

MEMBER OF THE NATIONAL ASSOCIATION OF STATE AGENT ORANGE PROGRAMS

THE OKLAHOMA AGENT ORANGE FOUNDATION  
P.O. Box 849  
Lexington, OK 73051

AGENT ORANGE REPORT XXI

*See study C  
for pre-Vietnam  
VA knowledge  
of a 2,4-D  
thyroid effect.*

A. "Chloracne from pentachlorophenol-preserved wood"

Cole et al., Contact Dermatitis 1986; 15: 164-168. Dr. Cole works in the Dermatology Service, VAMC, Long Beach, CA.

"The eruption was characterized by the presence of multiple small yellow-white papules present diffusely over the entire body. Involved areas included the malar regions of the face, post-auricular area, the trunk, buttocks, thighs and lower legs."

"Occasional papules were inflamed. Clinically it was thought that these papules represented closed comedones."

"The diagnosis of chloracne requires the presence of a multitude of open and closed comedones and small, straw-colored cysts."

"The condition can be distinguished from acne vulgaris because of the unusual distribution of lesions & the lack of inflammation."

"A small epithelial-lined cystic structure was present, which communicated with the surface. The lining epithelium was composed of atrophic but normal-appearing epidermis. Contained within the cyst was keratin-like material. No sebaceous glands were noted and there was no evidence of sebaceous metaplasia. The microscopic picture was thought to be that of a comedone and a pathologic diagnosis of chloracne was made."

"Chloracne is caused by the ingestion, inhalation, or transcutaneous penetration of certain halogenated aromatic hydrocarbons."

"It appears that our patient absorbed a sufficient amount of a chloracnegenic substance percutaneous to cause clinical disease."

"...condition improved remarkably after treatment with Accutane." Accutane ACCORDING TO THE CDC IS "A DEVASTATING HUMAN TERATOGEN". Hoffman-LaRoche, THE MANUFACTURER DOES NOT DISPUTE THIS FACT,

THIS RECENT VA STUDY PROVIDES A EXCELLENT DIAGNOSTIC DESCRIPTION OF CHLORACNE. HOWEVER, IN 1980, THE VA KNEW THAT: "IN MAN, AS IN THE MONKEY AND RABBIT, HISTOLOGICAL APPEARANCE OF SKIN LESIONS PROGRESSES FROM DILATED HAIR FOLLICLES FILLED WITH KERATIN TO THE DISAPPEARANCE OF SEBACEOUS GLANDS AND THE REPLACEMENT OF FOLLICLES WITH KERATIN". COLE ET AL., 1986, ALSO FOUND "KERATIN-LIKE MATERIAL" AND "NO SEBACEOUS GLANDS".

"OBSERVATIONS THAT LIPID METABOLISM IS DISTURBED BY TCDD, THAT OIL ACCUMULATES ON THE SKIN PRIOR TO THE DEVELOPMENT OF CHLORACNE, AND THAT CERTAIN FATTY ACIDS CAN CAUSE FOLLICULAR KERATOSIS HAS LED TO THE SUGGESTION THAT FATTY ACID METABOLISM MAY PLAY A ROLE IN THE ETIOLOGY OF CHLORACNE CAUSED BY TCDD (Vos, 1978)."

THE PREVIOUS TWO QUOTATIONS (VA, 1980 AND Vos, 1978) WERE FOUND ON PAGE 6-18 OF THE "REVIEW OF LITERATURE ON HERBICIDES, INCLUDING PHENOXY HERBICIDES AND ASSOCIATED DIOXINS", VOL. I, WHICH WAS PREPARED FOR BARKLEY M. SHEPARD, M.D., FORMER DIRECTOR OF THE VA AGENT ORANGE PROJECTS OFFICE, IN WASHINGTON, D.C.

ALSO, FOUND IN THE ABOVE MENTIONED "ANALYSIS OF LITERATURE" IS A STATEMENT BY Greig, 1979, "IN MAN, LESIONS USUALLY DO NOT OCCUR IN THE FOLLICLES OF BEARD HAIR, POSSIBLY BECAUSE BEARD HAIR FACILITATES DRAINAGE OF SEBUM AND KERATINACEOUS DEBRIS".

ALL OF THE ABOVE SUGGESTS THAT THE VA KNOWS WHAT CHLORACNE IS AND KNOWS HOW TO PROPERLY DIAGNOSE THIS PATHOLOGIC RESULT OF DIOXIN EXPOSURE. AT THE PRESENT TIME CHLORACNE IS THE ONLY DISEASE THE VA ASSOCIATES WITH AGENT ORANGE EXPOSURE. HOWEVER, ACCORDING TO S.S. Epstein, M.D., Dept. of Preventive Med., Univ. of Ill. Med. Center, Chicago, "...CHLORACNE IS GENERALLY, BUT NOT INVARIABLY, ASSOCIATED WITH A WIDE RANGE OF OTHER SYMPTOMS AND OBJECTIVE SIGNS OF MULTI-SYSTEM DISEASE." HE CONTINUES, "THERE IS THUS A PROBABILITY THAT A BIAS HAS DEVELOPED, PARTICULARLY IN THE EARLY LITERATURE, IN THE OVER-EMPHASIS OF THE DERMATOLOGICAL ASPECTS OF DIOXIN AND IN THE FAILURE TO RECOGNISE SYSTEMIC TOXICITY IN THE ABSENCE OF OVERT SKIN DISEASE. THIS MAY WELL HAVE RESULTED IN SUBSTANCIAL UNDER-REPORTING OF DIOXIN TOXICITY. THESE CONSIDERATIONS HAVE BEEN FURTHER STRENGTHENED BY REPORTS OF DIOXIN-INDUCED SYSTEMIC DISEASE IN THE ABSENCE OF CHLORACNE (Bleiberg et al., 1964; Oliver, 1975; Scarisbrick & Martin, 1981; Martin, 1983) AND BY THE ABSENCE OF A HISTORY OF CHLORACNE IN CASES OF SOFT-TISSUE SARCOMA IN WORKERS EXPOSED TO PHENOXY HERBICIDES AND CHLORINATED PHENOLS (Honchar & Halperin, 1981; Johnson et al., 1981; Moses and Selikoff, 1981)."

#### B. "Dermatologic Evaluation"

Lathrop et al., USAF, Ranch Hand II: Baseline Morbidity Study Results, Chapter XV, 1984.

"Since only acne after 1961 could be possibly induced by herbicide exposure, cases of post-1961 acne were placed in time reference to each individual's RVN tour(s)."

"Reported acne (Post SEA) relative risk: 1.18..."

SINCE ANY RELATIVE RISK OVER 1.00 SHOWS A POSSIBLE POSITIVE ASSOCIATION, THIS SUGGESTS THAT A RELATIVE RISK OF 1.18 FOR REPORTED ACNE POST-SEA MAY BE ASSOCIATED WITH HERBICIDE EXPOSURE.

- C. "Some Effects of 2,4-Dichlorophenoxyacetic Acid on Thyroid Function in the Rat: Effects on Iodine Accumulation."

Florsheim (Radiology Service, VA Hospital, Long Beach, CA.) and Velcoff, *Endocrinology* 71(1):1-6, 1962.

"Thus 2,4-D appears to be one of the few agents other than iodide itself that has been shown to alter the serum iodide pool specifically."

THIS RESEARCH ARTICLE SHOWS THAT THE VA KNEW IN THE EARLY 60'S THAT 2,4-D WOULD PROBABLY EFFECT THYROID FUNCTION IN HUMANS.

- D. "Enhanced Thyroxine Metabolism and High Uptake Goiters in Rats After a Single Dose of 2,3,7,8-TCDD"

C. H. Bastomsky, *Endocrinology* 101:292-296, 1977.

"Sephadex uptake of serum [125I] T3 (triiodothyronine) was reduced in the TCDD group."

THIS STUDY DESCRIBES HYPOTHYROIDISM CAUSED BY TCDD.

- E. "Agent Orange Study Finds Adverse Effects"

J. Raloff, *Science News* 125:132, 1984.

"The rate of uptake for..." "...T3, showed Ranch Handers might have more of a tendency to develop an underactive thyroid."

THIS ARTICLE DESCRIBES HYPOTHYROIDISM IN RANCH HANDERS.

- F. "Endocrine Function"

Lathrop et al., USAF, Ranch Hand II: Baseline Morbidity Study Results, Chapter XVI-6, 1984.

"Table XVI-6-10: Ranch Hand - Ground Enlisted Personnel Dose-Response Data."

"T3 (triiodothyronine) Age	p<0.001"
"T3 %Body Fat	p<0.003"

"...decreasing T3 uptakes are associated with advancing age in both groups with the slope being much steeper in Ranch Handers."

THE ABOVE DOCUMENTATION DESCRIBES HYPOTHYROIDISM IN RANCH HANDERS WHICH PROBABLY IS A TRUE "HERBICIDE EFFECT".

"The Ranch Hand group was found to differ from the comparison group with respect to proportions of individuals in normal and abnormal thyroid hormone categories."

HOWEVER, IN THE "SUMMARY", THE USAF AUTHORS WROTE THE FOLLOWING:

"Thus, in sum, no definite herbicide effect on thyroid function can be demonstrated; however, it also CANNOT\* be confidently asserted that a herbicide effect on thyroid function has NOT\* occurred."  
 (\*-emphasis added)

#### G. "Environmental Goitrogens"

Eduardo Gaitan, M.D., Chief, Endocrinology Section, VAMC, Jackson, MS., in "The Thyroid Gland", 1986.

"Pollutants that cause goiter are known as environmental goitrogens and will be the center of the discussion..."

"For instance, an increased prevalence of primary hypothyroidism (11%) was documented among workers from a plant that manufactured PBB's and PBB oxides. These subjects had elevated titers of antithyroid microsomal antibodies, indicating that hypothyroidism was probably a manifestation of lymphocytic autoimmune thyroiditis, perhaps a PBB-induced pathogenic autoimmune response..."

THIS STUDY DESCRIBES HYPOTHYROIDISM AND SHOWS THAT THE VA MAY BE AWARE OF A POSSIBLE AUTOIMMUNE EFFECT OF DIOXIN, SINCE PBB'S AND DIOXIN AFFECT THE HUMAN BODY IN A SIMILAR WAY. IN FACT, White et al., (Tox. Appl. Pharm. 84:209-219, 1986) SUGGEST THAT, "EPIDEMIOLOGICAL STUDIES MIGHT REVEAL A PREVALENCE OF AUTOIMMUNE DYSFUNCTION IN HIGH-RISK GROUPS EXPOSED TO DIOXINS".

#### H. "Hypothyroidism in Workers Exposed To Polybrominated Biphenyls"

Bahn et al., N. E. J. Med. 302(1):31-33, 1980. EPA funded.

"In summary, a cohort of male PBB workers was found to have a statistically significant increase in the prevalence of primary hypothyroidism (four of 35 men)."

"The common exposure of these four men to PBB's, PBBO's and bromine suggests that these substances could have caused the hypothyroidism."

"The development of thyroid abnormalities in animals given PBB's and PBBO's supports this hypothesis."

THIS STUDY DESCRIBES HYPOTHYROIDISM WHICH WAS CAUSED BY A PATHOGENIC AUTOIMMUNE RESPONSE DUE TO EXPOSURE TO PBB's.

I. "Role of Thyroid Hormones and Brown Adipose Tissue in the Toxicity of TCDD."

Karl K. Rozman, in Banbury Report 18: "Biological Mechanisms of Dioxin Action", 1984, pp. 345-354.

"Data presented in this paper point towards brown adipose tissue as the likely primary target of TCDD toxicity."

"Brown adipose tissue, in conjunction with thyroid hormones, appears to regulate the homeostasis of fat mobilization and utilization."

"It seems that TCDD interferes with this process, resulting in a disturbance of the fat mobilization/utilization equilibrium."

"It is suggested that this is the cause of what is commonly called wasting syndrome."

"Thus, HYPOTHYROIDISM\* can be considered the genetically coded response (via induction of glucuronosyl transferase) whereby the organism attempts to respond to a severe interference with its energy mobilization." (\* - emphasis added)

J. "Effect of Thyroidectomy and Thyroxine on 2,3,7,8-Tetrachlorodibenzo-p-Dioxin-Induced Immunotoxicity"

Pazdernik and Rozman, Life Sciences, 36:695-703, 1985.

"It is well established that TCDD exposure reduces immunofunction;..."

"This study points to the importance of thyroid status in TCDD-induced immunotoxicity."

"Thyroid hormones are important for the development and maintenance of the immune system."

"It is conceivable that thyroid hormones exert their influence on hemopoiesis and lymphoiesis via marrow adipose cells in the hemopoitic microenvironment." [see A.O. XIX study A]

"Thus, since TCDD-induced immunotoxicity is dependent on the permissive action of thyroid hormones, we suggest that marrow adipose cells might be the target site at which TCDD exerts its immunotoxicity."

THE TWO STUDIES ON THIS PAGE, AS WELL AS THE STUDIES ON THE PREVIOUS TWO PAGES, ALL DESCRIBE HOW THE PHENOXY ACID HERBICIDES AND THEIR DIOXIN CONTAMINANTS EFFECT THYROID FUNCTION. IN HUMANS THIS EFFECT CAN CAUSE AN AUTOIMMUNE RESPONSE WHICH MAY RESULT IN HYPOTHYROIDISM AND SUBSEQUENT REDUCTION IN IMMUNOFUNCTION.

K. "Modulation of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-Mediated Myelotoxicity by Thyroid Hormones"

Hong et al., Biochemical Pharmacology 36(8):1361, 1987. This research was done by the National Institute of Environmental Health Sciences (NIEHS).

"Several lines of evidence have indicated that thyroid hormones share common molecular properties with TCDD and can modulate its toxicity."

"Stimulated by the observation that TCDD and thyroid dysfunction cause similar nonspecific changes, including loss of body weight, bradycardia (slow heart rate), alopecia (loss of hair), hirsutism (excess hair), hyperkeratosis (disturbance of the skin --caused by TCDD-- that may result in a diagnosis of chloracne), and altered levels of triglycerides and cholesterol, a number of investigators have noted various molecular and cellular relationships between thyroid hormone action and TCDD toxicity."

"Cellular studies have provided additional support relating thyroid hormones and TCDD actions."

"While physiological levels of thyroid hormones are required to maintain normal immune function, excessive amounts cause hyperplasia of lymphoid organs and immunosuppression similar to that seen with TCDD."

"Lamb et al. have shown that co-administration to pregnant mice of exogenous T3 (triiodothyronine) or T4 (thyroxine) with TCDD also potentiates the induction of CLEFT PALATE\* in offspring when compared to incidences observed from separate administration of TCDD or thyroid hormones." (\* - emphasis added)

"Furthermore, myelotoxicity by both TCDD and thyroid hormone segregated with the Ah locus in congenic mice."

"Regardless of the mechanism of action, these data provide evidence that thyroid hormones can induce and regulate toxicological processes associated with polyhalogenated aromatic hydrocarbons."

THIS RESEARCH BY NIEHS SHOWS THAT THE SYSTEMIC EFFECTS OF DIOXIN CONTAMINATION IN THE HUMAN BODY MAY BE THE UNDERLYING REASON FOR MOST THE DISEASES AND MEDICAL CONDITIONS ASSOCIATED WITH PHENOXY ACID HERBICIDE EXPOSURE. THESE DISEASES AND OTHER MEDICAL CONDITIONS ASSOCIATED WITH HERBICIDE AND DIOXIN EXPOSURE AND SUBSEQUENT THYROID DYSFUNCTION INCLUDE, BUT ARE NOT LIMITED TO: CHLORACNE (HYPERKERATOSIS), HYPOTHYROIDISM, LEUKEMIA, LYMPHOMA, IMMUNOSUPPRESSION, AND BIRTH DEFECTS. THUS, TCDD MIMICS THE ACTION OF EXCESS THYROID HORMONES IN THE HUMAN BODY. REMEMBER, THE PHENOXY ACID HERBICIDES WERE DESIGNED, AS CHEMICAL WARFARE AGENTS, TO MIMIC NATURAL PLANT HORMONES, WHICH ARE SIMILAR TO SOME HUMAN HORMONES, i.e. SEROTONIN AND THYROXINE.

SUMMARY OF THE STUDIES REVIEWED FOR AGENT ORANGE REPORT #21  
 WRITTEN BY THE OKLAHOMA AGENT ORANGE FOUNDATION

- STUDY A: DESCRIBES A VA CHLORACNE DIAGNOSIS AND SHOWS THAT CHLORACNE IS HYPERKERATOSIS OF THE SKIN WHICH MAY BE CAUSED BY TCDD.
- STUDY B: SHOWS AN EXCESS OF ACNE IN USAF RANCH HAND II STUDY WHICH MAY BE DUE TO HERBICIDE EXPOSURE.
- STUDY C: DESCRIBES PRE-VIETNAM VA KNOWLEDGE OF 2,4-D's THYROID EFFECTS.
- STUDY D: SHOWS HYPOTHYROIDISM CAUSED BY TCDD.
- STUDY E: DESCRIBES HYPOTHYROIDISM AS AN ADVERSE HEALTH EFFECT WHICH WAS FOUND BY THE USAF RANCH HAND II STUDY. THE RANCH HAND II STUDY, THE BASELINE MORBIDITY RESULTS, IS THE LARGEST STUDY TO DATE ON THE HUMAN HEALTH EFFECTS OF EXPOSURE TO AGENT ORANGE.
- STUDY F: SHOWS THE THYROID FUNCTION DATA FROM RANCH HAND II WHICH SUPPORTS THE CONCLUSION THAT THE HYPOTHYROIDISM MAY BE THE RESULT OF A HERBICIDE EFFECT.
- STUDY G: DESCRIBES VA KNOWLEDGE OF HYPOTHYROIDISM, AN AUTOIMMUNE EFFECT, CAUSED BY EXPOSURE TO POLYHALOGENATED AROMATIC HYDROCARBONS SIMILAR TO TCDD. ALSO, White et al., SUGGEST THAT "EPIDEMIOLOGICAL STUDIES MIGHT REVEAL A PREVALENCE OF AUTOIMMUNE DYSFUNCTION IN HIGH RISK GROUPS EXPOSED TO DIOXINS".
- STUDY H: SHOWS THAT THIS PATHOGENIC AUTOIMMUNE EFFECT RESULTS IN HYPOTHYROIDISM.
- STUDY I: DESCRIBES HYPOTHYROIDISM AS "THE GENETICALLY CODED RESPONSE" TO TCDD TOXICITY.
- STUDY J: DESCRIBES HOW THE AUTOIMMUNE EFFECT, HYPOTHYROIDISM, CAUSES IMMUNOSUPPRESSION.
- STUDY K: SHOWS THAT THE SYSTEMIC EFFECTS OF TOXIC EXPOSURE, SUCH AS HYPOTHYROIDISM, MAY BE RESPONSIBLE FOR MANY IF NOT ALL OF THE DISEASES AND MEDICAL CONDITIONS ASSOCIATED WITH DIOXIN EXPOSURE.

EVEN BY COMPARING THE LETTERS OF THE WORDS FOR THYROXINE AND DIOXIN (TCDD) WE SEE SIMILARITIES:

THYROXINE = TETRA --IODO -----THYR OXIN E  
 DIOXIN = TETRA CHLORO DIBENZODI OXIN

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P.O. Box 849

Lexington, OK 73051

SUMMARY: AGENT ORANGE REPORT XXI

STUDY/ ARTICLE	AUTHOR	YR.	BRIEF REVIEW	9/13/87
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- A. VA 86 DESCRIBES A VA CHLORACNE DIAGNOSIS AND SHOWS THAT CHLORACNE IS HYPERKERATOSIS OF THE SKIN. HYPERKERATOSIS CAN BE CAUSED BY TCDD.
  - B. USAF 84 SHOWS AN EXCESS OF ACNE IN USAF RANCH HAND II STUDY WHICH MAY BE DUE TO HERBICIDE EXPOSURE.
  - C. VA 60 PRE-VIETNAM KNOWLDEGE: 2,4-D THYROID EFFECT.
  - D. Bastomsky 77 SHOWS HYPOTHYROIDISM CAUSED BY TCDD.
  - E. Raloff 84 DESCRIBES HYPOTHYROIDISM AS AN ADVERSE HEALTH EFFECT WHICH WAS FOUND BY THE USAF RANCH HAND II (RH II) STUDY. THIS STUDY IS THE LARGEST TO DATE ON THE HUMAN HEALTH EFFECTS OF TCDD.
  - F. USAF 84 SHOWS THE THYROID FUNCTION DATA FROM RH II WHICH SUPPORTS THE CONCLUSION THAT HYPOTHYROIDISM IS THE RESULT OF A HERBICIDE EFFECT.
  - G. VA 86 DESCRIBES VA KNOWLEDGE OF HYPOTHYROIDISM, AN AUTOIMMUNE EFFECT, CAUSED BY EXPOSURE TO POLYHALOGENATED AROMATIC HYDROCARBONS SIMILAR TO TCDD. ALSO, White et al., (Tox Appl Pharm 84:209, 1986) SUGGEST EPIDEMIOLOGICAL STUDIES MIGHT REVEAL A PREVALENCE OF AUTOIMMUNE DYSFUNCTION IN HIGH RISK GROUPS EXPOSED TO TCDD.
  - H. EPA 80 SHOWS THAT THIS PATHOGENIC AUTOIMMUNE EFFECT RESULTS IN HYPOTHYROIDISM.
  - I. Rozman 84 DESCRIBES HYPOTHYROIDISM AS "THE GENETICALLY CODED RESPONSE" TO TCDD TOXICITY.
  - J. Pasdernik 85 DESCRIBES HOW THIS AUTOIMMUNE EFFECT, HYPOTHYROIDISM, CAUSES IMMUNOSUPPRESSION.
  - K. Hong 87 SHOWS THAT THE SYSTEMIC EFFECTS OF TOXIC EXPOSURE, SUCH AS HYPOTHYROIDISM, MAY BE RESPONSIBLE FOR MANY IF NOT ALL OF THE DISEASES AND MEDICAL CONDITIONS ASSOCIATED WITH DIOXIN EXPOSURE.