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Chapter 17

THE HEALTH EFFECTS OF 2,4,5-T AND ITS TOXIC CONTAMINANTS

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I am grateful to Drs. McConnell and Smuckler who preceded me. They have provided an excellent scientific introduction to the story of workplace events and their adverse health effects from the production of 2,4,5-T which started in 1949.

In October, 1949, my colleagues and I, at the the Kettering Laboratory, were asked to examine four workers who had become ill following an industrial process accident which occurred in March of that year in a plant making 2,4,5-T. A kettle, in which trichlorophenol was being made, overheated and developed excessive pressure and part of the contents was emitted through a safety valve and broken pipe connector into the plant building and its surroundings. We did not know it at the time, but 2,3,7,8-TCDD was a toxic component of that kettle effusion. The medical community was first alerted to the health problems arising from the manufacturing process of 2,3,5-T through this accident.

Those employees involved in the clean-up of the building and the restoration of equipment to resume production developed acute symptoms involving the respiratory tract; they complained of skin and eye irritation, headache, dizziness and nausea. These symptoms subsided within one to two weeks. They were followed by an acneform eruption, severe muscle pain affecting the extremities, thorax and shoulders, fatigue, nervousness and irritability, dyspnea, complaint of decreased libido and intolerance to cold. The first four persons we examined had severe generalized chloracne, hepatic enlargement and tenderness, peripheral neuritis, a delayed prothrombin time, and an increase in total serum lipids (Ashe and Suskind, 1949-1950). Transaminase tests were not yet developed at that time. Histological exam of a nerve biopsy in a worker with pedal sensory loss showed myelin degeneration.

All of them had severe generalized chloracne involving face, trunk, genitalia, upper and lower extremities (Figure 1-4).

A total of 36 subjects were followed, in a series of examination, until 1953. By that time, the symptoms and findings observed in 1949 and 1950 referable to the liver and nervous system had subsided. There was some persistence of the acne but considerable improvement was noted in most cases (Suskind, 1953).

The toxic contaminant of the 2,4,5-T process was identified in 1957 as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Kimmig and Schulz, 1957). A considerable amount of research has been carried out in the past ten years on the nature of its toxic action in animals. It is, as many of you know, the most potent acnegen on record.



FIGURE 1.

In 1955 we were able to demonstrate that the cellular events which are the consequence of the cutaneous exposure to contaminated trichlorophenol include:

1. Initial hyperkeratinization of the opening of the sebaceous gland into the follicle lumen followed by hyperkeratinization of the follicle orifice.
2. Modulation of the undifferentiated cells lining of the sebaceous acinus and instead of differentiating into sebum producing cells, they differentiate into keratinocytes.
3. The above process (2) produces the comedo and eventually an inclusion keratin cyst or closed comedone.
4. The above process also results in disappearance of sebaceous elements and the hair follicles which are replaced by the comedo and/or keratin cyst.

In 1978 we were able to return to the scene. A standard mortality analysis was conducted on the workers exposed to the runaway reaction materials (Zack and Suskind, 1980). As of 1979, the SMRs for all causes of death was 0.69 with 32 deaths observed and 46.41 expected. For the categories of cancer and cardiovascular diseases, the SMRs were 1.00, and 0.68 respectively. Because of the small size of the cohort and small numbers of deaths, the results cannot be regarded as conclusive, but suggest no significant difference from expected death rates. We pause here to comment and question. Here is a cohort which was heavily exposed to TCDD. Disabling health effects were observed acutely, subacutely, and subchronically. If risks were substantial for



FIGURE 2.

hepatic, cardiac, pulmonary disease and cancer, we should have detected them even in this small cohort in the mortality analysis. One of this group died of a malignant fibrous histiocytoma, originating in the skin. It is classified as a soft tissue sarcoma. Another, not in this accident group but exposed to the process and who had chloracne, died of a liposarcoma. The frequency data of soft tissue sarcomas for the general population is inadequate since those occurring in specific organ systems are classified under ICD # for tumors of the stomach, or CNS, or kidney, or where ever they are found. The clear association of soft tissue sarcomas and TCDD is still to be determined.

We then returned to the plant site and carried out a clinical study on 436 employees of this plant to determine and identify the possible long-term effects of chemicals associated with the production of 2,4,5-T including TCDD, and to determine the increased risk for the adverse effects which have been observed in the subacute phase in man, as well as those noted in experimental animals. The examination program attempted to determine possible increased risk for cutaneous, pulmonary, cardiovascular, gastrointestinal, hepatic, renal, neurobehavioral problems, reproductive and birth defect problems, effects on lipid metabolism and the possibility of increased risk for cancer. The population included those exposed to the process accident, as well as those exposed to the normal processes of manufacturing and included chemical operators, service employees, such as pipefitters, mechanics, etc. The controls were never associated in any way with the 2,4,5-T process or its materials.



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FIGURE 3.

The cohorts consisted of the following:

204 - Exposed

163 - Not Exposed

51 - Of Questionable Exposure

The examination included: an interview, clinical laboratory examination of blood and urine, pulmonary function tests, ECG, chest x-ray, nerve conduction velocity measurements, and a complete physical examination, including skin examination by dermatologists. During the dermatological examination biopsies and skin scrapings were taken as deemed appropriate by the physician. The nerve conduction velocity measurements were obtained for most subjects from two nerves: the peroneal nerve for motor function and the sural nerve for sensory function.

Clinical laboratory analyses included: blood calcium, phosphorous, BUN, creatinine, BUN/creatinine ratio, uric acid, glucose (CS), total protein, albumin, globulin, albumin/globulin ratio, total bilirubin, direct bilirubin, Transaminase SGO, Transaminase SGP, alkaline phosphatase, LDH, cholesterol, iron, total lipids, sodium, potassium, chloride, G-glutamyl transpeptidase, triglycerides, CBC and differential, thyroxine R.I.A., thyroxine binding globulins. Urinalysis included routine examination as well as coproporphyrins and uroporphyrins. Blood serum lipid fraction was analyzed for plasma cholesterol, plasma triglyceride, plasma HDL, and estimated plasma LDL.

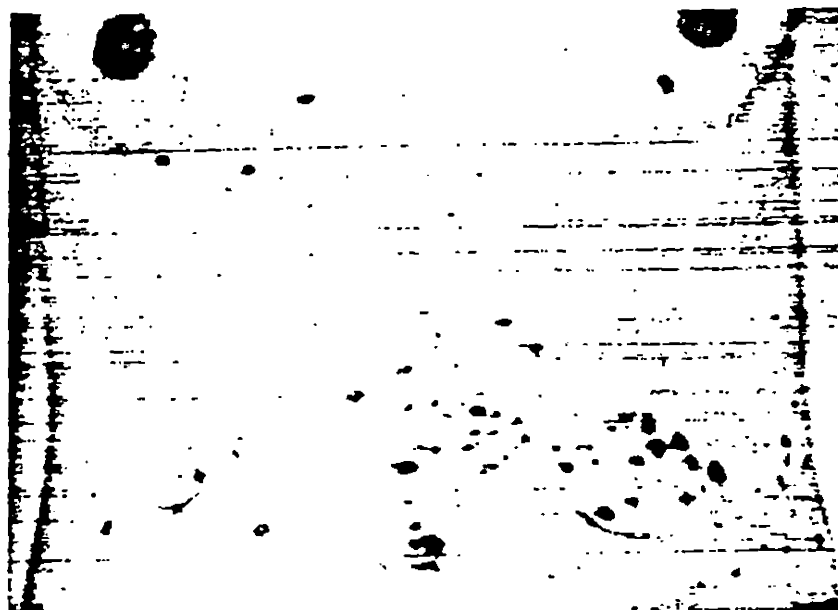


FIGURE 4.

A few words about the characteristics of the cohorts. Because of the time interval between the beginning of the process (1948), when it was terminated (1969), and the examination itself (1979), it was not possible to match the exposed and not exposed group for age and employment status. There was a 10 year mean age difference between the exposed and not exposed groups. There was a greater percentage of retired and terminated persons in the exposed than the not exposed. 86% of the not exposed were active employees; 55% of the exposed were active employees.

The following factors were considered in the analysis of the data - exposed versus not exposed versus questionably exposed: relationship to age, history or presence of chloracne - the hallmark of absorption and biological response; smoking, alcohol, other exposures than 2,4,5-T, (e.g. mining, welding, farming, etc).

As to drinking and smoking habits, there were no significant differences in alcohol consumption in the two groups. When smoking habits were compared by pack years the exposed group was significantly higher. There was a 19 pack year difference between the exposed and not exposed for present smokers and a 7 pack year difference between the exposed and not exposed in former smokers. This is a reflection of the difference in age (10 years) and smoking habits of the older age group.

When illnesses elicited by medical history were compared, the differences are found in the history of chloracne, acne vulgaris and peptic ulcer. Chloracne occurred in 86.27% of the exposed but did not occur in the not exposed and questionable exposure group. History of acne vulgaris occurred more frequently in the not exposed group than in the exposed group. A history of upper gastrointestinal ulcer occurred almost 4 times more frequently in the exposed group than in the not exposed ($p < 0.005$). When the medical history of the exposed and not exposed are compared for two (2) age groups, less than 50 vs. 50 years and older skin cancer and cerebrovascular accidents, hypertension, and coronary artery disease were related to age not exposure. Exposure, not age, appears to be associated with a history of gastrointestinal ulcer.

Since chloracne appeared to be the prime clinical indicator of exposure, a marker of absorption and biological response, the study subjects were further classified into three sub-groups within the exposed populations: those who never had developed chloracne, those who only had a history of chloracne, and those whose chloracne persisted and noted on clinical examination. As in the exposed versus not exposed group, the history of hypertension, cerebrovascular accident (CVA) and coronary artery disease were clearly age-related not chloracne related.

In the physical examination no differences in blood pressure findings were noted between the exposed and not exposed groups. The following criteria for abnormal systolic and diastolic values were used: for the groups < 50 (140/90) and for the groups > 60 (160/95). There were no significant differences in % of exposed or not exposed population with diastolic 80 or less, between 80-89, 80-94 and those considered abnormal, >90 for <59, ≥95 for ≥60.

52.7% of those who were clearly exposed were found to still have chloracne. Among the exposed 59.1% were found to have actinic elastosis in contrast to 30.1% among the not exposed. There is a significant difference in the occurrence of actinic elastosis between the exposed and not exposed in both age groups even though age is a factor in this clinical finding. Actinic elastosis is a problem found in persons of light coloration exposed over many years to sunlight (farmers skin, sailors skin). It is characterized by swelling and fragmentation of the elastic tissue elements of the skin.

It was observed that actinic elastosis is found predominately in the subjects with persistent chloracne (74.8%) but it also occurs significantly in those with a history of chloracne only 47.1%.

The frequency of abnormal plasma lipid findings were compared for exposed, not exposed and questionably exposed. No significant differences were noted in cholesterol, triglycerides, HDL and LDL levels. Smoking appeared to have no effect on the differences between these groups. Logistic regression was used to detect associations of abnormal lipid findings with exposure. After adjusting for pack years smoked, no significant differences between exposed and not exposed could be found.

When the lipid levels of the exposed group only are examined in relation to the occurrence of chloracne, the HDL levels in those with persistent chloracne are found to be somewhat lower than of the group with a history only of chloracne or those who never had chloracne. It is also interesting to note that those who had a history only of chloracne have somewhat higher LDL levels than those who had chloracne currently or never. I cannot comment on the real significance of this. The numbers are small.

No differences in mean values or out-of-range values for alkaline phosphatase, SGOT, SGPT, Gamma GT were found when the exposed were compared to the not exposed or those with chloracne were compared to those who only had a history of the skin problem or no history of chloracne.

Consistent differences in abnormal pulmonary function values (FEV₁, FVC, FEV₁/FVC and FEF₂₅₋₇₅) were found between the exposed and not exposed groups. Among present smokers only there was a significant difference in pulmonary function values between the exposed and not exposed group. There are no differences in pulmonary function values among persons who have formerly smoked or among persons who have never smoked when the exposed were compared to the non exposed.

Nerve conduction velocity determinations were made. All subjects reporting diabetes or reporting a high weekly alcohol intake were eliminated from the data analysis (high weekly alcohol intake was defined as greater than or equal to 35 oz. alcohol per week). After these deletions, there were 319 with complete sural examination and 336 with complete peroneal examination remaining. The data from the nerve conduction velocity

study were adjusted according to the deJesus method.

Using analysis of covariance after adjusting for age as well as using the Z score method, there appeared to be no differences in nerve conduction velocity, in latency or in amplitude ratios for peroneal and sural nerves.

In presenting the information on reproductive and birth defects, it should be understood that all of the data depended on personal recall of such information as number of pregnancies, miscarriages, live births, stillbirths, infant mortality, etc. Factors which affect accuracy are obvious - e.g. interviews of male subject only, age of subject, and change in cultural attitudes about reproductive matters. It is also influenced by the fact that the pregnancies, miscarriages, and stillbirths were not designated in a time period related to exposure e.g., pre, during, or post exposure.

Fisher's exact test was used to compare the reported occurrence or reproductive anomalies in the exposed group to the not exposed group. The data on reproductive and birth defect findings indicated no significant differences were found in either the frequencies or miscarriages, in the rate of birth defects or of stillbirths.

From this study one can conclude that for those exposed to the 2,3,5-T process persistent effects are cutaneous and involve the pilosebaceous apparatus and the elastic tissue of the dermis. Chloracne may persist for as long as 30 years.

→ The data are suggestive that for the exposed there was an increased risk for upper gastrointestinal ulcer; that in those who currently smoke and have been exposed to 2,4,5-T process materials there may be an association of abnormal pulmonary function findings when compared to those who smoke but who were never exposed; that among those in whom chloracne persists there is (although numbers are small) an association with low HDL levels and further for those with only a history of chloracne there is an association with higher LDL levels.

There is no evidence from this study population that there are identifiable long-term effects on the cardiovascular system, on the liver, on renal or on peripheral nerve function. From recall of medical problems there is no indication of an increase risk for infections. There is no indication, on the basis of historical information (recognizing all of its weaknesses) that there was a greater risk for miscarriages, stillbirths, or birth defects among the families in which the male parent was exposed.

Finally, it is appropriate to summarize the acute, subacute or subchronic and long-term effects of TCDD from trichlorophenol or 2,4,5-T contamination. I have assembled these in three tables (Tables 1-3). Workers exposed to TCP runaway reactions or from poor plant hygiene may initially develop eye, respiratory, skin and gastrointestinal irritation, as well as headache and malaise. Ten days to several weeks after this initial exposure, one observes the subacute and eventually sunchronic features which include: chloracne, peripheral neuritis, liver dysfunction, hyperpigmentation, hirsutism of the face, irritability and nervousness. Porphyrria cutanea tarda, and/or uroporphyrinuria have not been observed in populations which have only been exposed to trichlorophenol or 2,4,5-T; but only in mixed exposures as in the New Jersey (Bleiberg *et al.*, 1964) and Czechoslovakian (Jirasek *et al.*, 1973) incidents. The laboratory findings in the subacute or subchronic state include: peripheral nerve, myelin damage, elevated SGOT, GGTP, triglyceride and total lipids. In our very early observations of subacute effects there was an increased prothrombin time found.

The long-term health effects have been described in the major part of this presentation and are summarized in Table 3.

TABLE 1. Human Health Effects - TCDD

<u>Clinical Features</u>	<u>Acute - (Following TCP Runaway Reaction and/or Poor Plant Hygiene)</u>
	Eye, respiratory, skin and GI irritation
	Headache
	Malaise

TABLE 2. Human Health Effects - TCDD - Subacute or Subchronic

	<u>Clinical Features</u>	<u>Laboratory Findings</u>
Constant	Acne	
Inconstant	Neuromuscular symptoms, pain in skeletal muscles, chest, extremities = peripheral neuritis fatigue	Myelin degeneration on biopsy
Inconstant	Enlarged tender liver	Elevated SGOT Elevated GGTP Elevated prothrombin in time Elevated triglyceride Elevated total lipids
Rare	Porphyrria cutanea tarda (only in mixed 2,4,5-T and 2,4-D exposures)	Uroporphyrinuria
Inconstant	Hyperpigmentation	
Inconstant	Hirsutism of face	
Inconstant	Irritability and nervousness	

TABLE 3. Human Health Effects

	<u>Clinical Findings</u>	<u>Laboratory or Test Findings</u>
Common	Persistent chloracne	
	Increased frequency of actinic elastosis associated with chloracne	
	Male hirsutism	
Suggestive	Increased frequency upper GI ulcer	Abnormal PFT among present smokers Abnormal HDL among those with persistent chloracne

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