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REVIEW OF EXPOSURE AND PATHOLOGY DATA FOR SEVEN CASES REPORTED AS SOFT TISSUE SARCOMA AMONG PERSONS OCCUPATIONALLY EXPOSED TO DIOXIN-CONTAMINATED HERBICIDES

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Data from two Swedish studies (1,2) and a review of four U.S. studies (3) of dioxin-exposed workers have suggested that occupational exposure to dioxin-contaminated products is associated with an increased risk of soft tissue sarcoma (STS). Soft tissue sarcomas are malignant neoplasms arising throughout the body from mesenchymal supporting tissue other than bone (4). The principal types of histopathologic subtypes and their frequencies are listed in Table 1.

Table 1. Histopathologic varieties of sarcoma of soft tissue.*

Histopathological Variety	Percentage of Total Cases
Rhabdomyosarcoma	19.2
Fibrosarcoma	19.0
Liposarcoma	18.2
Malignant fibrohistiocytoma	10.5
Sarcoma of Soft Tissue, type unspecified	10.0
Synovial sarcoma	6.9
Leiomyosarcoma	6.5
Malignant schwannoma	4.9
Angiosarcoma	2.7
Other types	1.9

* Table presented in Suit, H.D., Sarcoma of soft tissue, CA-A Cancer Journal for Clinicians 1978; 28:284-295.

The percentages were derived from a study of 1,215 sarcomas by the Task Force for Sarcoma of Soft Tissue of the American Joint Committee on Cancer (5).

Dioxins are generated as unintended contaminants during the chemical manufacture of chlorinated phenoxy acetic acids and chlorinated phenols. The most toxic of the 75 dioxin isomers, 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD), is generated during

the production of trichlorophenol (TCP) and its derivative, the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Industrial workers who produce chlorinated phenoxy acetic acids and chlorophenols, and herbicide applicators who spray these products, potentially have been exposed to the products and their dioxin contaminants. In 1977, several cases of soft tissue sarcoma were reported among Swedish lumberjacks who had had prior exposure to phenoxy herbicides. This clinical observation led researchers in Sweden to conduct two separate case control studies (1,2). Both studies found that persons with occupational exposure to phenoxy acids or chlorophenols had a fivefold increased risk of developing a soft tissue sarcoma.

At about the same time, four studies (6-9) were conducted in U.S. manufacturing plants of workers exposed to the herbicide 2,4,5-T and its chemical precursor, trichlorophenol. The dioxin isomer contaminating these products is the most toxic form, 2,3,7,8-TCDD. None of the four studies found any statistically significant excess in total mortality or in death from cancer which was attributed to dioxin exposure. However, each cohort was small and of insufficient statistical power to allow adequate evaluation of rare causes of death. Honchar (3) reviewed the deaths in the four cohorts, and found that three (2.9%) of the total 105 deaths in the merged cohorts were reported to be from soft tissue sarcoma. Based on national statistics, only 0.07% of deaths was expected to be due to this cause. Table 2 lists these three deaths as Cases 1 to 3. Subsequently, Dr. Ralph Cook of Dow Chemical Company reported a fourth, living person in one of these cohorts as having a soft tissue sarcoma (10). This individual, Case 4, is now deceased. Dr. Marion Moses of Mt. Sinai reported an additional case of soft tissue sarcoma in an individual (Case 5) employed at one of the same four chemical manufacturing sites (11). Subsequently, two additional persons, Cases 6 and 7, were reported to have soft tissue sarcomas (12). They worked at a chemical manufacturing site which produced 2,4,5-T, but which had not been previously studied, and their exposures had not been confirmed at the time of the reports.

Table 2. Exposure data from original publications for the seven U.S. workers.

Case Number	Type of Exposure	Type of Report	Reference
1	TCP	Mortality Study	Zack, J. and Suskind, R.S. Journal of Occupational Medicine 1980; 22:11-14.
2	2,4,5-T	Mortality Study	Zack, J. and Gaffey, W.R. Environmental Science Research 1983; 26:575-591.
3	TCP	Mortality Study	Cook, R.R. et al. Journal of Occupational Medicine 1980; 22:530-32.
4	TCP	Case Report	Cook, R.R. Lancet 1981; i:618-619.
5	TCP, 2,4,5-T	Case Report	Moses, M. and Selikoff, I.J. Lancet 1981; i: 1370.
6	Chlorophenols	Case Report	Johnson, F.E. et al. Lancet 1981; i:40.
7	Chlorophenols	Case Report	Johnson, F.E. et al. Lancet 1981; i:40.

We have obtained detailed employment records, medical and pathological reports, tissue specimens and death certificates for these seven individuals and present here detailed descriptions of our occupational and pathologic reviews. We hope, through this report, to focus attention on the problems associated with the study of soft tissue sarcomas in dioxin-exposed populations. In addition to our work at the National Institute for Occupational Safety and Health (NIOSH), studies of the health effects of dioxin are underway at the Centers for Disease Control (CDC), the Veterans Administration (VA), the National Institutes of Health (NIH), and various state agencies in this country. Other organizations, both here and abroad, are also conducting studies of soft tissue sarcoma, and the International Agency for Research on Cancer (IARC) of the World Health Organization is considering an International Dioxin Registry.

EXPOSURE DATA FOR THE SEVEN CASES

Table 3 presents the exposure history of each individual. We used a rigorous criterion of exposure. An individual was considered exposed to products contaminated with 2,3,7,8-TCDD if he had a company record of assignment to a department producing trichlorophenol or 2,4,5-T.

Table 3. Work history information for the seven U.S. workers.

Case Number	Facility	Years of Employment	Job Title	Duration of Exposure (Years)
1	A	1946-1978	TCP Operator	1.9
2	A	1946-1972	2,4,5-T Operator	2.0
3	B	1950-1975	Maintenance	3.5
4	B	1951-1982	TCP Operator Plant Mechanic (TCP Department)	19.0
5	A	1943-1975	Maintenance Service	--
6	C	1978-1980	Production Worker	--
7	C	1951-1980	Production Worker	11 days

The work histories confirmed the original reports that Cases 1, 2, and 4 were production workers assigned to the trichlorophenol or 2,4,5-T departments. Case 3 was a maintenance worker identified by the company as assigned to a building where trichlorophenol was produced. Case 5 was a maintenance and service worker for 32 years in a chemical manufacturing site which produced trichlorophenol, 2,4,5-T, and many other chemicals, but he had no record of specific assignment to a trichlorophenol or 2,4,5-T department. Case 6 worked two and one-half years in a plant which made 2,4,5-T. He was a production worker but had no record of assignment to the 2,4,5-T area. Case 7 is the father of Case 6 and was a production worker at the same facility for 29 years. His work history showed no record of assignment to the 2,4,5-T area, although he did work for 11 days

following hire in 1951 in a pentachlorophenol area. Pentachlorophenol is contaminated with hexa-, hepta- and octachlorinated isomers of dioxin, but does not contain 2,3,7,8-TCDD. These last three individuals illustrate some of the difficulties encountered in attempting to verify exposure in chemical workers. In general, production workers do have records of regular assignment to specific departments within complex chemical manufacturing plants, although their records do not show temporary changes in assignments. However, maintenance workers such as Case 5 often work throughout an entire facility and never have recorded assignments in specific departments. From our examination of their work histories we concluded that these three workers did not meet our stringent criterion of exposure, since they had no records of assignment to a 2,4,5-T or trichlorophenol process. However, absence of such documentation does not eliminate the possibility that they were exposed to dioxin contaminated products during their routine activities.

PATHOLOGY DATA FOR THE SEVEN CASES

Table 4 summarizes clinical observations obtained from company medical records, hospital records, and pathology reports for the seven individuals. All cases were reported to have soft tissue sarcomas.

Table 4. Medical information for the seven U.S. workers.

Case Number	Tumor	Onset of Tumor	Age at Onset	Chloracne
1	Malignant fibrous histiocytoma	1978	58	yes
2	Adenocarcinoma, bladder	1958	34	yes
	Liposarcoma, rectum	1972	49	
3	Fibrosarcoma	1973	52	dermatitis
4	Malignant fibrous histiocytoma	1979	58	yes
5	Neurogenic sarcoma	1980	57	no

Table 4. Continued.

Case Number	Tumor	Onset of Tumor	Age at Onset	Chloracne
6	Fibrosarcomatous mesothelioma	1980	33	no
7	Liposarcoma	1980	53	no

Cases 1, 2, and 4 had records of diagnosed chloracne. Case 3 had dermatitis of the face and neck while assigned to the trichlorophenol building during a period when 49 trichlorophenol workers developed chloracne (8). But no chloracne was found in the records of Cases 5, 6, and 7.

Table 5 presents data on the latency of the tumors (time from first exposure to diagnosis of the tumor) for each individual.

Table 5. Latency of tumors for seven U.S. workers.

Case Number	First Assignment to 2,4,5-T or TCP Department	STS Tumor Onset	Latency* (Years)	Age at Onset
1	1949	1978	29	58
2	1950	1971	21	49
3	1964	1973	9	52
4	1951	1979	28	58
5	never	1980	N.A.**	57
6	never	1980	N.A.	33
7	never	1980	N.A.	53

* Time from first exposure to onset of tumor.
** Not applicable.

Adequate latency for development of cancer was experienced by the four individuals with records of assignment to trichlorophenol or 2,4,5-T departments (Cases 1 to 4). Since no records of specific departmental assignment to TCP or 2,4,5-T departments exist for the

remaining three individuals, latency cannot be assigned for exposure to 2,3,7,8-TCDD.

DEATH CERTIFICATE DATA VS. PATHOLOGIC DIAGNOSES AND ICD CODING CATEGORIES

Table 6 compares the diagnoses made by the attending pathologists with the information on the death certificates.

Table 6. Comparison of death certificate data with original pathologic diagnoses for the seven U.S. workers.

Case Number	Death Certificate	Original Pathology
1	Malignant fibrous histiocytoma	Malignant fibrous histiocytoma
2	Liposarcoma	Liposarcoma
3	Fibrosarcoma	Fibrosarcoma
4	Malignant fibrous histiocytoma	Malignant fibrous histiocytoma
5	Carcinomatosis	Myxoid neurogenic sarcoma
6	Metastatic mesothelioma	Fibrosarcoma consistent with fibrosarcomatous mesothelioma
7	N.A.*	Myxoid liposarcoma

* Not applicable. Individual is alive.

Of the six deceased cases, all of whom had hospital diagnoses of soft tissue sarcoma, only four had soft tissue sarcoma noted on their death certificates (Cases 1 to 4). A similar finding was noted in a study of the accuracy of death certificates conducted by Percy et al. in 1981 (13). They reviewed almost 50,000 hospital diagnoses and death certificates and found that of 252 soft tissue sarcomas diagnosed in hospital records, only 142 death certificates for those individuals (55%) reported the soft tissue sarcomas. Hence using

death certificates as the primary source of cases may lead to underascertainment of cases.

We found in our review that all four death certificates with notations of soft tissue sarcoma (Cases 1 to 4) belonged to persons who had diagnoses of soft tissue sarcoma made by the attending pathologists. In contrast, Percy (13) found in her large study that only 56% of death certificates with notation of soft tissue sarcoma were supported by hospital records with the diagnoses of soft tissue sarcoma. Hence using death certificates as the primary source of cases and not confirming hospital or pathologic information may lead to overascertainment. Researchers conducting epidemiologic studies should be fully aware of possible underascertainment or overascertainment.

Table 7 illustrates another issue in the use of death certificate data: consistency in classification by nosologists, the experts who code cause of death from death certificates according to the rules of the International Classification of Disease System (14).

Table 7. Comparison of death certificate information and nosologic coding of the information.

Case Number	Death Certificate	ICD Category* Original Publication**	ICD Category* Honchar Review***
1	Malignant fibrous histiocytoma	173.9	171

* World Health Organization, Manual of the International Statistical Classification Diseases, Injuries and Causes of Death, Geneva. Ninth Revision, 1975.

** Zack, J.A. and Suskind, R.S. Journal of Occupational Medicine 1980; 22:11-14.

*** Honchar, P.A. and Halperin, W.E. Lancet 1981; i:268-269.

Case 1 was reported in the original publication as having a malignant fibrous histiocytoma, which was coded in ICD Category 173.9, "Other malignant neoplasm of skin, site unspecified". Honchar indicated in

her review (3) that the choice of her nosologist was ICD 171, "Malignant neoplasm of connective and other soft tissue". Misclassification in ICD categories could introduce significant error. The data in Table 7 suggest that coding by more than one trained nosologist may be desirable.

Another important issue of classification not addressed by this review has serious implications for studies of soft tissue sarcoma. The International Classification of Disease System is a site-oriented classification scheme. Therefore, sarcomas that develop in the parenchymatous organs such as the uterus or stomach are coded into the ICD categories for the organ site. Only soft tissue sarcomas of the supporting tissue of the body not specified as arising in organs are coded in the ICD Category 171. It is possible, therefore, to select soft tissue sarcoma cases for case control studies in two ways. For the early Swedish studies (1,2) cases were selected by their histopathologic characteristics; approximately 60% of these cases are coded in categories other than ICD 171 (15). A current case control study in New Zealand (16) includes only soft tissue sarcoma cases coded as ICD 171. Such differences in study design must be recognized when evaluating results. The problem presented by the ICD dual classification scheme is slightly different for cohort mortality studies. It is possible to compare sarcomas coded as ICD 171 with those arising in the national population; however, we are not aware of population rates for soft tissue sarcoma coded into other ICD categories.

ORIGINAL REPORT DATA VS. NEW REVIEW DATA

Table 8 compares the original pathologic diagnoses for the seven individuals with the diagnoses selected in two independent pathologic reviews of tissue specimens.

Table 8. Comparison of the original pathology reports with reports of two reviewers.*

Case Number	Original Pathology	Review #1	Review #2
1	Malignant fibrous histiocytoma	Malignant fibrous histiocytoma	Malignant fibrous histiocytoma
2	Invasive pleomorphic liposarcoma	Poorly differentiated carcinoma	Carcinoma, poorly differentiated
3	Fibrosarcoma	Clear cell carcinoma with spindling, renal	Spindle cell renal carcinoma
4	Malignant fibrous histiocytoma	Malignant fibrous histiocytoma	Malignant schwannoma
5	Myxoid neurogenic sarcoma	Leiomyosarcoma	Malignant fibro-histiocytoma
6	Fibrosarcoma	Malignant schwannoma	Malignant schwannoma
7	Liposarcoma	Myxoid liposarcoma	Myxoid liposarcoma

* The tissue specimens were reviewed by one of the authors (W.O.R.) and also by Franz M. Enzinger, M.D. and Sharon M. Weiss, M.D. of the Armed Forces Institute of Pathology, Washington, DC.

Although all seven individuals received diagnoses of soft tissue sarcoma by the original pathologists, only five of the cases were diagnosed as soft tissue sarcoma in each of the two reviews. In both reviews Cases 2 and 3 were identified as carcinomas rather than sarcomas. These results indicate that review of tissue specimens by pathologists with expertise in diagnosing soft tissue sarcomas is necessary for epidemiologic studies. A difficult problem arises for cohort mortality studies because there is no comparison group for cases ascertained by expert pathologists. Rates of disease commonly used for comparison are those taken from compilations of population rates based on information from death certificates.

The adequacy of diagnosis of histological subtypes of soft tissue sarcoma is another issue raised by the data in Table 8. Although the original pathologists and the reviewers all agreed that five individuals had soft tissue sarcomas, they agreed on the histological subtype for only two individuals, Cases 1 and 7. Even the expert

reviewers disagreed on subtype diagnoses for Cases 4 and 5. Because of the difficulties involved in diagnosing the histological subtypes, particularly when only a limited amount of tissue is available for review, we recommend that epidemiologic studies continue to focus on the outcome soft tissue sarcoma, and assess the distribution of subtypes only cautiously and with a recognition of the limitations involved.

The next two tables summarize the exposure histories and the pathologic findings and compare them to the information published in the original reports. Table 9 presents data for the four production workers identified in company studies (6-10) as 2,4,5-T or trichlorophenol-exposed workers.

Table 9. Comparison of original reports with results from this review for production workers identified by companies as TCP* or 2,4,5-T workers.

Case Number	Reported Exposure		Cause of death	
	Original Report	This Review	Original Report	This Review
1	TCP	TCP	STS	STS
2	2,4,5-T	2,4,5-T	STS	Carcinoma
3	TCP	TCP	STS	Carcinoma
4	TCP	TCP	STS	STS

* Terms: TCP, trichlorophenol; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; STS, soft tissue sarcoma.

The reported exposures were confirmed by documentation that the four individuals had been assigned to 2,4,5-T or TCP processes. All had been reported as having soft tissue sarcomas, but we report that the two expert pathologists confirm that only two individuals (Cases 1 and 4) had soft tissue sarcomas. Both of these individuals worked in trichlorophenol processes, had diagnosed chloracne, and were present during incidents of unusual operating conditions with probable exposure to 2,3,7,8-TCDD. The histological subtype of malignant fibrous histiocytoma was selected by all three pathologists for Case 1. Case 4 also received a diagnosis of malignant fibrous

histiocytoma from the original pathologist and one reviewer. The second reviewer identified the subtype as a neurogenic schwannoma.

Table 10 presents the same comparison for the three individuals originally described in case reports by physicians (11,12).

Table 10. Comparison of original reports with results from this review for production workers originally described as case reports by physicians.

Case Number	Reported Exposure: Original Report	Reported Exposure: This Review	Pathologic Diagnosis: Original Report	Pathologic Diagnosis: This Review
5	Possibly 2,4,5-T,* TCP	None	STS	STS
6	Possibly chlorophenols	None	STS	STS
7	Possibly chlorophenols	PCP	STS	STS

* Terms: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; TCP, trichlorophenol; PCP, pentachlorophenol; STS, soft tissue sarcoma.

Review of the tissue specimens for all three workers were confirmed that they had soft tissue sarcomas. Examination of the work history records of the individuals did not document assignment to 2,4,5-T or trichlorophenol departments. However, Case 7 worked briefly upon hire in a pentachlorophenol department.

CONCLUSION

Swedish research (1,2) has drawn attention to the issue of soft tissue sarcoma and dioxin exposure. While each of the original four U.S. studies (6-9) reported non-positive findings, a reanalysis (3) and further reports (10,11) strengthened the suspicion that an association might exist. Honchar (3) and Cook (10) called for detailed examination of the data. We present the detailed assessment of exposure history and pathologic diagnosis and report that of the four soft tissue sarcoma cases identified by death certificates among

the TCP and 2,4,5-T workers, two are confirmed following pathologic review of tissues as soft tissue sarcoma. It is not possible to use our data to draw a definitive conclusion regarding the suspected association because we are not aware of any population rates for soft tissue sarcoma based upon pathologic review of tissue specimens.

Cases 5, 6 and 7 were originally described in the literature as individual case reports. All three are confirmed as cases of soft tissue sarcoma. Our review of their work histories did not find any record of assignment to 2,4,5-T or trichlorophenol departments, although Case 7 worked briefly in a pentachlorophenol department, a product contaminated with isomers of dioxin considered to be less toxic than 2,3,7,8-TCDD. Although these workers do not meet our stringent criterion of exposure by virtue of assignment to a 2,4,5-T or TCP department, we cannot exclude the possibility that they had undocumented contact with 2,4,5-T or TCP.

This review examines the complexities in evaluating the dioxin exposure of individuals and the pathologic diagnoses of soft tissue sarcoma. It emphasizes the need for carefully-designed large epidemiologic studies to adequately assess whether there is an association of soft tissue sarcoma with exposure to dioxin-contaminated products. We have shown that the use of the death certificate, even with the original pathologic diagnosis may lead to overascertainment or underascertainment of cases of soft tissue sarcoma. Finally, we reassert that further research, particularly the completion of National Institute for Occupational Safety and Health studies based upon approximately 6,000 U.S. workers, is necessary to confirm or refute the association first suggested in the Swedish studies.

ABSTRACT

We have reviewed medical and exposure records and pathology specimens of seven U.S. chemical workers reported in the literature to be cases of soft tissue sarcoma (STS) and to have had dioxin exposure. The cases were of interest because two Swedish studies demonstrated a strong association between STS and dioxin exposure.

Four U.S. workers from four small mortality cohorts had been reported to have died of soft tissue sarcoma. We found that these individuals had employment records of assignment to production of TCP and 2,4,5-T which are contaminated with the most toxic dioxin isomer, 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), but pathologic review of their tissue indicates that only two are cases of soft tissue sarcoma. Three additional individuals had been described by physicians as case reports. They are confirmed as cases of soft tissue sarcoma, but we did not find any record of assignment to these production departments. One person worked briefly in the production of pentachlorophenol, which is contaminated with other isomers of dioxin. We suggest that identification of cases of STS through either death certificates alone or through pathology records can lead to errors of ascertainment. We reassert that further research, particularly the completion of studies by the National Institute for Occupational Safety and Health based upon approximately 6,000 U.S. workers, is necessary to confirm or refute the association first suggested in the Swedish studies.

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