzo-p-dioxins, Human, Review

In this article the authors review evidence for the carcinogenicity of TCDD as provided by studies of exposed humans and in vitro and in vivo animal studies. They conclude that, although the human evidence is inconclusive, the animal evidence makes it likely that a small number of human malignancies may be due to the action of TCDD. (44 references)

Balarajan, R., and Acheson, E. 1984. Soft tissue sarcomas in agriculture and forestry workers. J. Epidemiol. Community Health 38:113-116

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Phenoxy herbicide formulations, Human

Bannister, R., Mason, G., Kelley, M., and Safe, S. 1985. The effects of cytosolic receptor modulation on the AHH-inducing activity of 2,3,7,8-TCDD. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat, Mouse, Abstract

This abstract indicates that pretreatment of mice or rats with 2,2',4,4',5,5'-hexachlorobiphenyl enhances the induction of AHH activity by a single injection of TCDD seven days later presumably by increasing the concentration of the Ah receptor. This study is similar to Safe et al. 1985.

Barnes, D.G., Bellin, J., and Cleverly, D. 1985. Interim risk assessment procedures for mixtures of CDDs/CDFs. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This is an abstract of a symposium presentation in which the authors review approaches for assessing the risks of mixtures of chlorinated dioxins and dibenzofurans containing congeners other than TCDD.

Beardsley, T. 1985. Compensation for U.S. veterans. Nature 315:90

KEYWORDS: Cancer, Reproductive effects, Porphyria cutanea tarda, Occupational exposure, Phenoxy herbicide formulations, Human, Review

This news article summarizes the status of research sponsored by the Veterans Administration to satisfy the Congressional mandate to provide a sound scientific and medical basis for responding to compensation claims from veterans based on exposure to phenoxy herbicides and radiation from atomic tests.

Bernard, P.A., Toyoshima, E., Eccles, C.U., Mayer, R.F., Johnson, K.P., and Max, S.R. 1985. 2,4-Dichlorophenoxyacetic acid (2,4-D) reduces acetylcholinesterase activity in rat muscle. Exp. Neurol. 87:544-556

KEYWORDS: Acute toxic effects, Neurobehavioral effects, Mechanism of toxic action, Exposure by injection, 2,4-D and its esters, Rat

Birmingham, B., et al. 1985. Chlorinated dioxins and dibenzofurans in Ontario: Analysing and controlling the risks. Presented at the 5th International Symposium on Chlorinated Dioxins and Related

Compounds, Bayreuth, FRG (September 16-19, 1985) 2 pages (abstract)

KEYWORDS: Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This is an abstract of a symposium presentation in which the authors describe the development and conclusions of a scientific criteria document on the health effects of chlorinated dibenzo-dioxins. The document was prepared by an expert committee under the auspices of the government of Ontario.

Birnbaum, L.S. 1985. The role of structure in the disposition of halogenated aromatic zenobiotics. Environ. Health Perspect. 61:11-20

KEYWORDS: Metabolism, Chlorinated dibenzo-p-dioxins, Review

The author reviews information on the influence of structure on the absorption, distribution, metabolism, and excretion of chlorinated aromatic hydrocarbons including polychlorinated dibenzodioxins. (84 references)

Birnbaum, L.S., Weber, H., Harris, M.W., Lamb, J.C., and McKinney, J.D. 1985. Toxic interaction of specific polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin: Increased incidence of cleft palate in mice. Toxicol. Appl. Pharmacol. 77:292-302

KEYWORDS: Mouse, Oral exposure, Teratogenic effects, Chlorinated dibenzo-p-dioxins

Bombick, D.W., Madhukar, B.V., Brewster, D.W., and Matsumura, F. 1985. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) causes increases in protein kinases particularly protein kinase C in the hepatic plasma membrane of the rat and the guinea pig. Biochem. Biophys. Res. Commun. 127:296-302

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Hepatic effects, Mechanism of toxic action, Other toxic effect, Exposure by injection, Chlorinated dibenzo-p-dioxins, Guinea pig, Rat

Single i.p. injections of TCDD in rats and guinea pigs cause an increase in protein kinase levels in hyatic plasma membranes. They conclude that TCDD may influence EGF receptors by phosphorylation.

Brown, N.A. 1985. Are offspring at risk from their father's exposure to toxins? Nature 316:110

KEYWORDS: Commentary, Genotoxicity, Teratogenic effects, Phenoxy herbicide formulations, Human

The author discussed the possible mechanisms by which exposure of a male to a toxic substance might result in birth defects in

his offspring. He concluded that genetic damage to stem cells for spermatogonia is the only plausible means by which defects could be produced in conceptuses conceived long after the exposure. He pointed out that there is no strong evidence that Agent Orange or its components produce this type of an effect.

Chapman, D.E., and Schiller, C.M. 1985. Dose-related effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in C57BL/6J and DBA/2J mice. Toxicol. Appl. Pharmacol. 78:147-157

KEYWORDS: Acute toxic effects, Hepatic effects, Lethality, Mechanism of toxic action, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Mouse

A study of body weight loss and lipid parameters in "responsive" and "non-responsive" strains of mice given a single oral dose of TCDD inidcates that lipid changes were not simply due to decreased feed consumption in this species.

Clark, D.A., Gauldie, J., and Sweeney, G. 1984. Dose response, time-course and mechanism for suppression of cytotoxic T cell generation by 2,3,7,8-tetrachlorodibenzo-p-dioxin. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 421-434

KEYWORDS: Immunological effects, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

The authors review studies performed in their laboratory of the immunosuppressive effects of TCDD in mice. Of specific interest is the suppression of cytotoxic T lymphocytes which the authors suggest is the result of promotion of suppressor T cells in the thymic epithelium. (20 references)

Commoner, B., Webster, T., and Shapiro, K. 1985. Environmental levels and health effects of PCDDs and PCDFs. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Commentary, Abstract

This abstract of a symposium presentation suggests that "background" levels of polychlorinated dibenzodioxins and dibenzofurans in adipose tissues and human breast milk, possibly derived from municipal and industrial incinerators, may pose an unacceptable risk of cancer in the general population.

Constable, J.D., and Hatch, M.C. 1985. Reproductive effects of herbicide exposure in Vietnam: Recent studies by the Vietnamese and others. Teratogen. Carcinogen. Mutagen. 5:231-250

KEYWORDS: 2,4-D and its esters, 2,4,5-T and its esters, Chlorinated dibenzo-p-dioxins, Environmental exposure, Human, Epidemiologic investigation, Reproductive effects, Teratogenic effects, Review

This review of the possible reproductive effects of the use of herbicides in Vietnam stresses the results of unpublished epidemiology studies carried out in Vietnam. Their reported findings have been considered previously (Clement 1984), but the lack of detailed reports of methods and results prevents critical evaluation.

Cook, R.R., Bond, G.G., Olson, R.A., and Ott, M.G. 1985. Mortality experience of chemical workers exposed to chlorinated dioxins. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Abstract

Dan, B.B. 1985. Vietnam veterans' risk for fathering children with birth defects. JAMA 254:610

KEYWORDS: Commentary, Phenoxy herbicide formulations, Teratogenic effects, Epidemiologic investigation, Human

This response to Sterling and Arundel's criticisms (1985) of his letter (Dan 1984, see Volume VI of this review (Clement 1985)) notes that the few statistically significant associations of specific birth defects with possible exposure of fathers to Agent Orange in Vietnam are probably the chance result of investigating many end points. Furthermore, he notes that there is no plausible biological explanation for the pattern of statistically significant defects observed.

De Moro, G.B.M., Duffard, R.O., and De Duffard, A.M.E. 1985. Chick brain hypomyelination produced by 2,4-dichlorophenoxyacetic butyl ester treatment. Neurotoxicology 6:133-138

KEYWORDS: Mechanism of toxic action, Neurobehavioral effects, Reproductive effects, Other route of exposure, 2,4-D and its esters, Avian species

Dencker, L., Hassoun, E., D'Argy, R., and Alm, G. 1985. Fetal thymus organ culture as an in vitro model for the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin and its congeners. Mol. Pharmacol. 27:133-140

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Other toxic effect, In vitro study, Chlorinated dibenzo-p-dioxins, Mouse

The authors studied the effect of TCDD and structurally related compounds on cultured fetal mouse thymuses. TCDD and related compounds inhibited lymphoid development in a manner consistent with their affinity for the Ah receptor. The expression of the effect was dependent upon whether the thymuses were taken from "receptive" mouse strains.

Denison, M.S., and Wilkinson, C.F. 1985. Identification of the Ah receptor in selected mammalian species and induction of aryl hydrocarbon hydroxylase. Eur. J. Biochem. 147:429-435

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat, Hamster, Mouse, Guinea pig, Rabbit, Other toxic effect

The Ah receptor was isolated and characterized from rats, mice, guinea pigs, rabbits and ferrets. Interspecies comparisons revealed a wide range of affinity and binding capacity and there was no correlation between cytosodic Ah receptor levels and 3-MC induction of AHH.

Denison, M.S., Wilkinson, C.F., and Okey, A.B. 1985. Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin: Comparative studies in mammalian and nonmammalian species. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Abstract

This abstract of a symposium presentation summarizes studies of the presence and properties of the Ah receptor in a wide variety of mammalian and non-mammalian species. Except for chicken embryos, Ah receptor was not found in non-mammalian species. In mammals there are subtle interspecies differences in molecular size, response to high ionic strength, and ligand binding specificity.

Dufresne, M.J., and Dosescu, J. 1985. Analysis of Ah gene locus by somatic cell hybridization: Expression of Ah regulatory gene product of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mouse L-cell x mouse hepatoma cell hybrids. Somatic Cell Mol. Genet. 11:53-61

KEYWORDS: Chlorinated dibenzo-p-dioxins, Enzyme induction or inhibition, Cultured mammalian cells, Mouse

Dyro, F.M. 1985. Conduction velocities and Agent Orange exposure. Electroencephalogr. Clin. Neurophysiol. 60:112

KEYWORDS: Epidemiologic investigation, Neurobehavioral effects, Environmental exposure, Phenoxy herbicide formulations, Human, Abstract

Eisen, H.J. 1984. The nuclear TCDD - Ah receptor complex and the induction of cytochrome P_1-450 mRNA. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 201-211

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

Eisen, H.J., Schecter, A.J., Cresteil, T., and Jaiswal, A.K. 1985. Actions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the human hepatoblastoma HepG2 tissue culture cell line. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Enzyme induction or inhibition, Hepatic effects, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Abstract

Erickson, J.D., and Mulinare, J. 1985. Vietnam veterans' risk for fathering children with birth defects. JAMA 254:609-610

KEYWORDS: Commentary, Phenoxy herbicide formulations, Teratogenic effects, Epidemiologic investigation, Human

This is a response by Erickson and Mulinare to the letter of Sterling and Arundel (1985). They note the difficulty of determining the exposure of Vietnam veterans to Agent Orange and that maternal exposure in the animal studies showing induction of birth defects by the components of Agent Orange does not match the paternal exposure in questions for the children of Vietnam veterans.

Erickson, J.D., Mulinare, J., James, L.M., and Fitch, T.G. 1985. Design and execution of a very large birth defects case-control study. In Marois, M., ed. Prevention of Physical and Mental Congenital Defects, Part B: Epidemiology, Early Detection and Therapy, and Environmental Factors, Published by Alan R. Liss, Inc., New York Pp. 273-277

KEYWORDS: 2,4-D and its esters, 2,4,5-T and its esters, Chlorinated dibenzo-p-dioxins, Environmental exposure, Epidemiologic investigation, Human, Teratogenic effects, Review

The participants involved (Erickson et al. 1984 a,b) describe the methods used in the CDC study investigating a potential increase in the frequency of birth defects among the offspring of Vietnam veterans in the Atlanta, Georgia area. There is no discussion of findings.

Exon, J.H., Henningsen, G.J., Osborne, C.A., and Koller, L.D. 1984. Toxicologic, pathologic, and immunotoxic effect of 2,4-dichlorophenol in rats. J. Toxicol. Environ. Health 14:723-730

KEYWORDS: Immunological effects, Reproductive effects, Hepatic effects, Oral exposure, 2,4-D and its esters, Rat

Falk, H., Stehr, P.A., Stein, G.F., Sampson, E.J., Donnell, H.D., Jr., Schromm, W.F., Webb, K., and Gedney, W.B. 1984. A pilot epidemiologic study of health effects due to 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) contamination in Missouri. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 447-460

KEYWORDS: Chloracne, Epidemiologic investigation, Immunological effects, Neurobehavioral effects, Porphyria cutanea tarda, Other toxic effect, Renal effects, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human

This publication describes the pilot Missouri health effects study conducted among individuals residing in dioxin-contaminated areas of Missouri. The methods and results of this study have been described previously (Webb 1984 and Webb et al. 1984, in Volume VI of this review (Clement 1985)).

Fara, G.M., and Del Corno, G. 1985. Pregnancy outcome in the Seveso area after TCDD contamination. In Marois, M., ed. Prevention of Physical and Mental Congenital Defects, Part B: Epidemiology, Early Detection and Therapy, and Environmental Factors, Published by Alan R. Liss, Inc., New York Pp. 279-285

KEYWORDS: Chlorinated dibenzo-p-dioxins, Environmental exposure, Epidemiologic investigation, Human, Reproductive effects, Teratogenic effects

This discussion of the observed rates of birth defects and spontaneous abortions in the Seveso area recapitulates events through 1980. This ambiguous set of information has been discussed previously (Clement 1984, 1985).

Farrell, K., and Safe, S. 1985. The role of ornithine decarboxylase induction in the mechanism of action of 2,3,7,8-TCDD. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Enzyme induction or inhibition, Unspecified route of exposure, Chlorinated dibenzo-p-dioxins, Rat, Abstract

In this abstract the authors indicate that pretreatment of rats with an inhibitor can block the induction of ornithine decarboxylase activity in rats but it does not protect against the acute toxic effects of TCDD.

Fingerhut, M.A., Halperin, W.E., Honchar, P.A., Smith, A.B., Groth, D.H., and Russell, W.O. 1984. An evaluation of reports of dioxin

exposure and soft-tissue sarcoma pathology among chemical workers in the United States. Scand. J. Work Environ. Health 10:299-303

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Review

This publication is similar to Fingerhut et al. (1984) in Volume VI of this report (Clement 1985). The authors review 7 cases of soft-tissue sarcoma in individuals who may have been exposed occupationally to phenoxy herbicides and/or chlorophenols and conclude that misdiagnosis and inability to characterize exposure interfere with the interpretation of these reports.

Fingerhut, M.A., Halperin, W.E., Honchar, P.A., Smith, A.B., Groth, D.H., and Russell, W.O. 1984. An evaluation of reports of dioxin exposure and soft tissue sarcoma pathology in U.S. chemical workers. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 461-470

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Chlorinated dibenzo-p-dioxins, Human, Review

This analysis of seven reported cases of soft-tissue sarcoma among workers exposed to chlorinated dioxins has been published previously (see Fingerhut et al. 1984, in Volume VI of this review (Clement 1985)).

Fingerhut, M.A., Marlow, D.A., Halperin, W.E., and Honchar, P.A. 1985. The NIOSH dioxin registry: A status report. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Abstract

In this abstract of a symposium presentation the authors describe the basic design of the NIOSH cohort mortality study among approximately 6000 workers from 14 manufacturing facilities in which there was potential exposure to chlorinated dioxins. The results of this study should become available in 1986.

Fishbein, L. 1985. Health risk estimates for 2,3,7,8-tetrachlorodibenzodioxin: An overview. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This is an abstract of a symposium presentation in which the author reviewed available risk assessments for dioxins in environmental media and critically evaluated key assumptions and sources of uncertainty in those assessments.

Fleck, H. 1985. An Agent Orange: Case history. Milit. Med. 150:103-104

KEYWORDS: Chloracne, Neurobehavioral effects, Occupational exposure, Phenoxy herbicide formulations, Human

Fortunati, G.U. 1985. The Seveso accident. Chemosphere 14:729-737

KEYWORDS: Chloracne, Reproductive effects, Other study objective, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review

The author describes the events during and immediately following the accident at the ICMESA plant in Seveso. The emphasis of this review is on institutional responses to the accident but health effects are discussed briefly. (8 references)

Frank, R., Campbell, R.A., and Sirons, G.J. 1985. Forestry workers involved in aerial application of 2,4-dichlorophenoxyacetic acid (2,4-D): Exposure and urinary excretion. Arch. Environ. Contam. Toxicol. 14:427-435

KEYWORDS: Metabolism, Occupational exposure, 2,4-D and its esters, Human

Gasiewicz, T.A. 1984. Evidence for a homologous nature of Ah receptors among various mammalian species. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 161-175

KEYWORDS: Enzyme induction or inhibition, Hepatic effects, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

The author reviews information on the identification, physicochemical properties, and tissue distribution of the Ah receptor in various mammalian species. It is postulated that the receptor plays a basic role in epithelial tissue development but more research is needed to elucidate its exact function. (32 references)

Gasiewicz, T.A., Henry, E.C., Baggs, R., Rucci, G., and Schecter, A. 1985. Temporal and dose-related characteristics of biochemical and morphological alterations in the hamster induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Hepatic effects, Lethality, Other toxic effect, Exposure by injection, Chlorinated dibenzo-p-dioxins, Hamster, Abstract

A number of biochemical parameters were measured in hamsters given a single I.P. injection of TCDD. The results indicate that even though hamsters are much less sensitive than rats to the acute lethal toxicity of TCDD there is quantitative similarity between the species in the induction of cytochrome P-450 and associated hepatic enzyme activities.

Ghezzi, I., Assenato, G., Cannatelli, P., Merlo, F., Emmett, E., and Meazza, L. 1985. Medical monitoring of dioxin clean-up workers. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 2 pages (abstract)

KEYWORDS: Epidemiologic investigation, Occupational exposure, Chlorinated dibenzo-p-dioxins, Human, Abstract

This abstract of a symposium presentation describes a study that was published in full and reviewed in Volume VI of this review (see Ghezzi et al. 1984 in Clement 1985).

Gierthy, J.F., and Crane, D. 1985a. In vitro bioassay for dioxin-like activity based on alterations in epithelial cell proliferation and morphology. Fund. Appl. Toxicol. 5:754-759

KEYWORDS: Other study objective, Other dermal effects, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

The ability of very low concentrations of 2,3,7,8-TCDD and related compounds to induce the formation of "flat cells" in cultures of a nonkeratinizing derivative (XBF) or a keratinizing epithelial cell line (XB) is proposed as the basis of a qualitative/semi-quantitative bioassay for "dioxin-like" activity in environmental samples.

Gierthy, J.F., and Crane, D. 1985b. In vitro bioassay for dioxin-like compounds. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Other dermal effects, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Abstract

This is an abstract of Gierthy and Crane (1985a).

Gillner, M., Fernstrom, B., Gustafsson, J.-A., Cambilleau, C., and Bergman, J. 1985. A new structure-affinity relationship for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) receptor binding. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Abstract

This abstract describes studies in which empirical results of the relative binding affinities of various dioxin congeners were used to develop a computer model of the Ah receptor site. The resulting model, which takes into account Van der Waals' radii of atoms, suggests that all molecules that bind to the active site are relatively flat and fit a rectangle of 7 x 14 Angstroms.

Goldstein, J.A., and Hardwick, J. 1984. Regulation of a multigene family of P-450 isozymes by 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: BiologicalMechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 119-133

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

The authors review experimental evidence that the TCDD-receptor complex regulates the function of several sturctural genes that govern the transcription of a number of proteins including several cytochrome P-450 isozymes. Differences in gene expression between hepatic and non-hepatic tissues are noted.

Gonzalez, F.J., Kimura, S., and Nebert, D.W. 1985. Comparison of the flanking regions and introns of the mouse 2,3,7,8-tetrachlorodibenzo-p-dioxin-inducible cytochrome P1-450 and P3-450 genes. J. Biol. Chem. 260:5040-5049

KEYWORDS: Chlorinated dibenzo-p-dioxins, Enzyme induction or inhibition, Cultured mammalian cells, Mouse

Gough, M. 1985. Dioxin exposure at Monsanto. Nature 318:504

KEYWORDS: Cancer, Cardiovascular effects, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Commentary

Greenlee, W.F., Dold, K.M., and Osborne, R. 1984a. A proposed model for the actions of TCDD on epidermal and thymic epithelial target cells. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 435-444

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Other toxic effect, Immunological effects, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Review

Greenlee, W.F., Osborne, R., Hudson, L.G., and Toscano, W.A., Jr. 1984b.

Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 365-372

KEYWORDS: Other dermal effects, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Review

Greenlee, W.F., Dold, K.M., and Osborne, R. 1985a. Actions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on human epidermal keratinocytes in culture. In Vitro Cell. & Develop. Biol. 21:509-512

KEYWORDS: Chloracne, Other dermal effects, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Greenlee, W.F., Dold, K.M., Irons, R.D., and Osborne, R. 1985b. Evidence for direct action of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on thymic epithelium. Toxicol. Appl. Pharmacol. 79:112-120

KEYWORDS: Immunological effects, Mechanism of toxic action, Other toxic effect, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Greenlee, W.F., Osborne, R., Cook, J., Dold, K.M., Ross, L., Hudson, L.G., and Toscano, W.A. 1985c. Studies on the mechanisms of action of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on epithelial target cells. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Mechanism of toxic action, Other toxic effect, Other dermal effects, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Abstract

Greig, J. 1984. Differences between skin and liver toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mice. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 391-397

KEYWORDS: Hepatic effects, Mechanism of toxic action, Other dermal effects, Chlorinated dibenzo-p-dioxins

In this study of the response of different strains of mice to acutely toxic doses of TCDD it is shown that hepatic porphyria and the development of skin lesions are independent responses apparently under the control of separate gene loci.

Gustafsson, J-A., Poellinger, L., Lund, J., Gillner, M., and Hansson, L-A. 1984. Physicochemical characteristics of the TCDD receptor. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 153-160

KEYWORDS: Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

This is a review of studies of the properties of the hepatic TCDD receptor and a comparison of the properties of the receptor with those of steroid hormone receptors. This review is similar in content to Poellinger et al. 1985a.

Hahn, M.E., Gasiewicz, T.A., Goldstein, J.A., and Linko, P. 1985. Effect of hexachlorobenzene on the specific binding of 2,3,7,8-TCDD to the hepatic Ah receptor. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Porphyria cutanea tarda, Mechanism of toxic action, In vitro study, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat, Abstract

This abstract describes studies undertaken to investigate the interaction of hexachlorobenzene (HCB) with the Ah receptor. HCB was investigated because, like TCDD, it induces AHH and causes PCT. No evidence of receptor binding was found.

Hakansson, H., and Ahlborg, U.G. 1985. The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the uptake, distribution and excretion of a single oral dose of [11,12-3H]retinyl acetate and on the vitamin A status in the rat. J. Nutr. 115:759-771

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Hepatic effects, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat

Hakansson, H., Ahlborg, U.G., and Gottling, L. 1985. The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the distribution and excretion of the endogenous pool of vitamin A in the rat. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Hepatic effects, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat, Abstract

Hall, W., and MacPhee, D. 1985. The Agent Orange controversy in Australia: A contribution to the debate. Community Health Studies 9:109-119

KEYWORDS: Cancer, Epidemiologic investigation, Neurobehavioral effects, Reproductive effects, Environmental exposure, Phenoxy herbicide formulations, Human, Review, Commentary

In this review the authors examine claims made by the Vietnam Veterans' Association of Australia that exposure of Australian

servicemen in Vietnam has led to increased rates of cancer, defective births, and psychiatric disorders. They conclude that the claim of birth defects can be rejected and it is unlikely that there has been an increased incidence of cancer or psychiatric disorders. (45 references)

Hardell, L. 1985. On the relation of soft-tissue sarcoma and malignant lymphoma to exposure to phenoxy acids or chlorophenols: An updated overview of the Swedish studies. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Phenoxy herbicide formulations, Human, Review, Abstract

This abstract of a symposium presentation briefly describes the results of epidemiologic studies performed by the author showing an association between exposure to phenoxy herbicides and soft-tissue sarcoma and lymphoma. These studies have been discussed in Volume VI of this review (see JRB 1981, Clement 1985).

Hardell, L., Donellof, L., Nygren, M., Bansson, M., and Rappe, C. 1985. Levels of polychlorinated dibenzodioxins and dibenzofurans in adipose tissue of patients with soft-tissue sarcoma or malignant lymphoma exposed to phenoxy acids and of unexposed controls. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Cancer, Epidemiologic investigation, Metabolism, Occupational exposure, Phenoxy herbicide formulations, Human, Abstract

Hassan, M.Q., Stohs, S.J., and Murray, W.J. 1985a. Effects of vitamins E and A on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced lipid peroxidation and other biochemical changes in the rat. Arch. Environ. Contam. Toxicol. 14:437-442

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Hepatic effects, Lethality, Mechanism of toxic action, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat

The authors study the effects of vitamins E and A on TCDD-induced lipid peroxidation and reduced glutathione (GSH) levels in rats. Vitamin E protects against lipid peroxidation but not GSH depletion. Vitamin A protects against both lipid peroxidation and GSH depletion. Neither vitamin protects against body weight loss or lethality.

Hassan, M.Q., Stohs, S.J., Murray, W.J., and Birt, D.F. 1985b. Dietary selenium, glutathione peroxidase activity, and toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Toxicol. Environ. Health 15:405-415

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Hepatic effects, Mechanism of toxic action, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat

The authors studied the effect of TCDD on lipid peroxidation and enzymes that protect against lipid peroxidation in the livers of rats. TCDD inhibited selenium-dependent glutathione-peroxidase activity. Also, 0.10 ppm selenium in the diet was protective against TCDD toxicity. No correlation between glutathione peroxidase activity and lipid peroxidation was observed. The human health implications of these findings are unclear.

Hassoun, E.A.-M. 1985. Teratogenicity and in vitro fetal thymus toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin and its congeners: Segregation with the Ah locus. Acta Pharm. Suec. 22:175-176 (abstract)

KEYWORDS: Abstract, Cultured mammalian cells, In vitro study, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Mouse, Teratogenic effects

This abstract briefly summarizes the author's dissertation research, parts of which have been published in detail (Hassoun and Dencker 1982, see Volume IV of this review (Clement 1984)). The mechanism by which the Ah locus is involved in mice by comparing the relative potencies of TCDD, TCDF, and 3,3',4,4'-tetrachloroazoxybenzene; intercrossing strains of various susceptibilities; performing reciprocal transfers of fetuses; and studying an in vitro culture of fetal thymus.

Hay, A., and Silbergeld, E. 1985. Assessing the risk of dioxin exposure. Nature 315:102-103

KEYWORDS: Epidemiologic investigation, Cancer, Chloracne, Occupational exposure, Phenoxy herbicide formulations, Chlorinated dibenzo-p-dioxins, Human, Commentary

In this letter to the editor, the authors criticize the methods used to conduct mortality studies (Zack and Suskind 1980; Zack and Gaffey 1983) among workers from the Monsanto plant at Nitro, West Virginia. The criticism centers on methods used to assign workers to exposed and unexposed cohorts.

Hietanen, E., Ahotupa, M., Heinonen, T., Hamalainen, H., Kunnas, T., Linnainmaa, K., Mantyla, E., and Vainio, H. 1985. Enhanced peroxisomal beta-oxidation of fatty acids and glutathione metabolism in rats exposed to phenoxyacetic acids. Toxicology 34:103-111

KEYWORDS: Hepatic effects, Mechanism of toxic action, Other toxic effect, Oral exposure, 2,4-D and its esters, Rat

Using several measures of peroxisomal proliferation, the authors show that single oral doses of 2,4-D cause modest increases in

peroxisomal enzyme activity and conclude that 2,4-D is a weak peroxisomal proliferator that may induce hyperlipidermia by this mechanism.

Hildebrand, C.E., Gonzalez, F.J., Kozak, C.A., and Nebert, D.W. 1985a. Regional linkage analysis of the dioxin-inducible P-450 gene family on mouse chromosome 9. Biochem. Biophys. Res. Commun. 130:396-406

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

This is a study using the Southern blot hybridization technique to assess structural characteristics of two dioxin-inducible P-450 genes in mice and hamsters. These genes are located near the Mpi-1 locus in the middle portion of mouse chromosome 9.

Hildebrand, C.E., Gonzalez, F.J., McBride, O.W., and Nebert, D.W. 1985b. Assignment of the human 2,3,7,8-tetrachlorodibenzo-p-dioxin-inducible cytochrome P1-450 gene to chromosome 15. Nucleic Acids Res. 13:2009-2016

KEYWORDS: Chlorinated dibenzo-p-dioxins, Enzyme induction or inhibition, Human, Mouse, Hamster

Hildebrand, C.E., Stallings, R.L., Gonzalez, F.J., and Nebert, D.W. 1985c. Assignment of dioxin-inducible cytochrome P-450 gene family to Chinese hamster chromosome 4. Somatic Cell Genet. 11:391-395

KEYWORDS: Chlorinated dibenzo-p-dioxins, Enzyme induction or inhibition, Hamster, Cultured mammalian cells, In vitro study, Other study objective

Hill, R.H. 1985. Effects of polyhalogenated aromatic compounds on porphyrin metabolism. Environ. Health Perspect. 60:139-143

KEYWORDS: Porphyria cutanea tarda, Chlorinated dibenzo-p-dioxins, 2,4,5-T and its esters, Human, Review

The author defines porphyria and reviews the evidence that chronic hepatic porphyria and porphyria cutanea tarda are associated with exposure to halogenated aromatic hydrocarbons. TCDD and 2,4,5-T are two of the compounds discussed. (26 references)

Hiremath, C.B., Bayliss, D.L., and Bayard, S. 1985. Qualitative and quantitative cancer risk assessment of 2,3,7,8-tetrachloro-dibenzo-p-dioxin (2,3,7,8-TCDD). Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This abstract summarizes the procedure followed by the Carcinogen Assessment Group of the U.S. Environmental Protection Agency to estimate the risk of cancer among humans consuming water containing 1 ng/liter TCDD or breathing air containing 1 pg/m^3 TCDD.

Hoar, S.K., Blair, A., Holmes, F.F., Boysen, C., and Robel, R.J. 1985. Herbicides and colon cancer. Lancet 1:1277-1278

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Phenoxy herbicide formulations, Human

Hobson, L.B. 1984. Human effects of TCDD exposure. Bull. Environ. Contam. Toxicol. 33:696-701

KEYWORDS: Chloracne, Cancer, Porphyria cutanea tarda, Reproductive effects, Environmental exposure, Occupational exposure, Chlorinated dibenzo-p-dioxins, Human, Review

In this symposium talk the author reviews the available information on the human health effects of PCDDs and concludes that the available evidence for an association between exposure to these compounds and most of the postulated adverse effects is inconclusive. (6 references)

Houk, V.N. 1985. Uncertainties in dioxin risk assessment. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Reproductive effects, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This abstract describes some assumptions and the uncertainties that result when these assumptions are applied to assessing the risks of adverse human health effects from exposure to dioxin-contaminated soil.

Houk, V.N., and Stehr, P.A. 1985. Status of Centers for Disease Control dioxin studies of U.S. populations. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Epidemiologic investigation, Reproductive effects, Other toxic effect, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This abstract of a symposium presentation summarizes the status of studies conducted by the United States Centers for Disease Control on the health effects of dioxins in exposed human populations. Included are epidemiological studies of humans

exposed to dioxin in soil, reproductive toxicity surveys, and a study of adipose tissue levels.

Hudson, L.G., Toscana, W.A., Jr., and Greenlee, W.F. 1985. Regulation of epidermal growth factor binding in a human keratinocyte cell line by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 77:251-259

KEYWORDS: Mechanism of toxic action, Other dermal effects, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Ideo, G., Bellati, G., Bellobuono, A., and Bissanti, L. 1985. Urinary D-glucaric acid excretion in the Seveso area, polluted by tetrachlorodibenzo-p-dioxin (TCDD): Five years of experience. Environ. Health Perspect. 60:151-157

KEYWORDS: Epidemiologic investigation, Enzyme induction or inhibition, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human

This paper is identical to Ideo (1984) which was reviewed in Volume V of this review (Clement 1985).

Israel, D.I., Estolano, M.G., Galeazzi, D.R., and Whitlock, J.P. 1985. Superinduction of cytochrome P_1-450 gene transcription by inhibition of protein synthesis in wild type and variant mouse hepatoma cells. J. Biol. Chem. 260:5648-5653

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

In this study the simultaneous addition of TCDD and cyclohexinide (an inhibitor of protein synthesis) to a culture of Hexa 1c1c7 cells resulted in a ten-fold higher induction of cytochrome P-450 mRNA than did TCDD by itself implying a second control mechanism for the regulation of cytochrome P-450 gene transcription.

Jaiswal, A.K., Gonzalez, F.J., and Nebert, D.W. 1985a. Human dioxin-inducible cytochrome P_1-450: Complementary DNA and amino acid sequence. Science 228:80-83

KEYWORDS: Chlorinated dibenzo-p-dioxins, Enzyme induction or inhibition, Cultured mammalian cells, Human

Jaiswal, A.K., Nebert, N.W., and Eisen, H.W. 1985b. Comparison of aryl hydrocarbon hydroxylase and acetanilide 4-hydroxylase induction by polycyclic aromatic compounds in human and mouse cell lines. Biochem. Pharmacol. 34:2721-2731

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

In this study the authors assess the ability of TCDD to induce aryl hydrocarbon hydroxylase (AHH) activity in cultured human breast cancer cells in culture. Despite the fact that TCDD induces AHH activity in these cells, no receptor similar to that found in other mammalian cells for TCDD could be found by a variety of methods, suggesting that the presence of such a receptor may not be required for AHH induction.

Jansing, R.L., and Shain, W. 1985. Aryl hydrocarbon hydroxylase induction in adult rat hepatocytes in primary culture by several chlorinated aromatic hydrocarbons including 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fund. App. Toxicol. 5:713-720

KEYWORDS: Other study objective, Hepatic effects, Enzyme induction or inhibition, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

The authors investigated the ability of TCDD and related chlorinated aromatic hydrocarbons to induce aryl hydrocarbon hydroxylase (AHH) activity in primary cultures of adult rat hepatocytes. 2,3,7,8-TCDD induced AHH activity at concentrations as low as 10^{-11}M. The activity of other structural analogues correlated with their relative activity in other bioassays.

John-Greene, J.A., Ouellette, J.H., Jeffries, T.K., Johnson, K.A., and Rao, K.S. 1985. Teratological evaluation of picloram potassium salt in rabbits. Food Chem. Toxicol. 23:753-756

KEYWORDS: Reproductive effects, Teratogenic effects, Oral exposure, Picloram, Rabbit

Jones, P.B.C., Galeazzi, D.R., Fisher, J.M., and Whitlock, J.P. 1985. Control of cytochrome P1-450 gene expression by dioxin. Science 227:1499-1502

KEYWORDS: Chlorinated dibenzo-p-dioxins, Enzyme induction or inhibition, Cultured mammalian cells, Mouse

Kaye, C.I., Rao, S., Simpson, S.J., Rosenthal, F.S., and Cohen, M.M. 1985. Evaluation of chromosomal damage in males exposed to Agent Orange and their families. J. Craniofacial Genetics & Developmental Biol. Suppl. 1:259-265

KEYWORDS: Phenoxy herbicide formulations, Environmental exposure, Epidemiologic investigation, Genotoxicity, Cultured mammalian cells, Human

Kelling, C.K., Christian, B.J., Inhorn, S.L., and Peterson, R.E. 1985. Hypophagia-induced weight loss in mice, rats, and guinea pigs treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fundam. Appl. Toxicol. 5:700-712

KEYWORDS: Acute toxic effects, Hepatic effects, Mechanism of toxic action, Other toxic effect, Oral exposure, Exposure by injection, Chlorinated dibenzo-p-dioxins, Guinea pig, Rat, Mouse

In this study of the mechanism of acute toxicity of TCDD, the authors measure body weight loss and food intake in rats, mice and guinea pigs given a single acutely toxic dose of TCDD. Comparison of treated animals with pair-fed controls indicates that hypophagia accounts for the weight loss seen in treated animals.

Kerkvliet, N.I., Brauner, J.A., and Matlock, J.P. 1985. Humoral immunotoxicity of polychlorinated diphenyl ethers, phenoxyphenols, dioxins and furans present as contaminants of technical grade pentachlorophenol. Toxicology 36:307-324

KEYWORDS: Immunological effects, Oral exposure, Herbicide impurities other than PCDDs, Mouse

The authors studied the effect of impurities found in technical pentachlorophenol, including hexachlorodibenzo-p-dioxin and heptachlorodibenzo-p-dioxin, on humoral immunity in mice. These dioxins, like TCDD, suppressed antibody responses in mice after a single oral dose.

Kester, J.E., and Gasiewicz, T.A. 1985. Rat liver Ah receptor: Chemical affectors of stability and TCDD binding. Chemosphere 14:967-970

KEYWORDS: Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Kimbrough R.D. 1984. The epidemiology and toxicology of TCDD. Bull. Environ. Contam. Toxicol. 33:636-647

KEYWORDS: Chloracne, Cancer, Enzyme induction or inhibition, Mechanism of toxic action, Neurobehavioral effects, Reproductive effects, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review

In this talk, presented at a symposium, the author reviews the results of animal experiments, human epidemiology studies and case reports to assess the current state of knowledge regarding the health effects of exposure to chlorinated dioxins, especially 2,3,7,8-TCDD. The author also reviews the role of CDC in the discovery of extensive dioxin contamination in Missouri. (18 references)

Kimbrough, R.D. 1985. Laboratory and human studies on polychlorinated biphenyls (PCBs) and related compounds. Environ. Health Perspec. 59:99-106

KEYWORDS: Cancer, Epidemiologic investigation, Reproductive effects, Metabolism, Chlorinated dibenzo-p-dioxins, Review

The author reviews the effects of halogenated aromatic hydrocarbons in humans and experimental animals. The emphasis is on PCBs and PBBs but a number of the most relevant studies of TCDD effects are discussed. (77 references)

Kimbrough, R.D., Falk, H., Stehr, P., and Fries, G. 1984. Health implications of 2,3,7,8-tetrachlorodibenzodioxin (TCDD)contamination of residential soil. J. Toxicol Environ. Health 14:47-93

KEYWORDS: Cancer, Reproductive effects, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review

This review and risk assessment is a slightly modified version of the CDC approach that sets 1 ppb TCDD in the soil of residential areas as a level of concern. Earlier versions of this assessment were included in Volume VI of this review (Clement 1985).

Kleopfer, R.D. 1985. 2,3,7,8-TCDD contamination in Missouri. Chemosphere 14:739-744

KEYWORDS: Chloracne, Lethality, Other study objective, Environmental exposure, Chlorinated dibenzo-p-dioxins, Review

In this symposium presentation, the author reviews the history of dioxin contamination in the state of Missouri indicating the source and distribution of that contamination. He also discusses remedial options in depth. (7 references)

Knutson, J.C., and Poland, A. 1984. XB cells: An in vitro model for the differentiation and proliferation response to 2,3,7,8-TCDD. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 381-389

KEYWORDS: Chloracne, Mechanism of toxic action, Other dermal effects, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Review

Kociba, R. 1984. Evaluation of the carcinogenic and mutagenic potential of 2,3,7,8-TCDD and other chlorinated dioxins. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 73-84

KEYWORDS: Cancer, Genotoxicity, Chlorinated dibenzo-p-dioxins, Review

The author reviews studies in experimental animals of the carcinogenic and mutagenic potential of chlorinated dioxins, including TCDD, and concludes that the preponderance of the evidence supports a nongenetic mechanism of carcinogenesis for TCDD. (42 references)

Kociba, R.J. 1985. Concluding summary: Toxicology and epidemiology. Chemosphere 14:717-720

KEYWORDS: Cancer, Epidemiologic investigation, Mechanism of toxic action, Other toxic effect, Chlorinated dibenzo-p-dioxins, Review

This is a summary of the key points of papers that were presented on the toxicology of dioxins at the 4th International Symposium on Chlorinated Dioxins and Related Compounds in Ottawa, Ontario, October 1984.

Kociba, R.J., and Cabey, O. 1985. Comparative toxicity and biologic activity of chlorinated dibenzo-p-dioxins and furans relative to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Chemosphere 14:649-660

KEYWORDS: Acute toxic effects, Chloracne, Cancer, Enzyme induction or inhibition, Genotoxicity, Lethality, Reproductive effects, Other dermal effects, Chlorinated dibenzo-p-dioxins, Review

The authors review quantitative indicators of the biologic activity of chlorinated dibenzo-p-dioxin and dibenzofuran congeners as assessed by in vivo and in vitro responses. The analysis indicates that 2,3,7,8-TCDD is the most active congener and the other congeners have a wide range of biologic activity. (44 references)

Kogan, M.D., and Clapp, R.W. 1985. Mortality among Vietnam veterans in Massachusetts, 1972-1983. Massachusetts Office of Commissioner of Veterans Services, Agent Orange Program, Massachusetts (January 18, 1985) 29 pages

KEYWORDS: Cancer, Epidemiologic investigation, Other toxic effect, Occupational exposure, Phenoxy herbicide formulations, Human

Krowke, R. 1985. Studies on the distribution and embryotoxicity of different PCDDs in mice and marmosets. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Abstract, Chlorinated dibenzo-p-dioxins, Mouse, Metabolism, Teratogenic effects, Other species

This abstract reports that the concentration of TCDD increases over three weeks in marmosets treated with an acute subcutaneous dose of TCDD. In mice, the pregnant state was found to alter the pharmacokinetics of TCDD and 2,3,7,8-TCDD was found to be 4 times more teratogenic than 1,2,3,7,8-PCDD.

Kurl, R.N., and Villee, C.A. 1985. A metabolite of riboflavin binds to the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) receptor. Pharmacology 30:241-244

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Other toxic effect, In vitro study, Chlorinated dibenzo-p-dioxins, Rat

In vitro binding studies using rat liver cytosol preparations show that the TCDD receptor binds lumichrome, a metabolite of riboflavin. Lumichrome competitively inhibits the binding of

TCDD. The authors point out that lumichrome is the first endogenous chemical that has been shown to bind to the receptor but the physiological significance of this binding is unclear.

Kurl, R.N., Loring, J.M., and Ville, C.A. 1985. Control of 2,3,7,8-tetrachlorodibenzo-p-dioxin binding protein(s) in the hamster kidney. Pharmacology 30:245-254

KEYWORDS: Mechanism of toxic action, Renal effects, In vitro study, Chlorinated dibenzo-p-dioxins, Hamster

The authors study the properties of the TCDD receptor present in the kidneys of hamsters. Experiments using castrated and hypophysectionized males reveal that the receptor is under endocrine control but steroid hormones do not compete with TCDD for the receptor.

Lathrop, G.D., Wolfe, W.D., Albanese, R.A., and Moynahan, P.M. 1984. An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 471-474

KEYWORDS: Chloracne, Cancer, Cardiovascular effects, Epidemiologic investigation, Neurobehavioral effects, Reproductive effects, Occupational exposure, Phenoxy herbicide formulations, Human, Review

This is a brief summary of the methods and results of the epidemiologic investigation of health effects in Air Force personnel engaged in herbicide operations in Vietnam, commonly referred to as the Ranch Hand morbidity study. This study was reviewed in Volume VI of this review (Clement 1985).

Lawrence, C.E., Reilly, A.A., Quickenton, P., Greenwald, P., Page, W.F., and Kuntz, A.J. 1985. Mortality patterns of New York State Vietnam veterans. Am. J. Public Health 75:277-279

KEYWORDS: Cancer, Epidemiologic investigation, Environmental exposure, Phenoxy herbicide formulations, Human

This proportional mortality study among Vietnam veterans in New York State was discussed previously (see Volume VI of this review (Clement 1985)).

Luster, M.I., Tucker, A.N., Hong, L., Boorman, G.A., and Patterson, R. 1984. In vivo and in vitro effects of TCDD on stem cell and B cell differentiation. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 411-419

KEYWORDS: Immunological effects, Oral exposure, Chlorinated dibenzo-p-dioxins, Mouse

Luster, M.I., Hong, L.H., Boorman, G.A., Clark, G., Hayes, H.T., Greenlee, W.F., Dold, K., and Tucker, A.N. 1985. Acute myelotoxic responses in mice exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol. Appl. Pharmacol. 81:156-165

KEYWORDS: Acute toxic effects, Hematological effects, Immunological effects, Mechanism of toxic action, Oral exposure, In vitro study, Chlorinated dibenzo-p-dioxins, Mouse

Lynge, E. 1985. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br. J. Cancer 52:259-270

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Phenoxy herbicide formulations, Human

Madhukar, B.V., Brewster, D.W., and Matsumura, F. 1984. Effects of in vivo-administered 2,3,7,8-tetrachlorodibenzo-p-dioxin on receptor binding of epidermal growth factor in the hepatic plasma membrane of rat, guinea pig, mouse, and hamster. Proc. Natl. Acad. Sci. USA 81:7407-7411

KEYWORDS: Acute toxic effects, Hepatic effects, Mechanism of toxic action, Other toxic effect, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat, Guinea pig, Mouse, Hamster

A preprint of this paper was included in Volume VI of this review (Clement 1985). This study suggests that some of the toxic effects of TCDD may be mediated through interference with binding of epidermal growth factor (EGF) to its receptor.

Marlow, D.A., Fingerhut, M.A., and Halperin, W.E. 1985. An exposure matrix for the NIOSH dioxin registry. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Abstract

This abstract of a symposium presentation is a companion to the presentation by Fingerhut et al. 1985 and describes methods used to ascertain and classify potential chlorinated dioxin exposure among workers in the NIOSH dioxin registry mortality study.

Matsumura, F. 1984. Biochemical aspects of action mechanisms of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related chemicals in animals. In Matsumura, F., ed. Differential Toxicities of Insecticides and Halogenated Aromatics. Pergamon Press. Pp. 453-467

KEYWORDS: Enzyme induction or inhibition, Acute toxic effects, Mechanism of toxic action, Hepatic effects, Chlorinated dibenzo-p-dioxins, Review

The author reviews the recent literature relevant to the mechanism of acute toxicity of TCDD with emphasis on enzyme induction and alterations in the function and constituents of plasma membranes. (75 references)

Matsumura, F., Madhukar, B.V., Bombick, D.W., and Brewster, D.W. 1984. Toxicological significance of pleiotropic changes of plasma membrane functions particularly that of EGF receptor caused by 2,3,7,8-TCDD. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 267-287

KEYWORDS: Hepatic effects, Mechanism of toxic action, Other toxic effect, Chlorinated dibenzo-p-dioxins, Review

The authors review studies of the effects of TCDD on the hepatic plasma membrane in rats. Based on their observations they conclude that TCDD modulates receptors for epidermal growth factor (EGF) in a number of tissues. (46 references)

Matsumura, F., Madhukar, B.V., Bombick, D.W., and Brewster, D.W. 1985. Molecular basis of TCDD caused changes in receptors on the hepatic plasma membrane. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Hepatic effects, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Guinea pig, Mouse, Hamster, Abstract

This abstract of a symposium presentation summarizes studies of the effects of TCDD on the plasma membrane of hepatocytes, particularly the EGF receptor. These studies have been published as full papers over the last several years (see Volumes IV and VI of this review (Clement 1984, 1985)).

McConnell, E.E. 1984. Clinicopathologic concepts of dibenzo-p-dioxin intoxication. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 27-37
KEYWORDS: Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

The authors review information on the toxicology of polychlorinated dibenzo-p-dioxins and emphasizes the uniqueness of the large interspecies variability and the long-time course of lethality of these compounds. (41 references)

McConnell, E.E. 1985. Comparative toxicity of PCBs and related compounds in various species of animals. Environ. Health Perspect. 60:29-33

KEYWORDS: Acute toxic effects, Hematological effects, Hepatic effects, Lethality, Chloracne, Other toxic effect, Chlorinated dibenzo-p-dioxins, Other species, Avian species, Guinea pig, Hamster, Nonhuman primate, Mouse, Rat, Rabbit, Review

The author reviews the toxicology of polyhalogenated aromatic hydrocarbons with emphasis on interspecies variability in both sensitivity and qualitative manifestations of toxicity. The review also discusses the relative potencies of these compounds, including the polychlorinated dibenzo-p-dioxins. (33 references)

McKinney, J.D., Chae, K., Oatley, S.J., and Blake, C.C.F. 1985a. Molecular interactions of toxic chlorinated dibenzo-p-dioxins and dibenzofurans with thyroxine binding prealbumin. J. Med. Chem. 28:375-381

KEYWORDS: Mechanism of toxic action, Other toxic effect, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

The authors postulate that the receptor responsible for the toxic effects of TCDD and structurally similar chlorinated aromatic hydrocarbons is different from the receptor responsible for AHH induction. They also postulate that the active site is similar to the thyroxine binding site of thyroxine binding prealbumin. Using computer simulation and in vitro binding assays with structural analogues of TCDD and TCDF they provide supporting evidence for their hypothesis.

McKinney, J.D., Fawkes, J., Jordan, S., Chae, K., Oatley, S., Coleman, R.E., and Briner, W. 1985b. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) as a potent and persistent thyroxine agonist: A mechanistic model for toxicity based on molecular reactivity. Environ. Health Perspect. 61:41-53

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat, Guinea pig, Other species

McMillin, R.B., and Samples, J.R. 1985. Iritis after herbicide exposure. Am. J. Ophthalmol. 99:726-727

KEYWORDS: Other toxic effect, Occupational exposure, 2,4-D and its esters, Human

McNulty, W.P. 1985. Toxicity and fetotoxicity of TCDD, TCDF and PCB isomers in rhesus macaques (Macaca mulatta). Environ. Health Perspect. 60:77-88

KEYWORDS: Hepatic effects, Mechanism of toxic action, Reproductive effects, Subchronic toxic effects, Other dermal effects, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Nonhuman primate

Meyne, J., Allison, D.C., Bose, K., Jordan, S.W., Ridolpho, P.F., and Smith, J. 1985. Hepatotoxic doses of dioxin do not damage mouse bone marrow chromosomes. Mutat. Res. 157:63-69

KEYWORDS: Cytotoxicity, Chlorinated dibenzo-p-dioxins, Genotoxicity, Mouse, Other route of exposure, Acute toxic effects, Hepatic effects

Mittler, J.C., Ertel, N.H., Peng, R.X., Yang, C.S., and Kiernan, T. 1984. Changes in testosterone hydroxylase activity in rat testis following administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Ann. N. Y. Acad. Sci. 438:645-648

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Reproductive effects, Exposure by injection,Chlorinated dibenzo-p-dioxins, Rat

Mofenson, H., Becker, C., Kimbrough, R., Lawrence, R., Lovejoy, F., and Winter, W. 1985. Commentary on 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD). Vet. Hum. Toxicol. 27:434-438

KEYWORDS: Other study objective, Environmental exposure, Occupational exposure, Chlorinated dibenzo-p-dioxins, Human, Review

This is the same report of the Scientific Review Committee of the American Academy of Clinical Toxicology that is published in Clinical Toxicology.

Mofenson, H., Becker, C., Kimbrough, R., Lawrence, R., Lovejoy, F., Winters, W., Carracio, T.R., Hardel, L.K., Rumack, B.H., and Spyker, D. 1985. Commentary on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Clin. Toxicol. 23:191-204

KEYWORDS: Other study objective, Environmental exposure, Occupational exposure, Chlorinated dibenzo-p-dioxins, Human, Review

This is a somewhat superficial review of available information relevant to the human health effects of TCDD prepared by the Scientific Review Committee of the American Academy of Clinical Toxicology. (43 references)

Moore, R.W., Potter, C.L., Theobald, H.M., Robinson, J.A., and Peterson, R.E. 1985. Androgenic deficiency in male rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 79:99-111

KEYWORDS: Acute toxic effects, Reproductive effects, Mechanism of toxic action, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat

Moses, M., and Prioleau, P.G. 1985. Cutaneous histologic findings in chemical workers with and without chloracne with past exposure

to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Am. Acad. Dermatol. 12:497-506

KEYWORDS: Chloracne, Other dermal effects, Occupational exposure, Phenoxy herbicide formulations, Chlorinated dibenzo-p-dioxins, Human

Mukerjee, D., Stara, J.F., Ris, C.H., and Schau, J.L. 1985. Rationale for assessment of risk from exposure to 2,3,7,8-TCDD. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Reproductive effects, Environmental exposure, Chlorinated dibenzo-p-dioxins, Review, Abstract

This abstract of a symposium presentation summarizes the basis of a human health risk assessment of TCDD performed by the Office of Health and Environmental Assessment of the U.S. Environmental Protection Agency.

Mullison, W.R. 1985. A toxicological and environmental review of picloram. Proc. West. Soc. Weed Sci. 38:21-92

KEYWORDS: Picloram, Review

This author summarizes the toxicological and environmental information on picloram and determines that it has low toxicity to mammals, birds, and aquatic organisms. He concludes that use of picloram as an herbicide according to labelled directions does not present a significant risk to wildlife, livestock, pets, or humans.

Nagayama, J., Kiyohara, C., Masuda, Y., and Kuratsune, M. 1985a. Genetically mediated induction of aryl hydrocarbon hydroxylase activity in human lymphoblastoid cells by polychlorinated dibenzofuran isomers and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch. Toxicol. 56:230-235

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Nagayama, J., Kiyohara, C., Nishizumi, M., Horie, A., Handa, S., Yamaguchi, S., and Masuda, Y. 1985b. Comparative toxicologic study with 2,3,7,8-tetrachlorodibenzo-p-dioxin in inbred strains of mice. Chemosphere 14:949-952

KEYWORDS: Enzyme induction or inhibition, Hepatic effects, Lethality, Other toxic effect, Subchronic toxic effects, Exposure by injection, Chlorinated dibenzo-p-dioxins, Mouse

The toxic effects of 6 or 12 weekly injections of TCDD were studied in "responsive" and "non-responsive" strains of mice.

AHH induction and liver pathology were greater in the "responsive" strain.

Nagayama, J., Kuroki, H., Masuda, Y., Handa, S., and Kuratsune, M. 1985c. Genetically mediated induction of aryl hydrocarbon hydroxylase activity in mice by polychlorinated dibenzofuran isomers and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch. Toxicol. 56:226-229

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Hepatic effects, Mechanism of toxic action, Exposure by injection, Chlorinated dibenzo-p-dioxins, Mouse

Neal, R.A. 1985. Mechanisms of the biological effects of PCBs, polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans in experimental animals. Environ. Health Perspect. 60:41-46

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Mechanism of toxic action, Metabolism, Chlorinated dibenzo-p-dioxins, Review

The author reviews information on the mechanism of action of polychlorinated aromatic hydrocarbons, primarily TCDD. Emphasis is placed on observations that neither the concentration nor the affinity of the Ah receptor correlates with acute lethality and that Ah receptor binding is not a sufficient requirement for manifestations of toxicity. (43 references)

Neal, R., Gasiewicz, T., Geiger, L., Olson, J., and Sawahata, T. 1984. Metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian species. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 49-60

KEYWORDS: Metabolism, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

The authors review published information on the metabolism and excretion of TCDD and other chlorinated dioxins as determined in in vivo and in vitro studies. It is concluded that interspecies differences in metabolism and elimination do not correlate with interspecies differences in acute lethal toxicity. (20 references)

Newell, K.W., Ross, A.D., and Renner, R.M. 1984. Phenoxy and picolinic acid herbicides and small-intestinal adenocarcinoma in sheep. Lancet 1:1301-1305

KEYWORDS: Cancer, Epidemiologic investigation, Environmental exposure, Phenoxy herbicide formulations, Other species

Nygren, M., Hansson, M., Rappe, C., Dommellof, L., and Hardell, L. 1985. Analysis of polychlorinated dibenzo-p-dioxins and dibenzofurans in adipose tissue from soft-tissue sarcoma patients and controls. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Metabolism, Cancer, Occupational exposure, Phenoxy herbicide formulations, Chlorinated dibenzo-p-dioxins, Human, Abstract

O'Toole, B.I. 1985. The feasibility of ascertaining exposure to pesticides by self report in Australian Vietnam veterans. Community Health Studies 9:120-130

KEYWORDS: Epidemiologic investigation, Other study objective, Environmental exposure, Phenoxy herbicide formulations, Human

The author, who is one of the authors of the Australian Veterans' Health Studies, describes the methodology used in those studies to determine exposure to Agent Orange in Vietnam. It is concluded that it is virtually impossible to ascertain exposure objectively.

Okey, A.B., Roberts, E.A., Golas, C.L., and Manchester, D.K. 1985. Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): Identification and characterization in human tissues. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Mechanism of toxic action, Other toxic effect, Chlorinated dibenzo-p-dioxins, Human, Abstract

Okino, S.T., Quattrochi, L.C., Barnes, H.J., Osanto, S., Griffin, K.J., Johnson, E.F., and Tukey, R.H. 1985. Cloning and characterization of cDNAs encoding 2,3,7,8-tetrachlorodibenzo-p-dioxin-inducible rabbit mRNAs for cytochrome P-450 isozymes 4 and 6. Proc. Natl. Acad. Sci. USA 82:5310-5314

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Using monoclonal antibody techniques the authors identified the nucleic acid sequence of rabbit DNA that codes for TCDD-inducible mRNA.

Olson, J.R., and Wroblewski, V.J. 1985. Metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in isolated hepatocytes from guinea pigs and rats. Chemosphere 14:979-982

KEYWORDS: Acute toxic effects, Metabolism, In vitro study, Chlorinated dibenzo-p-dioxins, Rat, Guinea pig

In vitro studies of TCDD metabolism by cultured hepatocytes from rats and guinea pigs indicate that TCDD pretreatment causes an increase in TCDD metabolism in the rat but not in the guinea pig.

Osborne, R., Dold, K.M., and Greenlee, W.F. 1984. Cell culture models to study mechanisms of toxicity of chlorinated aromatic compounds to skin and thymus. CIIT Activities 4:1-7

KEYWORDS: Mechanism of toxic action, Other toxic effect, Other dermal effects, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Review

This review focuses on the results of studies of the mechanism by which TCDD causes epidermal proliferation and thymic atrophy. The authors present the results of numerous studies using cultured epithelial cell lines that suggest that these responses are mediated by the Ah receptor and are the result of TCDD-enhanced commitment of these cells to terminal differentiation. (24 references)

Osborne, R., and Greenlee, W.F. 1985. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) enhances terminal differentiation of cultured human epidermal cells. Toxicol. Appl. Pharmacol. 77:434-443

KEYWORDS: Chloracne, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Confluent cultures of normal human epidermal cells were incubated for four days with 10 nM TCDD. Treatment enhanced terminal differentiation and increased keratinization of cells as indicated by histologic appearance, decreased thymidine incorporation, increased envelope formation and decreased EGF binding. The authors speculate that the mechanism for human chloracne involves TCDD binding to the Ah receptor.

Paustenbach, D.J., and Murray, F.J. 1985. A critical examination of assessments of the health risks associated with 2,3,7,8-TCDD in soil. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Other toxic effect, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This is an abstract of a symposium presentation in which the authors critically examine some of the key assumptions involved in establishing "safe" levels for TCDD in environmental media. They conclude that soil levels of TCDD up to 100 ppb may be acceptable in certain non-residential areas.

Pazdernik, T.L., and Rozman, K.K. 1985. Effect of thyroidectomy and thyroxine on 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced immunotoxicity. Life Sci. 36:695-703

KEYWORDS: Acute toxic effects, Immunological effects, Mechanism of toxic action, Other toxic effect, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat

The authors study the role of the thyroid gland in the acute toxicity of TCDD. Thyroidectomy of male rats protected against the immunotoxicity of TCDD as assessed by spleen anti-SRBC assay and against other toxic effects such as body weight loss and thymic involution. Thyroid hormone replacement therapy partially abolished the protective effect.

Pearce, N.E., Smith, A.H., and Fisher, D.O. 1985. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. Am. J. Epidemiol. 121:225-237

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Phenoxy herbicide formulations, Human

Pearce, N.E., Smith, A.H., Howard, J.K., Sheppard, R.A., Giles, H.J., and Teague, C.A. 1985. Case-control study of non-Hodgkin's lymphoma, and exposure to phenoxy herbicides, chlorophenols, fencing work and meat works employment. Br. J. Ind. Med. 29 pages (in press)

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Phenoxy herbicide formulations, 2,4,5-T and its esters, Human

Peterson, R.E., Seefeld, M.D., Christian, B.J., Potter, C.L., Kelling, C.K., and Keesey, R.E. 1984. The wasting syndrome in 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity: Basic features and their interpretation. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 291-308

KEYWORDS: Acute toxic effects, Lethality, Mechanism of toxic action, Other toxic effect, Chlorinated dibenzo-p-dioxins, Review

The authors review studies from their laboratory of the wasting syndrome which occurs in rats, mice, and guinea pigs following an acutely toxic dose of TCDD. They conclude that TCDD lowers the level of regulated body weight in a dose-dependent fashion and that hypophagia occurs as a result.

Pocchiari, F., Cattabeni, F., Porta, G.D., Fortunati, U., Silano, V., and Zapponi, G. 1985. Exposure assessment in the Seveso area to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Other toxic effect, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Abstract

This abstract describes an exposure assessment which was performed in Seveso, Italy to estimate the daily intake of TCDD and other chlorinated dioxins by humans living in an area where the average soil TCDD level was 12 ppt.

Poellinger, L., and Gullberg, D. 1985. Characterization of the hydrophobic properties of the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Mol. Pharmacol. 27:271-276

KEYWORDS: Hepatic effects, Mechanism of toxic action, Other study objective, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Gel permeation chromatography studies of liver cytosol from male Sprague-Dawley rats indicate that the TCDD receptor is retained (adsorbed to) hydrophobically interacting matrices. In this respect, the TCDD receptor is more hydrophobic than are steroid hormone receptors.

Poellinger, L., Lund, J., and Gustafsson, J.A. 1985a. The rat liver receptor protein for 2,3,7,8-tetrachlorodibenzo-p-dioxin: A comparison with steroid hormone receptors. Chemosphere 14:963-966

KEYWORDS: Hepatic effects, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

In this paper, presented at a symposium, the authors reviews data published in other articles that suggest similarities in size, shape and physico-chemical properties between the cytosolic "TCDD receptor" and monomeric steroid hormone receptors.

Poellinger, L., Lund, J., and Gustafsson, J.A. 1985b. The receptor for 2,3,7,8-TCDD: Structure, possible functions and relationship to endocrine receptors: An overview. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review, Abstract

This is an abstract of a symposium presentation in which the authors present an overview of the current state of knowledge regarding the structure and biochemical properties of the cytosolic receptor that binds TCDD.

Poellinger, L., Wilhelmsson, A., Lund, J., and Gustafsson, J.A. 1985c. Biochemical characterization of the rat liver receptor for 2,3,7,8-TCDD: A comparison to the rat liver glucocorticoid receptor. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Mechanism of toxic action, Other toxic effect, Chlorinated dibenzo-p-dioxins, Review, Abstract

This is an abstract of a symposium presentation in which the authors discuss the similarities between the Ah receptor and

the steroid hormone receptor. Both appear to regulate the rate of transcription of their target genes and have similar physico-chemical properties.

Poiger, H., and Buser, H.-R. 1984. The metabolism of TCDD in the dog and rat. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 39-47

KEYWORDS: Metabolism, Oral exposure, Chlorinated dibenzo-p-dioxins, Dog, Rat

Poiger, H. 1985. Pharmacokinetics and metabolism of PCDD/PCDF: An overview. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Metabolism, Chlorinated dibenzo-p-dioxins, Review, Abstract

This is an abstract of a symposium presentation in which the author reviews studies on the pharmacokinetics and metabolism of TCDD. Current evidence suggests that PCDDs and PCDFs may be eliminated more slowly by primates than by rodents.

Poiger, H., and Schlatter, C. 1985a. Influence of phenobarbital and TCDD on the hepatic metabolism of TCDD in the dog. Experientia 41:376-378

KEYWORDS: Enzyme induction or inhibition, Metabolism, Oral exposure, Chlorinated dibenzo-p-dioxins, Dog

Poiger, H., and Schlatter, C. 1985b. Pharmacokinetics of 2,3,7,8-TCDD in man. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Acute toxic effects, Metabolism, Oral exposure, Chlorinated dibenzo-p-dioxins, Human, Abstract

Poland, A. 1984. Reflections on the mechanism of action of halogenated aromatic hydrocarbons. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mecahnisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 109-117

KEYWORDS: Mechanism of toxic action, Enzyme induction or inhibition, Other toxic effect, Chlorinated dibenzo-p-dioxins, Review

This review serves as an introduction to a series of papers on the mechanism of action and the role of receptor binding of TCDD. It is a summary of a variety of experimental studies aimed at identifying the role of the Ah receptor. (2 references)

Poland, A., Knutson, J.C., and Glover, E. 1984. Histologic changes produced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in the skin of mice carrying mutations that affect the integument. J. Invest. Dermatol. 83:454-459

KEYWORDS: Acute toxic effects, Chloracne, Mechanism of toxic action, Other dermal effects, Dermal exposure, Chlorinated dibenzo-p-dioxins, Mouse, Rat, Rabbit

Powell, R.L. 1984. Dioxin in Missouri: 1971-1983. Bull. Environ. Contam. Toxicol. 33:648-654

KEYWORDS: Other study objective, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review

In this talk, presented at a symposium, the author reviews the history of environmental contamination by TCDD in the State of Missouri and the responses to that contamination.

Pratt, R.M. 1985. Receptor-dependent mechanisms of glucocorticoid and dioxin-induced cleft palate. Environ. Health Perspect. 61:35-40

KEYWORDS: Chlorinated dibenzo-p-dioxins, Mechanism of toxic action, Teratogenic effects, Mouse, Review

The author summarized how the propensity for formation of cleft palate in various strains of mice is correlated with their carrying the gene for the high affinity Ah receptor for TCDD. This receptor is expressed in the affected tissue in the embryo. Binding with TCDD alters terminal differentiation of these medical epithelial cells and prevents fusion of the palate.

Pratt, R.M., Grove, R.I., Kim, C.S., Dencker, L., and Diewert, V.M. 1984. Mechanism of TCDD-induced cleft palate in the mouse. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 61-71

Puhvel, S.M., Reisner, R.M., and Ertl, D.C. 1985a. Effect of TCDD on murine epidermal keratinocytes in vitro. Chemosphere 14:971-973

KEYWORDS: Other dermal effects, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Puhvel, S.M., Sakamoto, M., and Reisner, R.M. 1985b. Localization of TCDD in hairless mouse skin. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Other dermal effects, Metabolism, Exposure by injection, Chlorinated dibenzo-p-dioxins, Mouse, Abstract

This is an abstract of a study in which the authors measured the distribution of radiolabelled TCDD in hairless mice after a single injection. TCDD achieved significant concentrations in the skin at 12 hours, indicating that skin effects are probably direct rather than secondary to systemic intoxication.

Rice, R.H., and Cline, P.R. 1984. Response of malignant epidermal keratinocytes to 2,3,7,8-TCDD. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 373-380

KEYWORDS: Chloracne, Mechanism of toxic action, Other dermal effects, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Review

Rifkind, A.R., Hattori, Y., Levi, R., Hughes, M.J., Quilley, C., and Alonso, D.R. 1984. The chick embryo as a model for PCB and dioxin toxicity: Evidence of cardiotoxicity and increased prostaglandin synthesis. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 255-266

KEYWORDS: Avian species, Chlorinated dibenzo-p-dioxins, Cardiovascular effects, Hepatic effects, Other toxic effect, Mechanism of toxic action, Review

The authors discussed the use of the chick embryo as an in vivo model in which several end points can be used to direct the mechanism of action of a toxin. Most of the work concerned polychlorinated biphenyls (PCBs). In this system, TCDD induced P-448 but did not increase mortality unlike PCBs that induced P-448, supporting the hypothesis that enzyme induction does not alone or directly produce toxicity.

Rifkind, A.B., Sassa, S., Reyes, J., and Muschuck, H. 1985. Polychlorinated aromatic hydrocarbon lethality, mixed-function oxidase induction, and uroporphyrinogen decarboxylase inhibition in the chick embryo: Dissociation of dose-response relationships. Toxicol. Appl. Pharmacol. 78:268-279

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Porphyria cutanea tarda, Lethality, In vitro study, Chlorinated dibenzo-p-dioxins, Avian species

The authors studied the effects of a single injection of TCDD on the embryo when injected directly into chicken eggs. Hepatic mixed function oxidase activity was maximally induced at doses below those which caused lethality or other toxic effects in the embryos. TCDD also had no effect on hepatic porphyrin levels or uroporphyrin decarboxylase activity in this assay system.

Roberts, E.A., Shear, N.H., Okey, A.B., and Manchester, D.K. 1985. The Ah receptor and dioxin toxicity: From rodent to human tissues. Chemosphere 14:661-674

KEYWORDS: Mechanism of toxic action, Enzyme induction or inhibition, Chlorinated dibenzo-p-dioxins, Review

Robertson, L.W., Regel, U., Filser, J.G., and Oesch, F. 1985. Absence of lipid peroxidation as determined by ethane exhalation in rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Arch. Toxicol. 57:13-16

KEYWORDS: Acute toxic effects, Hepatic effects, Mechanism of toxic action, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat

The authors measure ethane exhalation as an indication of lipid peroxidation in rats given a single i.p. dose of TCDD and conclude that TCDD does not cause lipid peroxidation. These findings are in contrast to previous findings of Stohs et al. 1984.

Rowley, B., and Sweeney, G.D. 1984. Release of ferrous iron from ferritin by liver microsomes: A possible role in the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Can. J. Biochem. Cell Biol. 62:1293-1300

KEYWORDS: Enzyme induction or inhibition, Hepatic effects, Mechanism of toxic action, Porphyria cutanea tarda, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat

Based on previous studies that iron deficiency partially protected against the acute toxic effects of TCDD, the authors study the influence of TCDD on a microsomal enzyme system that released ferous iron from ferritin. Although TCDD induces cytochrome P-450 it does not induce the ferritin iron reductase system.

Rozman, K. 1984a. Hexadecane increases the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): Is brown adipose tissue the primary target in TCDD-induced wasting symdrome? Biochem. Biophys. Res. Commun. 125:996-1004

KEYWORDS: Acute toxic effects, Lethality, Mechanism of toxic action, Metabolism, Other toxic effect, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat

The author investigated the mechanism of acute toxicity of TCDD in rats. Feeding of hexadecane, an aliphatic hydrocarbon, to rats prior to TCDD treatment increased the biliary excretion of TCDD but also increased the lethality indicating that rate of elimination was not important in determining acute letahlity.

Rozman, K.K. 1984b. Role of thyroid hormones and brown adipose tissue in the toxicity of TCDD. In Poland, A. and Kimbrough, R.D.,

eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 345-354

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Other toxic effect, Chlorinated dibenzo-p-dioxins, Review

The author reviews studies of the mechanism of acute toxicity of TCDD. Much of the work reviewed is published in Rozman 1984a, Rozman et al. 1985 and Pazdernik and Rozman 1985.

Rozman, K., Hazelton, G.A., Klaassen, C.D., Arlotto, M.P., and Parkinson, A. 1985. Effect of thyroid hormones on liver microsomal enzyme induction in rats exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicology 37:51-63

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Mechanism of toxic action, Other toxic effect, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat

Thyroidectomy of male rats prior to treatment with TCDD does not alter the ability of TCDD to induce cytochrome P-450 or microsomal AHH activity even though it protects against the acute toxic effects of TCDD suggesting that AHH induction and acute toxicity may not be directly related.

Safe, S., Sawyer, T., Bandiera, S., Safe, L., Zmudzka, B., Mason, G., Romkes, M., Denomme, M.A., and Fujita, T. 1984. Binding to the 2,3,7,8-TCDD receptor and AHH/EROD induction: In vitro QSAR. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 135-149

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, Other toxic effect, In vitro study, Chlorinated dibenzo-p-dioxins, Rat

The authors summarize quantitative structure-activity relationships for AHH induction and receptor binding among series of chlorinated dibenzo-p-dioxins, chlorinated dibenzofurans and chlorinated biphenyls.

Safe, S., and Mason, G. 1985. Synthesis, biologic and toxic properties of 2,3,7,8-TCDD metabolites. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Acute toxic effects, Metabolism, Enzyme induction or inhibition, Other toxic effect, Unspecified route of exposure, Herbicide impurities other than PCDDs, Rat, Abstract

This is an abstract of a study in which the authors synthesized 2-hydroxy-3,7,8-trichlorodibenzo-p-dioxin, a major urinary metabolite of 2,3,7,8-TCDD, and administered it to immature male Wistar rats. The metabolite was over three orders of

magnitude less active than the parent compound as determined by body weight loss, thymic atrophy, enzyme induction, and receptor binding.

Safe, S., Fujita, T., Homonko, K., and Denomme, M.A. 1985a. Properties of the 2,3,7,8-TCDD receptor: A QSAR approach. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Rat, Mouse, Hamster, Guinea pig, Abstract

This abstract of a symposium presentation describes studies of the affinity for dioxin congeners of the Ah receptor from several species in order to derive quantitative structure-activity relationships. Significant interspecies differences are described.

Safe, S., Piskorska-Pliszczynska, J., Denomme, M.A., Leece, B.A., Towner, R., and Li, S.M.A. 1985b. Modulation of 2,3,7,8-TCDD hepatic cytosolic receptor levels by PCBs and organochlorine pollutants. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Hepatic effects, Mechanism of toxic action, Unspecified route of exposure, Chlorinated dibenzo-p-dioxins, Rat, Abstract

This is an abstract describing a study of the potential for various halogenated aromatic hydrocarbons to elevate hepatic TCDD receptor levels in rats. Among chlorinated biphenyls, those which were least likely to bind to the receptor were most effective in elevating receptor levels.

Safe, S., Bandiera, S., Sawyer, T., Zmudzka, B., Mason, G., Romkes, M., Denomme, M.A., Sparling, J., Okey, A.B., and Fujita, T. 1985c. Effects of structure on binding to the 2,3,7,8-TCDD receptor protein and AHH induction - halogenated biphenyls. Environ. Health Perspect. 61:21-33

KEYWORDS: Mechanism of toxic action, Enzyme induction or inhibition, Exposure by injection, In vitro study, Chlorinated dibenzo-p-dioxins, Rat, Cultured mammalian cells

This paper describes a study of quantitative structure-activity relationships (QSAR) among a large group of halogenated biphenyls using TCDD as a reference point. The activities measured were in vivo AHH activity (rats), in vitro AHH activity, in vitro ethoxyresorufin O-deethylase activity, and in vitro binding to the Ah receptor (rat liver cytosol).

Safe, S., Mason, G., Keys, B., Farell, K., Zmudzka, B., Sawyer, T., Piskorska-Plazczynska, J., Safe, L., Romkes, M., and Bandiera,

S. 1985d. Polychlorinated dibenzo-p-dioxins and dibenzofurans: Correlation between in vitro and in vivo structure-activity relationships (SARs). Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Enzyme induction or inhibition, Hepatic effects, Other toxic effect, Chlorinated dibenzo-p-dioxins, Rat, Mouse, Cultured mammalian cells, Abstract

This abstract of a symposium presentation describes quantitative structure-activity studies of polychlorinated dibenzofurans using both in vivo and in vitro effects.

Sassa, S., De Verneuil, H., and Kappas, A. 1984. Inhibition of uroporphyrinogen decarboxylase activity in polyhalogenated aromatic hydrocarbon poisoning. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 215-224

KEYWORDS: Hepatic effects, Porphyria cutanea tarda, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Review

The authors review studies of the effects of polychlorinated aromatic hydrocarbons including TCDD on the activity of uroporphyrin decarboxylase and ALA synthase in in vitro systems. Their results suggest that these compounds require metabolic activation in order to inhibit uroporphyrin decarboxylase activity.

Schecter, A., Schaffner, F., Tiernan, T., and Taylor, M. 1984. Ultrastructural alterations of liver mitochondria in response to dioxins, furans, PCBs, and biphenylenes. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 177-190

KEYWORDS: Hepatic effects, Occupational exposure, Chlorinated dibenzo-p-dioxins, Herbicide impurities other than PCDDs, Human

Schecter, A. 1985. The Binghamton state office building revisited. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Hepatic effects, Metabolism, Occupational exposure, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Abstract

This is an abstract of a symposium presentation in which the author reviews the circumstances of, and the follow-up of, a PCB transformer fire in an office building in Binghamton, New York. Some PCDDs were present in the soot from this fire.

Some exposed individuals experienced health problems which may or may not have been related to the exposure.

Schecter, A., and Ryan, J.J. 1985. Dioxin and furan levels in human adipose tissue from exposed and control populations. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Metabolism, Occupational exposure, Chlorinated dibenzo-p-dioxins, Herbicide impurities other than PCDDs, Human, Abstract

This abstract of a symposium presentation describes analyses of human adipose tissues for polychlorinated dibenzo-p-dioxins and dibenzofurans. One individual who was exposed to soot from the Binghamton State Office Building fire had elevated levels of polychlorinated dibenzofurans and the congener pattern was similar to that in the soot.

Schecter, A., Gasiewicz, T.A., Eisen, H., and Schaffner, F. 1985a. Ultrastructural alterations in liver cells of humans, rats, and mouse hepatoma cells in response to 2,3,7,8-tetrachloro-dibenzo-p-dioxin and related compounds. Chemosphere 14:939-944

KEYWORDS: Acute toxic effects, Hepatic effects, Exposure by injection, In vitro study, Occupational exposure, Chlorinated dibenzo-p-dioxins, Herbicide impurities other than PCDDs, Cultured mammalian cells, Rat, Human

Schecter, A., Ryan, J.J., Weerasinghe, N.C.A., and Gross, M. 1985b. Chlorinated dibenzodioxins and dibenzofurans in human tissues from Vietnam. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Epidemiologic investigation, Metabolism, Environmental exposure, Phenoxy herbicide formulations, Human, Abstract

This abstract describes a study of adipose tissue levels of PCDDs and PCDFs in individuals from various geographical areas of Vietnam. No results are included in the abstract. A more recent report of this study and its results are included in Schecter et al. 1985c.

Schecter, A., Ryan, J.J., Gross, M., Constable, J., Baughman, R., and Meselson, M. 1985c. Comparisons of dioxin and furan exposed populations in North America and in Vietnam, 1970-1984. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Metabolism, Environmental exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Abstract

Schecter, A., Tiernan, T., Schaffner, F., Taylor, M., Gitlitz, G., VanNess, G.F., Garrett, J.H., and Wagel, D.J. 1985d. Patient fat biopsies

for chemical analysis and liver biopsies for ultrastructural characterization after exposure to polychlorinated dioxins, furans and PCBs. Environ. Health Perspect. 60:241-254

KEYWORDS: Hepatic effects, Metabolism, Other toxic effect, Occupational exposure, Chlorinated dibenzo-p-dioxins, Herbicide impurities other than PCDDs, Human

Schiller, C.M., Walden, R., Chapman, D.E., and Shoaf, C.R. 1984. Metabolic impairment associated with a low dose of TCDD in adult male Fischer rats. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 319-331

KEYWORDS: Acute toxic effects, Hepatic effects, Mechanism of toxic action, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat

This study looks at the effect of TCDD on serum lipids and hepatic lipid metabolism and storage in rats following oral administration of a single, acutely-toxic dose. TCDD causes a dramatic increase in serum triglycerides and cholesterol and lipid accumulation in the intestinal mucosa.

Schiller, C.M., Adcock, C.M., Moore, R.A., and Walden, R. 1985a. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and fasting on body weight and lipid parameters in rats. Toxicol. Appl. Pharmacol. 81:356-361

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat

The authors examine the effect of a single oral dose of TCDD on body weight and lipid levels in F-344 rats and conclude that whereas the decreased body weight is similar to those seen in fasted rat serum lipid level changes are not the same and therefore, the acute lethality is not due to simple starvation.

Schiller, C.M., Adcock, C.M., Shoaf, C.R., and Walden, R. 1985b. Alterations in lipid parameters and associated changes in 2,3,7,8-tetrachlorodibenzo-p-dioxin(TCDD)-induced mortality in rats. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Acute toxic effects, Other toxic effect, Mechanism of toxic action, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat, Abstract

This abstract of a symposium talk describes studies that have been published in full (see Schiller et al. 1984 and 1985a).

Schlatter, C. 1985. Toxicological evaluation of dioxins in the environment. Presented at the 5th International Symposium on

Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Metabolism, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review, Abstract

This is an abstract of a symposium presentation in which the author critically reviews approaches used to establish "safe levels" for dioxins in environmental media and compared and contrasted those to approaches used to establish new pesticide or food additive tolerances.

Schulz, C.O. 1985. Reviewing the literature on the health effects of phenoxy herbicides and associated dioxins. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Environmental exposure, Occupational exposure, Phenoxy herbicide formulations, Chlorinated dibenzo-p-dioxins, Review, Abstract

This abstract of a symposium presentation summarizes the status of the Veterans Administration's review of the scientific literature on the health effects of phenoxy herbicides and associated dioxins.

Schulze, G.E., Blake, J.W., and Dougherty, J.A. 1985. The metabolic fate of 2,4-dichlorophenoxyacetic acid-n-butyl ester in the Wistar rat. Arch. Toxicol. 57:231-236

KEYWORDS: Metabolism, Exposure by injection, 2,4-D and its esters, Rat

Schumacher, M.C. 1985. Farming occupations and mortality from non-Hodgkin's lymphoma in Utah. J. Occup. Med. 27:580-584

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Phenoxy herbicide formulations, Human

Seefeld, M.D., Keesey, R.E., and Peterson, R.E. 1984. Body weight regulation in rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 76:526-536

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat

Shepard, B.M., Kang, H.K., Enzinger, F., and Weatherbee, L. 1985. Soft- tissue sarcoma and military service in Vietnam: A case comparison analysis of hospitalized veterans. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Environmental exposure, Phenoxy herbicide formulations, Human, Abstract

Silbergeld, E.K. 1985. Reevaluation of epidemiologic data from Nitro, WV (USA). Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Epidemiologic investigation, Chloracne, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Abstract

This abstract of a symposium presentation describes a proportionate mortality analysis conducted among workers at the Monsanto plant in Nitro, West Virginia. The cohort was formed by combining cohorts from two previous mortality studies. The authors conclude that there is increased mortality due to bladder cancer, arterioschlerotic heart disease, and lung cancer in the cohort.

Sibergeld, E.K., and Mattison, D.R. 1985. Reproductive toxicology of TCDD: Clinical and experimental studies. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Abstract, Chlorinated dibenzo-p-dioxins, Reproductive effects, Teratogenic effects, Review

This abstract reviews the possible effects of TCDD on reproductive performance and in producing teratogenic outcomes of pregnancy.

Singh, S.V., and Awasthi, Y.C. 1985. Inhibition of human glutathione S-tranferases by 2,4-dichlorophenoxyacetate (2,4-D) and 2,4,5-trichlorophenoxyacetate (2,4,5-T). Toxicol. Appl. Pharmacol. 81:328-336

KEYWORDS: Enzyme induction or inhibition, Hepatic effects, Mechanism of toxic action, In vitro study, 2,4-D and its esters, 2,4,5-T and its esters, Cultured mammalian cells

In vitro studies using both human liver and human erythrocyte glutathione-S-transferases indicates that 2,4,-D and 2,4,5-T inhibit all isoenzymes. If this effect occurs in vivo it may interfere with the ability to conjugate active electrophiles and may also lead to increased rates of lipid peroxidation.

Smith, A.H., and Pearce, N.E. 1985. Update on soft tissue sarcoma and phenoxy herbicides in New Zealand. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Epidemiologic investigation, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Review, Abstract

This is an abstract of a symposium presentation in which the authors review recent epidemiologic studies of the association of various cancers and exposure to phenoxy herbicides in New Zealand. These studies are reviewed in this volume (see Pearce et al. 1985a,b) and in earlier volumes of the review (see Smith et al. in Volumes IV and VI of this review (Clement 1984 and 1985)).

Stehr, P.A., Stein, G.F., and Webb, K. 1984. An epidemiologic study of community exposures to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Presented at the 5th National Conference on Management of Uncontrolled Hazardous Waste Sites, November 7-9, Washington, DC Pp. 287-289

KEYWORDS: Epidemiologic investigation, Neurobehavioral effects, Immunological effects, Renal effects, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human

This article describes a pilot epidemiologic study of people living in a dioxin-contaminated area in Missouri. This study has been published elsewhere (see Webb et al. 1984 and Knutson 1984 in Clement 1985).

Stehr, P.A., Forney, D., Stein, G., Donnell, H.D., Falk, H., Hotchkiss, R., Spratlin, W.A., Sampson, E., and Smith, S.J. 1985a. The public health response to 2,3,7,8-TCDD environmental contamination in Missouri. Public Health Rep. 100:289-293

KEYWORDS: Cancer, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review

The authors briefly review the history of dioxin contamination in the State of Missouri and then outline the activities of the Centers for Disease Control in assessing and managing potential human health risks associated with that contamination. (16 references)

Stehr, P.A., Stein, G.F., and Webb, K. 1985b. A pilot epidemiologic study of health effects due to 2,3,7,8-TCDD contaminations in Missouri. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 2 pages (abstract)

KEYWORDS: Epidemiologic investigation, Immunological effects, Renal effects, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Abstract

This abstract of a symposium presentation describes a pilot epidemiology study of residents of a TCDD- contaminated area of Missouri. This study has been published as a full paper (Webb et al. 1984).

Stephens, R. 1985. Characterization and establishment of health criteria of a PCB fire contaminated building in San Francisco, California, USA. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Abstract

This is an abstract of a symposium presentation in which the author describes a transformer fire in a vault adjacent to an office building in San Francisco, California. The transformer contained PCBs, and PCDDs were detected in the building. No adverse health effects were described.

Sterling, T.D., and Arundel, A. 1985. Vietnam veterans' risk for fathering children with birth defects. JAMA 254:609

KEYWORDS: Commentary, Phenoxy herbicide formulations, Teratogenic effects, Epidemiologic investigation, Human,

The authors of this letter challenge the conclusion of an editorial by Dan (1984, see Volume VI) that exposure to Agent Orange is unlikely to be responsible for birth defects in the children of men who served in Vietnam. Sterling and Arundel state that suggestive epidemiological findings are consistent with the results of positive animal studies and the available epidemiological data are insufficient to exclude the possibility that Agent Orange could cause birth defects.

Stohs, S.J., Hassan, M.Q., and Murray, W.J. 1984. Induction of lipid peroxidation and inhibition of glutathione peroxidase by TCDD. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 241-253

KEYWORDS: Hepatic effects, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

The authors review evidence that TCDD causes some of its effects by inducing lipid peroxidation by suppressing peroxidases and depleting reduced glutathione. (28 references)

Suskind, R.R. 1985. Chloracne, "the hallmark of dioxin intoxication". Scand. J. Work Environ. Health 11:165-171

KEYWORDS: Chloracne, Cancer, Epidemiologic investigation, Hepatic effects, Respiratory effects, Neurobehavioral effects, Other toxic effect, Porphyria cutanea tarda, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Review

The author reviews studies of occupational cohorts that developed chloracne, presumably as a result of exposure to chlorinated dioxins, and concludes that within these cohorts

there is no indication that systemic intoxication occurs in the absence of chloracne. (30 references)

Sweatlock, J.A., and Gasiewicz, T.A. 1985. The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure on the concentration of beta-hydroxybutyrate and acetoacetate in the rat. Chemosphere 14:975-978

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Other toxic effect, Exposure by injection, Chlorinated dibenzo-p-dioxins, Rat

Serum levels of beta-hydroxybutyrate and acetoacetate were measured in rats following a single i.p. injection of TCDD. A dose of 100 ug/kg caused significant decreases in levels of these ketone bodies compared to both pair-fed and ad-libitum-fed controls, suggesting that TCDD alters lipid metabolism.

Sweeney, G., Barford, D., Rowley, B., and Goddard, G. 1984. Mechanisms underlying the hepatotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 225-239

KEYWORDS: Hepatic effects, Porphyria cutanea tarda, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

The authors review earlier studies of liver toxicity of TCDD as indicated by porphyria and histologic changes and conclude that hepatotoxicity is not due only to the induction of cytochrome P-450.

Thunberg, T. 1984. Effect of TCDD on vitamin A and its relation to TCDD-toxicity. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 333-344

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Hepatic effects, Chlorinated dibenzo-p-dioxins, Review

Toth, K., Olah, E., Somfai-Relle, S., and Sugar, J. 1984. Effect of herbicide 2,4,5-trichlorophenoxyethanol (TCPE) containing dioxin on mutation and induction of sister chromatid exchanges. Carcinogenesis 5:1725-1728

KEYWORDS: Cultured mammalian cells, Hamster, Cytotoxicity, Chlorinated dibenzo-p-dioxins, Genotoxicity, In vitro study, Microbial test system, Phenoxy herbicide formulations

Toyoshima, E., Mayer, R.F., Max, S.R., and Eccles, C. 1985. 2,4-Dichlorophenoxyacetic acid (2,4-D) does not cause polyneuropathy in the rat. J. Neurol. Sci. 70:225-229

KEYWORDS: Neurobehavioral effects, Exposure by injection, 2,4-D and its esters, Rat

Turkula, T.E., and Jalal, S.M. 1985. Increased rates of sister chromatid exchanges induced by the herbicide 2,4-D. J. Hered. 76:213-214

KEYWORDS: Cultured mammalian cells, 2,,4-D and its esters, Genotoxicity, Human, In vitro study

Turner, J.N., and Collins, D.N. 1985. Membrane proliferation and excretion from guinea pig hepatocytes exposed to 2,3,7,8-TCDD or PCB pyrolysis products. Chemosphere 14:983-986

KEYWORDS: Hepatic effects, Metabolism, Subchronic toxic effects, Oral exposure, Chlorinated dibenzo-p-dioins, Guinea pig

This is a preliminary report describing the formation of cytoplasmic vacuoles containing hyalin-like membrane arrays in the hepatocytes of guinea pigs given TCDD for 90 days. The authors propose that vacuole formation is part of a mechanism for excreting excess membrane into the sinusoids and bile canaliculi.

Vecchi, A., Graziani, A., Sironi, M., Fiume, D.D., Sfreddo-Gallotta, E., Saletti, M.C., and Cantoni, L. 1985a. Simultaneous administration of TCDD and TCDF at different ratios induces different effects. Chemosphere 14:957-951

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Immunological effects, Mechanism of toxic action, Exposure by injection, Chlorinated dibenzo-p-dioxins, Herbicide impurities other than PCDDs, Mouse

Vecchi, A., Sironi, M., Sfreddo-Gallotta, E., Graziani, A., and Cantoni, L. 1985b. Effect of cytochrome P450/448 inducers on TCDD immunosuppression. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Acute toxic effects, Immunological effects, Unspecified route of exposure, Chlorinated dibenzo-p-dioxins, Mouse, Abstract

Vickers, A.E.M., Sloop, T.C., and Lucier, G.W. 1985. Mechanism of action of toxic halogenated aromatics. Environ. Health Perspect. 59:121-128

KEYWORDS: Acute toxic effects, Enzyme induction or inhibition, Hepatic effects, Lethality, Mechanism of toxic action, Metabolism, Other toxic effect, Review

The authors review the current state of knowledge of the mechanism by which polychlorinated dibenzo-p-dioxins, especially

2,3,7,8-TCDD, cause acute lethality, enzyme induction, thymic atrophy, liver pathology, and other toxic effects in experimental animals. The properties of the cytosolic Ah receptor and interspecies differences are discussed in detail. (102 references)

Vos, J.G. 1984. Dioxin-induced thymic atrophy and suppression of thymus-dependent immunity. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 401-410

KEYWORDS: Immunological effects, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

Wacker, R., Poiger, H., and Schlatter, C. 1985. Pharmacokinetics and metabolism of 1,2,3,7,8-pentachlorodibenzodioxin in the rat. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Metabolism, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat, Abstract

This abstract of a symposium presentation describes a study of the disposition of a single oral dose of TCDD in rats. There was great variability among animals in the absorption of TCDD from the gut. Most of the TCDD was excreted via the feces. Bile cannulation revealed the presence of hydroxylated and conjugated metabolites.

Walden, R., and Schiller, C.M. 1985. Comparative toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in four (sub)strains of adult male rats. Toxicol. Appl. Pharmacol. 77:490-495

KEYWORDS: Acute toxic effects, Lethality, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Rat

Weber, H., and Birnbaum, L.S. 1985. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and 2,3,7,8-tetrachlorodibenzofuran (TCDF) in pregnant C57Bl/6N mice: Distribution to the embryo and excretion. Arch. Toxicol. 57:159-162

KEYWORDS: Acute toxic effects, Mechanism of toxic action, Metabolism, Teratogenic effects, Oral exposure, Chlorinated dibenzo-p-dioxins, Mouse

The authors studied the metabolism and excretion of TCDD in pregnant female mice given oral doses that had been shown to cause cleft palate in fetuses. Less than 0.5% of the administered dose was found in the embryos. If TCDD is teratogenic via direct action on the embryonic tissue, then it must be quite potent.

Weber, H., Harris, M.W., Haseman, J.K., and Birnbaum, L.S. 1985. Teratogenic potency of TCDD, TCDF and TCDD-TCDF combinations in C57BL/6N mice. Toxicol. Letters 26:159-167

KEYWORDS: Chlorinated dibenzo-p-dioxins, Mechanism of toxic action, Mouse, Teratogenic effects, Oral exposure

Weerasinghe, N.C.A., Schecter, A., Hardell, L., and Gross, M.L. 1985. Analysis of adipose tissue for 2,3,7,8-TCDD in persons with health problems possibly due to Agent Orange exposure. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

This abstract of a symposium presentation indicates that the presentation will include results of analyses for TCDD of adipose tissue from Vietnam veterans who have "health problems" that may be ascribed to exposure to Agent Orange. No results or conclusions are present in the abstract.

Whitlock, J.P., Jr., Israel, D.I., Galeazzi, D.R., and Miller, A.G. 1984. 2,3,7,8-Tetrachlorodibenzo-p-dioxin regulates cytochrome P_1-450 gene expression. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 191-200

KEYWORDS: Enzyme induction or inhibition, Mechanism of toxic action, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells, Review

The authors review studies conducted in cultured Hepa 1c1c7 cells that show that TCDD regulates the transcription of the structural gene for cytochrome P_1-450 by forming a TCDD-receptor complex that binds to the nucleus.

Wolfe, W.H., Lathrop, G.D., Albanese, R.A., and Moynahan, P.M. 1985a. An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides and associated dioxins. Chemosphere 14:707-716

KEYWORDS: Chloracne, Cancer, Cardiovascular effects, Epidemiologic investigation, Hematological effects, Hepatic effects, Immunological effects, Neurobehavioral effects, Renal effects, Reproductive effects, Respiratory effects, Occupational exposure, Phenoxy herbicide formulations, Human

In this talk, presented at a symposium, the authors describes the methodology and results of a cohort morbidity study among U.S. Air Force personnel who were involved in herbicide spraying (Operation Ranch Hand) in Vietnam. This study was reviewed in detail in Volume VI of this review (see Lathrop et al. 1984a in Clement 1985).

Wolfe, W.H., Lathrop, G.D., Albanese, R.A., Moynahan, P.M., and Moser, R. 1985. An epidemiologic investigation of the health effects of Herbicide Orange. Presented at the 189th ACS National Meeting, Miami Beach, Florida (April 28-May 3, 1985) 1 page (abstract)

KEYWORDS: Chloracne, Cancer, Cardiovascular effects, Epidemiologic investigation, Hematological effects, Immunological effects, Neurobehavioral effects, Renal effects, Reproductive effects, Respiratory effects,Occupational exposure, Phenoxy herbicide formulations, Human, Abstract

This abstract of a symposium presentation describes the results of a morbidity study among U.S. Air Force personnel engaged in the herbicide application program in Vietnam (Operation Ranch Hand, see Lathrop et al. 1984a in Volume VI of this review Clement 1985).

World Health Organization (WHO). 1984. 2,4-Dichlorophenoxyacetic acid (2,4-D). Environ. Health Criteria 29:1-151

KEYWORDS: Occupational exposure, Environmental exposure, 2,4-D and its esters, Human, Review

This is a detailed review of all the scientific information on the health effects of 2,4-D and its esters including information on properties, analytical methods, exposure, pharmacokinetics, and acute and chronic toxic effects. It concludes with a section on human health risks and recommendations on exposure. (546 references)

Wroblewski, V.J., and Olson, J.R. 1985. Hepatic metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the rat and guinea pig. Toxicol. Appl. Pharmacol. 81:231-240

KEYWORDS: Metabolism, In vitro study, Chlorinated dibenzo-p-dioxins, Cultured mammalian cells

Young, A.L. 1984. Determination and measurement of human exposure to the dibenzo-p-dioxins. Bull. Environ. Contam. Toxicol. 33:702-709

KEYWORDS: Metabolism, Occupational exposure, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Review

In this talk, presented at a symposium, the author reviews studies of TCDD levels in human tissues and concludes that individuals with no known exposure had detectable levels of TCDD in their adipose tissues and that among exposed individuals adipose tissue levels were highly variable. There was no correlation with health effects. (11 references)

Young, A.L., and Kang, H.K. 1985. Status and results of federal epidemiologic studies of populations exposed to TCDD. Chemosphere 14:779-790

KEYWORDS: Cancer, Epidemiologic investigation, Reproductive effects, Environmental exposure, Occupational exposure, Chlorinated dibenzo-p-dioxins, Phenoxy herbicide formulations, Human, Review

In this talk presented at a symposium, the authors reviewed the status of federally sponsored epidemiology studies designed to elucidate the human health effects of phenoxy herbicides and associated dioxins. Included are studies to assess human exposure to dioxin, cancer epidemiology studies, reproductive effect studies and mortality and mobidity studies. (14 references)

Zimmering, S., Mason, J.M., Valenzia, R., and Woodruss, R.C. 1985. Chemical mutagenesis testing on Drosophila. II. Results of 20 coded compounds tested for the National Toxicology Program. Environ. Mutagen. 7:87-100

KEYWORDS: Chlorinated dibenzo-p-dioxins, 2,4-D and its esters, 2,4,5-T and its esters, Genotoxicity, Other species, Oral exposure, Unspecified route of exposure

The negative results of testing 2,3,7,8-TCDD, 2,4-D, and 2,4,5-T for sex-linked recessive mutations in Drosophila were reviewed previously (see Volume VI of this review (Clement 1985)) from a prepublication copy of this article.