Occupational Chlorophenol Exposure and Soft Tissue Sarcoma Risk among Men Aged 30–60 Years

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To evaluate the association of chlorophenol exposure with soft tissue sarcoma risk independent of phenoxyherbicide exposure, the authors analyzed data from the Selected Cancers Study, a population-based case-control study that included 295 male soft tissue sarcoma cases, aged 32–60 years, from eight population-based cancer registries and 1,908 male controls. Chlorophenol exposure was assigned using both an intensity and a confidence estimate by an industrial hygienist based on verbatim job descriptions. Seventeen percent of the jobs rated as high intensity involved wood preservation, while 82% involved cutting oils. Soft tissue sarcoma risk, modeled using conditional logistic regression, was significantly associated with ever having high-intensity chlorophenol exposure (odds ratio = 1.79, 95% confidence interval 1.10–2.88). A duration-response trend was evident among more highly exposed subjects (p for trend < 0.0001). For subjects with 10 or more years of substantial exposure, the odds ratio was 7.78 (95% confidence interval 2.46–24.65). These results suggest that chlorophenol exposure independent of phenoxyherbicides may increase the risk of soft tissue sarcoma. Because of the large number of machinists in the exposed group and the complex composition of cutting fluids, it is possible that another exposure involved in machining is responsible for the observed excess risk. Am J Epidemiol 1998;148:693–703.

Chlorophenols, phenoxyherbicides, and dioxins are all suspected to increase soft tissue sarcoma risk in humans. However, the epidemiologic evidence is inconsistent. A Swedish case-control study by Hardell and Sandstrom (1) first identified a positive association between chlorophenols, alone and with phenoxyherbicides, and soft tissue sarcoma. Since then, numerous case-control and cohort studies have been conducted to consider the potential association between exposures to these chemical groups and soft tissue sarcoma (2–15). Relative risk estimates for chlorophenol exposure and soft tissue sarcoma observed in these studies range from 1.0 to 6.6 (1, 5, 11); similar values have been observed in studies considering phenoxyherbi-

cide manufacturing and application (13, 15, 16). Many of these studies have considered both chlorophenol and phenoxyherbicide exposure (1, 7–9, 11) as well as the potential for dioxin contamination of the specific phenoxyherbicides of interest (9, 14, 15).

Untangling the roles and interactions of chlorophenols, phenoxyherbicides, and dioxins in relation to soft tissue sarcoma has proven to be difficult because chlorophenols are used in the production of phenoxyherbicides, and dioxins have been found in the technical products of both chlorophenols and phenoxyherbicides. Chlorophenols have been used for a variety of purposes, including wood treatment, phenoxyherbicide manufacture, biocides in cutting oils and in glues, leather tanning, algicides, and termite control (17–20). Exposure to chlorophenols occurs through both inhalation and dermal routes, although dermal absorption was reported to be the more important exposure route in sawmill workers because of contact with chlorophenol-containing materials (21). Since the primary route of exposure to chlorophenols is expected to be through the skin, workers handling treated wood, machining with cutting fluids, and making leather goods are all anticipated to have daily occupational exposure to chlorophenols when they are used as biocides and preservatives in these products.
Soft tissue sarcoma is a rare cancer representing approximately 1 percent of all cancer deaths in adults (22). Due to the rarity of the cancer and the complex nature of chlorophenol and phenoxyherbicide use and exposure, studies with adequate sample size and exposure data are limited (16). To investigate the role of chlorophenol exposure independent of phenoxyherbicide use and production, we analyzed data from a large, population-based case-control study of incident soft tissue sarcoma cases in males on the basis of chlorophenol exposure assignments by an industrial hygienist.

**MATERIALS AND METHODS**

Data from the Selected Cancers Cooperative Study Group were used to investigate the role of chlorophenol exposure and soft tissue sarcoma. The Selected Cancers Study was a large, population-based case-control study conducted to evaluate the cancer risks of men who served in the US military in Vietnam (23). Six cancers were included in the study: soft tissue and other sarcomas, non-Hodgkin's lymphoma, Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer. This analysis will focus on the soft tissue sarcoma cases and controls.

The study population for the Selected Cancers Study was limited to men born between 1929 and 1953 to include the age group eligible for service in Vietnam. Cases were all men who were first diagnosed with sarcoma between December 1, 1984, and November 30, 1988, and who lived in the geographic regions of the eight participating cancer registries (Connecticut; Kansas; Iowa; Miami, Florida; Detroit, Michigan; San Francisco, California; Seattle, Washington; and Atlanta, Georgia). Any case with a definitive or tentative diagnosis of sarcoma was eligible for inclusion in the study; men with a diagnosis of Kaposi's sarcoma or mesothelioma were excluded. Case inclusion criteria was based on a list of more than 60 International Classification of Diseases for Oncology (24) morphologic codes and subclassifications; morphologic features were confirmed and classified by a review panel of three pathologists (23). Only confirmed cases were included. A common control group of living controls for all six of the cancer groups was obtained using random digit dialing. Controls were frequency matched on 5-year age interval and registry of the lymphoma case subjects (i.e., 40 matching strata).

For this analysis, the study population was limited to those soft tissue sarcoma cases and controls alive at the time of interview because they had more complete job history information. For comparability with previous studies of chlorophenols and sarcoma, this analysis was restricted to confirmed cases of soft tissue sarcoma (fibrohistiocytic, fatty, and muscular sarcomas as well as dermatofibrosarcoma protuberans and other soft tissue sarcomas). Strictly defined, soft tissue sarcomas are malignant neoplasms derived from the nonepithelial, extraskeletal tissue of the body exclusive of those arising in the reticuloendothelial system (lymphomas), from the glia (certain brain and spinal cord tumors), and from the supportive tissue of various parenchymal organs (e.g., mural smooth muscle of the gut). This definition was used to define cases in our report, with the notable exception that visceral sarcomas (the latter subset) were also included in the case definition for consistency with previous studies. These will be collectively referred to as soft tissue sarcomas. Subjects with a history of von Recklinghausen's neurofibromatosis (a condition that predisposes patients to sarcoma) and those with a self-report or registry report of acquired immune deficiency syndrome or a history of Gardner's syndrome were excluded from the analysis.

Exposure information was obtained via telephone interview by using a standardized questionnaire administered by trained personnel (23). Interviews were conducted soon after diagnosis; the median time from case diagnosis to interview was 90 days, with 90 percent of the interviews conducted within 1 year of diagnosis. Detailed data were collected regarding demographic characteristics, medical history, military service, phenoxyherbicide use, and occupational history. Subjects were asked to provide job title, main duties, type of business or industry, and dates of employment for every job that they had held for a year or longer from age 18 years until the time of interview. Information was also obtained regarding jobs held for shorter periods for questions pertaining to exposures of interest, such as working with cutting oils or wood preservative chemicals. All jobs held prior to the date of diagnosis for cases and the time of interview for controls were included.

Chlorophenol exposure was estimated by an experienced industrial hygienist on the basis of the verbatim job histories for those jobs that involved working with wood preservatives, cutting oils, sawmills, leather tanning, or shoe dust. Questions relating to potential chlorophenol exposure were selected prior to the assignment of exposure and were based on a review of the historical uses of chlorophenol in the United States. The industrial hygienist (R. F. H.) was experienced both in field industrial hygiene and in exposure estimation for occupational epidemiology studies using job descriptions and historical exposure information. The exposure estimate was assigned independently of outcome; the industrial hygienist reviewed jobs without knowledge of the subject's disease status. This chlorophenol exposure estimate did
not make use of information regarding the calendar time period or the duration of time the job was held. Each of the jobs was rated using the verbatim information on occupation, industry, and work responsibilities for potential exposure to chlorophenols. The information on work responsibilities consisted of short, narrative statements (e.g., cut trees, turned logs, ran drill press). Because of the nature of the information on occupation and job responsibilities, a qualitative exposure assessment strategy was selected; potential exposure intensity and level of confidence in the exposure estimate were assigned for each job. Exposure intensity was first assessed as one of four categories (unexposed or low, medium, or high exposure), and then the level of confidence associated with the assignment was identified (low, medium, or high). Because many of the chlorophenols are well-absorbed by the skin, the exposure assessment considered the potential for both dermal contact and inhalation. Industrial hygienist rating of exposure based on verbatim job history information has been used in previous occupational epidemiology studies to obtain comparable exposure measures across diverse industrial and occupational populations (25, 26).

Exposure groups were created on the basis of the industrial hygienist's assessment. Each job was classified as unexposed, minimal, moderate, or substantial exposure based on the matrix presented in figure 1. Those jobs with a confidence level of low were assigned as unexposed, regardless of the intensity. Jobs of low intensity with medium or high confidence were assigned as minimal exposure, as were jobs with medium intensity and medium confidence. Jobs with medium intensity and high confidence and those with high intensity and medium confidence were defined as moderate exposure. Those jobs with both high intensity and high confidence were considered as substantial exposure. This exposure definition is similar to that used by Siemiatycki et al. (25) to categorize exposure in a large, occupational case-control study. Duration of exposure at each level was calculated based on all jobs held at that exposure level. In cases of multiple chlorophenol exposed jobs during the same time period, only the highest exposure level during that period was included.

Data analysis consisted of calculation of adjusted odds ratios for the association of chlorophenol exposure and soft tissue sarcoma. Logistic regression models were constructed to include all known and suspected risk factors and potential confounders. Covariates included in all models were the matching factors (age and registry), race/ethnic groups (five categories: Asian, black, Hispanic, white, and other), Jewish religion, and medical radiation therapy 5 years prior to enrollment in the study. Suspected risk factors of interest evaluated included use of chemotherapy 5 years prior to study, herbicide use (both phenoxyherbicides and other types of herbicides), and occupational exposure to asbestos. Once the baseline logistic model was constructed, the role of chlorophenol was assessed using a number of exposure metrics: 1) ever versus never exposed; 2) hierarchical categories based on the industrial hygienist's exposure classification using both intensity and confidence estimates; and 3) duration-response modeling based on number of years at moderate or substantial exposure and then restricted to substantial exposure only. All analyses were conducted using conditional logistic regression to account for matching by 5-year age group and registry using SAS version 6.09 (27).

**RESULTS**

The study population was limited to the 301 soft tissue sarcoma cases alive at the time of interview and the 1,910 living controls from the Selected Cancers Study. In the Selected Cancers Study, 521 of the 612 identified incident sarcoma cases were interviewed; pathology specimens were obtained for 511 of the interviewed cases. Pathology review confirmed the diagnosis of sarcoma in 386 cases, and of these, 335 were confirmed to be soft tissue sarcoma. Thirty-four cases had proxy interviews and were excluded from this analysis. Men with a history of acquired immunodeficiency syndrome, Gardner's syndrome, or von Recklinghausen's disease were also excluded, leaving 295 soft tissue sarcoma cases and 1,908 controls. The selection strategy is presented in table 1. Table 2 presents the distribution of soft tissue sarcoma subtypes among the cases.

Demographic and medical history characteristics were similar between cases and controls (table 3). The study subjects ranged in age from 32 to 60 years at the time of interview, with a mean age of 46.4 years. Black subjects were more highly represented among the cases than among the controls ($p < 0.0001$). Cases...
percent were classified as having chlorophenol exposure. These jobs were mill work, leather work, and shoe dust. Sixty-one of those involving wood preservation, cutting oils, sawdust were not significantly different (p = 0.88). The proportions of subjects who reported jobs entailing work with or around wood preservatives, cutting oils, and sawdust were not significantly different between cases and controls.

A total of 1,054 jobs from the 12,856 jobs held by subjects were evaluated by the industrial hygienist for potential exposure to chlorophenol. These jobs were those involving wood preservation, cutting oils, sawmill work, leather work, and shoe dust. Sixty-one percent were classified as having chlorophenol exposure with medium or high confidence in the exposure estimate. A total of 299 jobs were classified as low intensity, 204 jobs as medium intensity, and 141 jobs as high intensity. Of the 141 high chlorophenol intensity jobs, 82 percent were associated with cutting oil exposure and 17 percent were associated with wood preservative exposure.

A total of 498 subjects (68 cases (23 percent) and 430 controls (23 percent)) were classified as exposed to any chlorophenol at any job with medium or high confidence by the hygienist. The odds ratio for any chlorophenol exposure was 1.06 (95 percent confidence interval (CI) 0.78–1.43). Using more restrictive definitions of exposure based both on intensity and on confidence in the exposure assignment, an elevated risk of soft tissue sarcoma was associated with higher intensities of exposure and greater confidence in the assignment of exposure. Subjects with jobs rated as high intensity and having a high confidence of exposure (18 cases and 61 controls) had a statistically significant odds ratio of 2.10 (95 percent CI 1.19–3.68). Table 5 presents the adjusted odds ratios for chlorophenol exposure and soft tissue sarcoma for all intensity levels and medium and high confidence levels. All logistic regression models were adjusted for the design variables (age and registry), racial group, Jewish religion, medical radiation therapy 5 years prior to interview, and the use of herbicides on a farm 5 or more years before diagnosis.

Subjects exposed to chlorophenol had between one and eight jobs that contributed to their lifetime chlorophenol exposure. Of the 492 subjects exposed to any level of chlorophenol, the duration of exposure ranged from 0.5 to 40 years, with a median exposure duration of 6 years for controls and 8.5 years for cases. Duration was not calculated for six subjects with missing employment dates. For subjects with moderate and substantial chlorophenol exposure, the median exposure duration was significantly greater among cases with a median exposure of 8 years compared with 3 years for controls (p = 0.018). Table 6 presents the exposure durations for three exposure categories: minimal exposure and higher, moderate exposure and higher, and substantial exposure alone.

Duration-response models were constructed using the number of years at jobs classified as either moderately or substantially exposed to chlorophenol. Duration-response was modeled using a four-level categorical variable (nonexposed and exposed <5 years, 5–9.5 years, ≥10 years) and as a continuous variable. All duration-response models included the same variables as the previous models. Elevated odds ratios were observed for exposure durations of more than 5 years, with a statistically significant duration-response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men with sarcoma (sample size)</th>
<th>Living controls (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases identified</td>
<td>612</td>
<td></td>
</tr>
<tr>
<td>Controls selected for interview</td>
<td></td>
<td>2,299</td>
</tr>
<tr>
<td>Interviewed</td>
<td>521</td>
<td>1,910</td>
</tr>
<tr>
<td>Pathology specimen obtained</td>
<td>511</td>
<td></td>
</tr>
<tr>
<td>Diagnosis confirmed</td>
<td>386</td>
<td></td>
</tr>
<tr>
<td>Soft-tissue sarcoma confirmed</td>
<td>335</td>
<td></td>
</tr>
<tr>
<td>Alive at time of interview</td>
<td>301</td>
<td>1,910</td>
</tr>
<tr>
<td>Excluded from analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>vonRecklinghausen's disease</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Gardner's syndrome</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total excluded</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Total available for analysis</td>
<td>295</td>
<td>1,908</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Soft-tissue sarcoma subtype</th>
<th>Sample size</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All soft-tissue sarcomas</td>
<td>295</td>
<td>100.0</td>
</tr>
<tr>
<td>Fibrohistiocytic</td>
<td>32</td>
<td>10.8</td>
</tr>
<tr>
<td>Lipomatous</td>
<td>53</td>
<td>18.0</td>
</tr>
<tr>
<td>Leiomyomatous</td>
<td>67</td>
<td>22.7</td>
</tr>
<tr>
<td>General (including fibromatous,</td>
<td>43</td>
<td>14.6</td>
</tr>
<tr>
<td>rhabdomyosarcomas, synovial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and vascular sarcomas)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma (undefined)</td>
<td>52</td>
<td>17.6</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>48</td>
<td>16.3</td>
</tr>
</tbody>
</table>
TABLE 3. Demographic and medical characteristics of the soft-tissue sarcoma cases and controls, Selected Cancers Study, 1984–1988

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 295)</th>
<th>Controls (n = 1,908)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Matching factors</td>
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<td></td>
</tr>
<tr>
<td>Registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>7.8</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>14.2</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>7.8</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>8.1</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>22.4</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>19.0</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>12.2</td>
</tr>
<tr>
<td>Age at interview (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td>9</td>
<td>3.1</td>
</tr>
<tr>
<td>35–39</td>
<td>49</td>
<td>16.6</td>
</tr>
<tr>
<td>40–44</td>
<td>58</td>
<td>19.7</td>
</tr>
<tr>
<td>45–49</td>
<td>68</td>
<td>23.1</td>
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<tr>
<td>50–54</td>
<td>65</td>
<td>22.0</td>
</tr>
<tr>
<td>55–60</td>
<td>46</td>
<td>15.6</td>
</tr>
<tr>
<td>Demographic factors</td>
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<td></td>
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<tr>
<td>Race/ethnic group</td>
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<td></td>
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<tr>
<td>White</td>
<td>214</td>
<td>72.5</td>
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<tr>
<td>Black</td>
<td>50</td>
<td>17.0</td>
</tr>
<tr>
<td>Asian</td>
<td>7</td>
<td>2.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21</td>
<td>7.1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Jewish religion</td>
<td>13</td>
<td>4.4</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>49</td>
<td>16.7</td>
</tr>
<tr>
<td>High school graduate</td>
<td>83</td>
<td>28.2</td>
</tr>
<tr>
<td>1–3 years of college</td>
<td>62</td>
<td>21.1</td>
</tr>
<tr>
<td>College graduate</td>
<td>100</td>
<td>34.0</td>
</tr>
<tr>
<td>Income (dollars)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$20,000</td>
<td>82</td>
<td>27.8</td>
</tr>
<tr>
<td>$20,000–$29,999</td>
<td>43</td>
<td>14.8</td>
</tr>
<tr>
<td>$30,000–$39,999</td>
<td>39</td>
<td>13.2</td>
</tr>
<tr>
<td>$40,000–$49,999</td>
<td>40</td>
<td>13.8</td>
</tr>
<tr>
<td>≥$50,000</td>
<td>90</td>
<td>32.9</td>
</tr>
<tr>
<td>Medical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy 5 years before</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>reference date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical radiation therapy 5 years</td>
<td>15</td>
<td>5.1</td>
</tr>
<tr>
<td>before reference date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of androgenic steroids</td>
<td>7</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* p < 0.05; *** p < 0.001.

Trend (p < 0.0001). Table 7 presents the odds ratios for the duration-response modeling. Figure 2 illustrates the duration-response trend for substantial exposure. The results of the modeling of years of chlorophenol exposure as a continuous variable were consistent with the categorical modeling. For each year of substantial chlorophenol exposure, an elevated odds ratio of 1.11 (95 percent confidence interval (CI) 1.05–1.18) was observed. When the analysis was limited to only those jobs with chlorophenol exposure from cutting oils, a similar duration-response was observed; analysis for chlorophenol exposure from other...
sources was not performed due to the small number of exposed cases. Only six subjects (one case and five controls) had substantial chlorophenol exposure not related to cutting oils, and none were exposed for more than 10 years.

**DISCUSSION**

In this data set, an increased risk of soft tissue sarcoma was associated with occupational exposure to chlorophenols as determined by an industrial hygienist using each subject’s verbatim job history information collected via structured interview. A strong association with soft tissue sarcoma was seen using both dichotomous and duration measures of chlorophenol exposure. Phenoxyherbicide use was not associated with soft tissue sarcoma in this group, although this study had sufficient power (>80 percent) to detect a twofold increase in soft tissue sarcoma risk. Due to the limited nature of the exposure information in the current study, potential for dioxin exposure could not be evaluated.

The observed odds ratios for chlorophenol are consistent with those seen in other investigations examining the role of occupational exposure to chlorophenols and soft tissue sarcoma. A Swedish study (2) focusing on jobs in forestry, farming, and horticulture found an odds ratio for chlorophenol exposure without phenoxyherbicides of 3.3 (95 percent CI 1.3–8.1). The authors noted that they did not consider chlorophenol exposure from cutting oils and shoe and leather work because of the difficulty of specifying exposure. Another Swedish study (7), using a different population also found an elevated risk of 5.25 (95 percent CI 1.69–16.3) for soft tissue sarcoma associated with phenoxyherbicides of 3.3 (95 percent CI 1.3–8.1). The authors noted that they did not consider chlorophenol exposure from cutting oils and shoe and leather work because of the difficulty of specifying exposure. Another Swedish study (7), using a different population also found an elevated risk of 5.25 (95 percent CI 1.69–16.3) for soft tissue sarcoma associated with high-grade chlorophenol exposure, defined as greater than 1 week. Hardell and Sandstrom (1) found an elevated risk of 5.6 for workers exposed to chlorophenols alone based on at least 1 day of exposure. While our study found elevated odds ratios with exposures of long duration, all odds ratios for high-intensity exposures were statistically significant and consistent with the odds ratios observed in these studies. Since phenoxyherbicide and chlorophenol exposure frequently occur concurrently, an international cohort of sprayers and manufacturers was assembled to evaluate the role of each of these chemical types as well as to determine the potential for dioxin exposure (9, 28, 29). In the most recent publication, a dose response was seen for the number of years that an individual worked with chemicals potentially containing dioxin (15); however, no excess sar-

### Table 4. Occupational and environmental characteristics of the soft-tissue sarcoma cases and controls, Selected Cancers Study, 1984–1988

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases (n=295)</th>
<th>Controls (n=1,900)</th>
<th>Odds ratio*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutting oils†</td>
<td>62</td>
<td>21.0</td>
<td>383</td>
<td>20.1</td>
</tr>
<tr>
<td>Dry cleaning</td>
<td>13</td>
<td>4.4</td>
<td>57</td>
<td>3.0</td>
</tr>
<tr>
<td>Herbicides on a farm more than 5 years before reference date</td>
<td>52</td>
<td>17.6</td>
<td>237</td>
<td>12.4*</td>
</tr>
<tr>
<td>Metal packing/processing</td>
<td>26</td>
<td>8.8</td>
<td>113</td>
<td>5.9</td>
</tr>
<tr>
<td>Leather work†</td>
<td>1</td>
<td>0.3</td>
<td>11</td>
<td>0.6</td>
</tr>
<tr>
<td>Pesticides</td>
<td>32</td>
<td>10.9</td>
<td>201</td>
<td>10.5</td>
</tr>
<tr>
<td>Phenoxyherbicide use</td>
<td>17</td>
<td>5.6</td>
<td>106</td>
<td>5.8</td>
</tr>
<tr>
<td>Pulp/seed/planting mill work†</td>
<td>25</td>
<td>8.5</td>
<td>106</td>
<td>5.7</td>
</tr>
<tr>
<td>Shoe work†</td>
<td>7</td>
<td>2.4</td>
<td>29</td>
<td>1.5</td>
</tr>
<tr>
<td>Solvent exposure</td>
<td>117</td>
<td>39.7</td>
<td>775</td>
<td>40.6</td>
</tr>
<tr>
<td>Vinyl chloride†</td>
<td>11</td>
<td>3.7</td>
<td>128</td>
<td>6.7*</td>
</tr>
<tr>
<td>Wood preservatives†</td>
<td>35</td>
<td>11.9</td>
<td>221</td>
<td>11.6</td>
</tr>
</tbody>
</table>

* p < 0.05.  † Questions evaluated for potential chlorophenol exposure.

### Table 5. Odds ratios for chlorophenol exposure and soft-tissue sarcoma, Selected Cancers Study, 1984–1988

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Cases (n=295)</th>
<th>Controls (n=1,900)</th>
<th>Odds ratio*</th>
<th>95% confidence interval</th>
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<tbody>
<tr>
<td>Low, medium, or high</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>68</td>
<td>430</td>
<td>1.06</td>
<td>0.78–1.43</td>
</tr>
<tr>
<td>Medium</td>
<td>44</td>
<td>248</td>
<td>1.16</td>
<td>0.81–1.67</td>
</tr>
<tr>
<td>High</td>
<td>25</td>
<td>97</td>
<td>1.79</td>
<td>1.10–2.86</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High confidence of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low, medium, or high</td>
</tr>
<tr>
<td>Medium or high</td>
</tr>
<tr>
<td>High</td>
</tr>
</tbody>
</table>

* All odds ratios are adjusted for matching factors (age, registry), race/ethnic group, Jewish religion, medical radiation 5 years or more prior to diagnosis, and herbicide use 5 years prior to diagnosis.

### Table 6. Chlorophenol exposure duration for sarcoma cases and controls, Selected Cancers Study, 1984–1988

<table>
<thead>
<tr>
<th>Exposure level</th>
<th>Cases (n=426)</th>
<th>Controls (n=59)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal, moderate, and substantial‡</td>
<td>11</td>
<td>18</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>9.79</td>
<td>7.50</td>
<td>0.03</td>
</tr>
<tr>
<td>SD</td>
<td>8.54</td>
<td>4.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Median</td>
<td>8.5</td>
<td>4.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Range</td>
<td>0.5–35</td>
<td>0.5–29</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* p value from Wilcoxon test.  ‡ Not calculated for subjects with missing employment dates.  § Exposure levels are defined in figure 1.  ¶ SD, standard deviation.
Chlorophenols and Soft Tissue Sarcoma

**TABLE 7. Odds ratios for soft-tissue sarcoma and length of chlorophenol exposure, Selected Cancers Study, 1984–1988**

<table>
<thead>
<tr>
<th>Exposure parameter</th>
<th>No. exposed</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>( p ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate and substantial exposure (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonexposed</td>
<td>268</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>9</td>
<td>0.70</td>
<td>0.33–1.50</td>
<td>0.0001</td>
</tr>
<tr>
<td>5–9.5</td>
<td>8</td>
<td>2.49</td>
<td>1.07–5.81</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>12</td>
<td>4.38</td>
<td>2.09–9.17</td>
<td></td>
</tr>
<tr>
<td>Years (continuous)</td>
<td>29</td>
<td>1.07*</td>
<td>1.03–1.11</td>
<td></td>
</tr>
<tr>
<td>Substantial exposure (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonexposed</td>
<td>277</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>4</td>
<td>0.66</td>
<td>0.23–1.91</td>
<td>0.0001</td>
</tr>
<tr>
<td>5–9.5</td>
<td>8</td>
<td>5.19</td>
<td>2.06–13.10</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>6</td>
<td>7.78</td>
<td>2.46–24.65</td>
<td></td>
</tr>
<tr>
<td>Years (continuous)</td>
<td>18</td>
<td>1.11*</td>
<td>1.05–1.18</td>
<td></td>
</tr>
</tbody>
</table>

* Odds ratio for each year of chlorophenol exposure.

...RESULTS...

circoma risk or dose response was observed for chlorophenol exposure alone. Only nine cases of soft tissue sarcoma were observed in this cohort of 21,863 subjects. No elevation of soft tissue sarcoma risk was observed in a case-control study in western Washington State that specifically collected information on chlorophenol exposure, primarily pentachlorophenol, and categorized jobs as low, medium, and high pentachlorophenol exposure (5). Cohort studies of pentachlorophenol-manufacturing workers (20,000 person-years) (30), pentachlorophenol-exposed sawmill workers (583,000 person-years) (31), and carpenters (27,000 deaths) (32) have not identified a significant increase in soft tissue sarcoma, but given the rarity of this disease, the cohort would have to have more than 1 million person-years to detect a twofold risk in soft tissue sarcoma.

Exposure was assigned based on verbatim job history information, which was evaluated for potential chlorophenol exposure associated with five types of jobs. While the industrial hygiene evaluation of exposure intensity and confidence has been used in other occupational investigations (25, 26) without measured values for exposure levels, the exposure metric is inherently qualitative. Combining across five different work environments with widely different types of exposure also contributes to the qualitative nature of the exposure estimate. However, the industrial hygiene

![Graph](https://example.com/graph.png)

**FIGURE 2.** Duration-response for soft tissue sarcoma for subjects with substantial chlorophenol exposure, Selected Cancers Study, 1984–1988. •, odds ratio; —, 95 percent confidence interval.

assignment of potential exposure would be expected to result in a more precise measure than a yes/no response to working with or near cutting oils, since people who worked near, but not with, these chemicals were classified as nonexposed or as having low-intensity exposure. The effect of this is illustrated by the fact that none of the crude measures based on the subjects' responses were significantly associated with soft tissue sarcoma, while the chlorophenol variable constructed from the industrial hygiene assessment was significantly associated with the disease.

In this study, cutting oil exposure, rather than the use of wood preservative chemicals, drove the chlorophenol risk estimates. However, given that only one of the eight cancer registries was in a region of the United States where forestry occupations were common and that manufacturing was a common occupation among men aged 30–60 years during the study period (1950–1988) in the geographic regions from which the cases were drawn, the large contribution of machinists in the group exposed to chlorophenol appears reasonable. The chlorophenol exposure assessment for jobs with cutting oil exposure included estimates of the probable intensity and frequency of both dermal and inhalation contact. Machinists, whose day-to-day activities would result in direct dermal and inhalation contact, were among the most highly exposed group. Chlorophenols, including 2,3,6-trichlorophenol, 2,3,4,6-tetrachlorophenol, and pentachlorophenol salts, were used as biocides in cutting oils from the early 1940s until the 1970s (33, 34). Chlorophenol biocides were largely phased out by 1980 due to greater efficacy and ease of disposal of other biocides (35). Since biocides are frequently added by the end user rather than the formulator, the type of biocide used and the exposure concentration are difficult to estimate (36); biocide levels in cutting oils have been reported to range up to 1 percent of the solution (37). The subjects in this study worked with cutting oils from 1951 until 1988. As illustrated in figure 3, the percent of cases with substantial chlorophenol exposure associated with cutting fluids is greater than the percent of controls with similar exposure over the entire exposure period, and therefore, chlorophenol use in cutting fluids cannot be distinguished analytically from any other aspect of cutting fluids using different periods of exposure. Additionally, given the high prevalence of machinists in the substantially exposed group (71/77) and the complexity of the mixtures used as metalworking fluids, other non-chlorophenol-related expo-
sures associated with cutting fluids may be driving the soft tissue sarcoma risk.

Soft tissue sarcoma has not been reported in the cohort mortality studies of machinists (38–41). Given the rarity of these tumors and the complex International Classification of Diseases for Oncology classifications (42), soft tissue sarcomas may not be present in sufficient numbers in mortality studies. None of the previous case-control studies identified or considered machining as a risk factor for soft tissue sarcoma; however, machining was not a common source of exposure in these studies.

The strengths of the study include the large number of sarcoma cases, pathology review by an expert panel, and the complete occupational histories obtained from the subjects directly rather than from their proxies. To the authors’ knowledge, this is the largest case-control study of soft tissue sarcoma with pathology review. The verbatim data were of sufficiently high quality that the industrial hygienist was able to use this information to classify exposure potential further and thereby improve the exposure estimate. By rating jobs by both intensity and confidence in the estimate, the potential for exposure misclassification was reduced, as evidenced by the stronger odds ratios as the exposure definition became more restrictive (table 5). Integrating over multiple industries and job types using chlorophenol has not been attempted in previous studies of soft tissue sarcoma and chlorophenol exposure. This increased the sample size of the exposed cases, although the relative exposure levels may not be directly comparable between industries and occupations. Separate analyses for each source of the suspected chlorophenol exposures were not attempted due to the small number of exposed cases in each category other than exposure from cutting oils.

While the study has many strengths, the limitations of this data set should be considered when evaluating the results. Since the data were collected for other purposes, this study population of men aged 32–60 years represents an unusual age range and gender-specific group for the study of cancer, and therefore, the results may not be directly comparable with population-based studies sampling from all cases arising in a community. As with any case-control study, the potential for recall bias exists. However, given that there was no a priori belief that cutting oils were associated with soft tissue sarcoma and that there was no difference between cases and controls in their self-reported exposure to cutting oils and wood preservatives (table 4), recall bias is unlikely to be responsible for the observed association with chlorophenols. Regarding potential sources of selection bias, cases who were excluded based on lack of pathology confirmation did not differ on demographic characteristics and exposures of interest from the cases used in the analysis. Controls were selected based on the matching factors of registry and age in 1968; no information on race was obtained during the screening interview. While selective participation of some racial groups over others cannot be excluded, the overrepresentation of black cases is consistent with the elevated incidence of sarcoma among blacks compared with whites (42).

To summarize, the Selected Cancers Study, with its large number of pathology-reviewed sarcoma cases and verbatim job histories, provided a powerful opportunity to investigate the association of chlorophenol exposure with soft tissue sarcoma risk. The authors constructed a chlorophenol variable that combined estimated exposures across industries and found a strong association of soft tissue sarcoma risk with this variable, both in the ever-never comparison and in the duration-response assessment. This association was found to be driven in large part by the contribution to the chlorophenol variable of cutting oil, an occupational exposure that itself has never previously been reported in association with sarcoma. Further, whereas previous studies have reported an association of soft tissue sarcoma with chlorophenols in the workplace, this is the first report of excess soft tissue sarcoma in relation to chlorophenols in cutting oils. The findings therefore support the hypothesis of an association of sarcoma with chlorophenol, but are also consistent with an association with some other component of cutting oils. Prior evidence favors chlorophenol as the responsible agent within cutting oils if the observed risk associated with cutting oils is real. Lack of certainty that chlorophenols were constituents of cutting oils in this particular study, however, detracts somewhat from confidence in attributing the dramatic pattern observed in these data to chlorophenol. Thus, while these findings support the hypothesis of an association of sarcoma with chlorophenol, the possibility that some other aspect of machining is important in sarcoma risk should be investigated in future studies.

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REFERENCES


