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by Demers PA, Schade WJ, Demers RY

Affiliation: Occupational Hygiene Program, University of British Columbia, Vancouver, Canada.

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/8079131
Lymphocytopenia and occupational exposures among pattern and model makers

by Paul A Demers, PhD,1 William J Schade, MD,2 Raymond Y Demers, MD2,3

DEMERS PA, SCHADE WJ, DEMERS RY. Lymphocytopenia and occupational exposures among pattern and model makers. Scand J Work Environ Health 1994;20:107—12.

OBJECTIVES — The study was performed to examine the relationship between a high prevalence of lymphocytopenia observed during a cancer screening program for pattern and model makers, who produce industrial prototypes and patterns, and 15 occupational exposures.

METHODS — The cases (N = 83) were workers with lymphocyte counts of less than 1000, while the referents (N = 529) had counts of 1500 or higher. Exposures at the current workplace, and at up to 19 previous pattern and model shops, were assessed with the use of a questionnaire.

RESULTS — Elevated risks were associated with exposure to epoxy resins (odds ratio (OR) 1.94, 95% confidence interval (95% CI) 1.02—3.70) and plastic dusts (OR 2.60, 95% CI 1.19—5.68) after adjustment for age and smoking status. No clear associations were found with duration of exposure or percentage of time potentially exposed. Although the results were based upon small numbers, epoxy resins and wood dust displayed the most consistent relationships in an analysis of changes in lymphocyte count and exposure status over time.

CONCLUSIONS — While firm conclusions cannot be drawn, the strongest associations observed in this study were for exposure to epoxy resins.

KEY TERMS — cancer, epoxy resins, immune system, lymphocytes, occupational disease.

Pattern and model makers are highly skilled workers responsible for producing prototypes and patterns for mass-production industries, such as the automobile manufacturing industry. Members of this trade are potentially exposed to a wide variety of substances, including natural and laminated woods, various metals, plastics, resins, and solvents (1). Several studies conducted in the 1980s found pattern and model makers to be at elevated risk for colon and rectal cancer (2—4). In response, a cancer screening program was initiated in 1981 for members of the Pattern and Model Makers League of North America (PML), the union representing these workers outside of large industries. The cancer screening was primarily directed towards detecting colon and rectal cancer, but other standard screening procedures, including blood chemistries and complete blood counts, were also performed.

In an analysis of the cancer screening results for 1981 and 1982, a relatively high proportion (26.2%) of participants was observed to have low lymphocyte counts (<1500 · mm⁻³) (5). By contrast, only 5.6% of a comparable occupational group had values of <1500 · mm⁻³. In an analysis of a subgroup of participants in the 1988 screening, a relationship was found between low counts of T cells and natural killer cells and employment as a pattern or model maker (6). In addition, a relationship between low total lymphocyte, T4, and natural killer cell counts and the presence of colon and rectal polyps was observed.

In order to explore whether these low lymphocyte counts were associated with occupational exposures, a case-referent study among pattern and model makers who participated in the screening program was performed.

Subjects and methods

The subjects were selected from among participants in the 1985 cancer screening program in Detroit, Michigan, and the surrounding region. All members of the PML associations representing workers in southeastern Michigan were eligible to attend the screening program. The participants (all men) were employed at “job shops,” which primarily produce patterns and models for automobile manufacturers and other mass-production industries.

Blood counts were performed with a standard instrument generating a three-part differential count, the Coulter “S plus IV.” Cases were defined as persons with lymphocyte counts of <1000 · mm⁻³. The referents were screening participants with counts of ≥1500 · mm⁻³. Persons with intermediate counts were excluded from the case-referent analysis. Because of
the relatively short half-life of lymphocytes and their ability to regenerate quickly, only screening participants who were currently employed were included in the analysis (7).

Prior to the screening, all of the participants were asked to complete a work history questionnaire designed to collect a detailed history of exposure to 15 different substances commonly encountered in the trade, including two substances identified by trade-name, Impreg® and Kirkcite®. Impreg® is cativo wood laminated and impregnated with a phenol-formaldehyde resin, such that the product is 30% resin, while Kirkcite® is a metal alloy composed primarily of zinc (90%) with smaller amounts of nickel, titanium, copper, and iron. Pattern and model making is frequently a life-long profession, and it is common for workers at "job shops" to change employers as frequently as every one or two years, either because of downturns in the industry resulting in layoffs or because of an advance in pay scale. Thus the work history questionnaire were excluded from the analysis.

Analyses were conducted using logistic regression to compare the history of exposure among the cases and referents. The mean age of the cases was 45 years and 20% were current smokers, while the mean age of the referents was 39 years and 43% were current smokers. Smoking was negatively associated with lymphocytopenia [odds ratio (OR) 0.34, 95% confidence interval (95% CI) 0.19—0.60], while age was somewhat positively associated (OR 2.29 for 30—39 years, OR 1.90 for 40—49 years, and OR 3.83 for ≥50 years relative to those <30 years of age). Thus a decision was made to adjust for age (<30, 30—39, 40—49, ≥50) and current smoking status in all of the analyses.

An alternate analysis was also performed to examine whether changes in exposure status over time led to a drop in lymphocyte counts. For this analysis, the subjects consisted of all PML screening participants who attended both the 1985 and 1981—1982 screening programs and were currently employed at the time of the 1985 screening. Our a priori hypothesis was that those workers not exposed to the potential causal agent or agents at either screening or during the time between should have little change in their lymphocyte counts, while those exposed at the first screening, but who ceased to be exposed prior to the second, should have an increase in their lymphocyte counts. On the other hand, decreases in lymphocyte count might be expected among those workers who began exposure between the two screenings or who were exposed at both.

### Results

A total of 864 men attended the 1985 screening and 858 had total lymphocyte counts performed. Of the 858, 86 (10%) had counts of ≤1000 · mm⁻³, 550 (64%) had counts of ≥1500 · mm⁻³, and 222 (26%) had intermediate counts. Thus there were 86 potential "cases" and 550 potential "referents." Two cases and 10 referents were not currently employed at the time of the screening, and one case and 11 referents did not provide an adequate work history for the analysis. After exclusions, 83 cases and 529 referents were available for the analysis.

No association was found with number of years employed as a pattern or model maker (OR 1.00, 95% CI 0.96—1.03) after adjustment for age and smoking status. As part of the occupational history, screening participants were queried as to the main material with which they worked. No association was found for primarily working with woods (OR 0.97, 95% CI 0.59—1.59), metals (OR 0.97, 95% CI 0.54—1.73), or plastics (OR 1.07, 95% CI 0.61—1.86). Table 1 lists the 15 specific exposures queried in the questionnaire with the percentage of cases and referents currently exposed and ever exposed.

| Exposure | Currently exposed | Ever exposed |
|----------|-------------------|--------------|
|          | Cases (N %)       | Referents (N %) | Cases (N %) | Referents (N %) |
| Hard wood | 53 (64) | 64 (66) | 63 (76) | 38 (73) |
| Soft wood | 66 (80) | 80 (72) | 69 (83) | 42 (81) |
| Impreg® | 51 (61) | 61 (61) | 62 (75) | 39 (72) |
| Kirkcite® | 10 (12) | 12 (13) | 23 (28) | 17 (22) |
| Others metals | 43 (52) | 52 (47) | 60 (72) | 35 (45) |
| Solvents | 62 (75) | 75 (75) | 68 (82) | 32 (42) |
| Cutting oils | 31 (37) | 37 (40) | 45 (54) | 26 (36) |
| Welding fumes | 21 (25) | 25 (23) | 39 (47) | 23 (45) |
| Epoxy resins | 60 (72) | 72 (67) | 70 (84) | 40 (76) |
| Polyesters | 44 (53) | 53 (51) | 54 (63) | 34 (63) |
| Other plastics | 47 (57) | 57 (57) | 59 (71) | 38 (68) |
| Plastic dusts | 63 (76) | 76 (71) | 75 (90) | 42 (85) |
| Fiber glass | 46 (55) | 55 (53) | 61 (73) | 37 (70) |
| Asbestos | 4 (5) | 5 (5) | 12 (14) | 6 (11) |
| Plasters | 26 (30) | 30 (28) | 44 (53) | 27 (52) |
having worked with epoxy resins was 1.95 (95% CI 1.03—3.71), while the corresponding odds ratio for plastic dusts was 2.81 (95% CI 1.29—6.12).

In table 3 the data from column 2 of table 2 are stratified by the percentage of time spent working with the material. No exposure appeared to have a clear association with this surrogate measure of dose that could not be ruled out as due to chance. Asbestos was excluded from the table because no cases or referents reported having used it more than 50% of the time. The odds ratios associated with exposure to both epoxy resins and plastic dusts were elevated for both those who had reported using the substances for less than 50% of the time and for those who reported using the substances more than 50% of the time. Table 4 lists the odds ratios by category of duration of exposure relative to no history of exposure. As in table 3, no exposure appeared to have a clear association with this additional surrogate measure of dose.

A total of 405 participants in the 1985 screening also attended the 1981—1982 cancer screening. This group consisted of 48 cases, 253 referents, and 104 men with lymphocyte counts between 100 and 1499 · mm⁻³ in 1985. The mean lymphocyte count at the earlier screening for persons defined as cases in the current study was 1677 · mm⁻³, while their mean for the 1985 screening was 798 · mm⁻³. The mean value for the intermediate group also dropped between the two screenings, from 1660 to 1286 · mm⁻³, while the mean value for the referents rose slightly during the same time period (from 2098 to 2241 · mm⁻³). Only exposure to soft wood and epoxy resins (table 5) displayed relationships with lymphocyte counts in the directions hypothesized a priori. A small number of participants, four in the case of both the soft wood and epoxy resin analyses, who had multiple changes in exposure status were excluded from the exposure-specific analyses. The analyses of all other exposures displayed either

Table 2. Odds ratios (OR) and 95% confidence intervals (95% CI) for lymphocytopenia among the pattern and model makers by exposure at the time of screening.

| Exposure            | Currently exposed | Currently exposed | OR* | 95% CI | OR* | 95% CI |
|---------------------|-------------------|-------------------|-----|--------|-----|--------|
| Hard wood           | 0.97              | 0.59—1.59        | 1.11| 0.64—1.95 |
| Soft wood           | 1.62              | 0.91—2.89        | 1.38| 0.73—2.58 |
| Impreg*             | 0.98              | 0.60—1.60        | 1.10| 0.63—1.92 |
| Kirkcote            | 0.93              | 0.45—1.93        | 0.04| 0.45—1.96 |
| Other metals        | 1.41              | 0.67—2.82        | 1.59| 0.91—2.77 |
| Solvents            | 1.18              | 0.68—2.06        | 1.27| 0.68—2.39 |
| Cutting oils        | 1.12              | 0.68—1.88        | 1.15| 0.67—1.97 |
| Welding fumes       | 1.03              | 0.60—1.79        | 1.13| 0.64—2.00 |
| Epoxy resins        | 1.54              | 0.91—2.62        | 1.94| 1.02—3.70 |
| Polysters           | 1.14              | 0.71—1.83        | 1.09| 0.65—1.81 |
| Other plastics      | 1.15              | 0.71—1.88        | 1.31| 0.76—2.25 |
| Plastic dusts       | 1.54              | 0.88—2.68        | 2.60| 1.19—5.68 |
| Fiber glass         | 1.25              | 0.78—2.04        | 1.38| 0.79—2.41 |
| Asbestos            | 1.10              | 0.36—3.32        | 1.18| 0.39—3.61 |
| Plasters            | 1.14              | 0.68—1.93        | 1.08| 0.62—1.89 |

* Adjusted for age group and cigarette smoking status.

Table 3. Odds ratios (OR) and 95% confidence intervals (95% CI) for lymphocytopenia among the pattern and model makers by exposure at the time of screening and the percentage of time exposed.

| Exposure            | Less than 50% | OR* | 95% CI | Greater than 50% | OR* | 95% CI |
|---------------------|---------------|-----|--------|------------------|-----|--------|
| Hard wood           | 1.16          | 0.64—2.08 | 0.99| 0.45—2.18 |
| Soft wood           | 1.61          | 0.84—3.07 | 0.98| 0.40—1.98 |
| Impreg*             | 1.20          | 0.64—2.24 | 0.99| 0.52—1.90 |
| Kirkcote            | 0.78          | 0.33—1.92 | 1.80| 0.47—7.08 |
| Other metals        | 1.53          | 0.76—3.00 | 1.63| 0.87—3.07 |
| Solvents            | 1.36          | 0.72—2.59 | 0.94| 0.40—2.20 |
| Cutting oils        | 1.19          | 0.68—2.08 | 0.90| 0.29—3.20 |
| Welding fumes       | 1.22          | 0.68—2.19 | 0.44| 0.06—3.52 |
| Epoxy resins        | 1.98          | 1.01—3.88 | 1.84| 0.85—3.99 |
| Polysters           | 0.95          | 0.55—1.66 | 1.61| 0.77—3.36 |
| Other plastics      | 1.24          | 0.70—2.22 | 1.48| 0.71—3.06 |
| Plastic dusts       | 2.76          | 1.25—6.18 | 2.23| 0.92—5.44 |
| Fiber glass         | 1.62          | 0.92—2.91 | 0.92| 0.42—2.03 |
| Plasters            | 1.22          | 0.69—2.15 | 0.30| 0.04—2.33 |

* Relative to never exposed and adjusted for age group and cigarette smoking status.

Table 4. Odds ratios (OR) and 95% confidence intervals (95% CI) for lymphocytopenia among the pattern and model makers by category of duration of exposure.

| Exposure | 0.1—4.9 years | OR* | 95% CI | 5.0—9.9 years | OR* | 95% CI | ≥10 years | OR* | 95% CI |
|----------|---------------|-----|--------|---------------|-----|--------|-----------|-----|--------|
| Hard wood| 1.47          | 0.70—2.07 | 1.06| 0.45—2.47 | 1.08| 0.58—2.01 |
| Soft wood| 1.29          | 0.58—2.88 | 0.66| 0.25—1.89 | 1.30| 0.67—2.60 |
| Impreg*  | 1.56          | 0.79—3.09 | 1.05| 0.48—2.30 | 0.94| 0.49—1.80 |
| Kirkcote | 1.00          | 0.48—2.11 | 1.39| 0.57—3.37 | 0.72| 0.28—1.83 |
| Other metals| 1.15          | 0.53—2.50 | 2.11| 1.01—4.43 | 1.60| 0.87—2.92 |
| Solvents | 1.22          | 0.51—2.92 | 1.51| 0.66—3.46 | 1.29| 0.66—2.50 |
| Cutting oils| 1.20          | 0.57—2.51 | 1.81| 0.85—3.87 | 0.93| 0.50—1.72 |
| Welding fumes| 0.79          | 0.37—1.69 | 1.49| 0.66—3.35 | 1.56| 0.85—2.87 |
| Epoxy resins| 1.68          | 0.82—4.28 | 2.14| 0.95—4.85 | 1.92| 0.96—3.84 |
| Polysters| 1.14          | 0.56—2.51 | 0.90| 0.36—2.31 | 1.03| 0.58—2.14 |
| Other plastics | 1.37     | 0.69—2.72 | 1.46| 0.65—3.29 | 1.47| 0.80—2.70 |
| Plastic dusts| 2.63          | 1.14—7.04 | 3.63| 1.41—9.39 | 2.60| 1.15—5.89 |
| Fiber glass| 1.31          | 0.64—2.67 | 2.36| 1.13—4.92 | 1.17| 0.62—2.21 |
| Asbestos | 1.42          | 0.51—3.90 | 1.11| 0.24—5.13 | 2.18| 0.71—6.75 |
| Plasters | 0.50          | 0.22—1.15 | 0.99| 0.46—2.21 | 1.36| 0.77—2.43 |

* Relative to never exposed and adjusted for age group and cigarette smoking status.
Table 5. Changes in the lymphocyte counts of the pattern and model makers between the 1981—1982 screening and the 1985 screening in relation to exposure status.

| Exposure          | Time of screening | Lymphocyte count | 1981—1982 | 1985 N | 1981—1982 | 1985 | Change | SE |
|-------------------|-------------------|------------------|-----------|-------|-----------|------|--------|----|
| Soft wood         | No, No            | 95               | 1864      | 1775  | —88       | 76   |        |    |
|                   | Yes, Yes          | 6                | 1948      | 2318  | 370       | 145  |        |    |
|                   | No, Yes           | 22               | 1885      | 1593  | —292      | 196  |        |    |
|                   | Yes, Yes          | 278              | 1974      | 1857  | —116      | 43   |        |    |
| Epoxy resins      | No, No            | 119              | 1821      | 1817  | —4        | 70   |        |    |
|                   | Yes, Yes          | 18               | 1758      | 1869  | 112       | 176  |        |    |
|                   | No, Yes           | 14               | 1751      | 1683  | —67       | 211  |        |    |
|                   | Yes, Yes          | 252              | 2021      | 1839  | —182      | 45   |        |    |
| Plastic dusts     | No, No            | 111              | 1833      | 1859  | 26        | 76   |        |    |
|                   | Yes, Yes          | 13               | 2112      | 1670  | —442      | 161  |        |    |
|                   | No, Yes           | 18               | 1837      | 1738  | —99       | 127  |        |    |
|                   | Yes, Yes          | 260              | 1978      | 1832  | —146      | 45   |        |    |
| Total             |                   | 405              | 1935      | 1825  | —111      | 54   |        |    |

The results for other exposures considered in this analysis were less consistent. Although current exposure to plastic dusts was associated with lymphocytopenia, the results of the sequential analysis were not in the predicted direction. Likewise, the sequential association with softwood was not substantiated by a clear association with current exposure. In addition, as was the case with epoxy resins, neither exposure showed evidence of a dose-response relationship with lymphocytopenia.

Many substances encountered in the work environment have been found to be immunotoxic (8). However, relatively few studies have been conducted to examine the relationship between work-related exposures and lymphocytopenia. Studies have found a relationship between exposure to asbestos and decreased T helper:suppressor ratios and lower numbers of natural killer cells (9—11). Decreased numbers of lymphocytes have also been associated with occupational exposure to solvents, particularly benzene (12, 13). In this analysis neither exposure to asbestos nor exposure to solvents was related to lymphocytopenia. The epoxy compounds typically used in pattern and model making are epichlorohydrin and diglycidyl resorcinol ether, along with hardeners such as diethylenetriamine and triethylenetetramine (1). Exposure to epoxy resins has not been previously associated with lymphocytopenia, although other lymphatic and hematopoietic effects have been observed. An increase in chromosome aberrations in the white blood cells of epoxy-exposed workers has been noted (14), and animal studies have shown glycidyl ether to cause a loss of lymphoid tissue in rats (15).

Although this study was undertaken to explore the relationship between depressed human lymphocyte counts and workplace exposure among pattern and model makers, it was also motivated by concern about the risk of cancer among members of this trade. An excess of colon and rectal cancer has been observed among pattern and model makers in studies of both mortality (2, 3, 16) and cancer (3, 4, 17, 18) incidence, and an excess of colon and rectal polyps has also been observed (19). Although two recent studies have not observed an excess (20, 21), the majority of the evidence indicates that these workers are or were at excess risk of colon and rectal cancer. The cause for the excess risk of cancer observed among these workers has not been identified. Initial suspicion had fallen on wood dust because it is a common exposure and an excess of nasal cancer had been observed in the wood furniture industry (22). However, the one study designed to examine this question did not find an excess of colon cancer associated with wood dust exposure (21).

The observation of a high prevalence of lymphocytopenia in this population has prompted the consideration that a toxic effect on the immune system, as reflected in depressed lymphocyte counts, could predispose the development of colon and rectal cancer. In a previous study of this population, a relationship
between low total lymphocyte, T4, and natural killer cell counts and the presence of colon and rectal polyps was observed (6). Another study, based on patient records from the Mayo Clinic, found that, of 510 healthy patients, 6% had lymphocyte counts of $< 1000 \cdot \text{mm}^{-3}$, while, of 227 patients with untreated gastrointestinal malignancies, 22.4% had counts of $< 1000 \cdot \text{mm}^{-3}$ (22). Thus it may be significant to the findings of colon and rectal neoplasia among pattern and model makers that epichlorohydrin has been classified as a probable human carcinogen while diglycidyl resorcinol ether has been classified as a possible human carcinogen (23).

There are some limitations that should be kept in mind when the results of this study are considered. First, the study population consisted of voluntary participants in a cancer screening program. Approximately 35% of the eligible workers participated in the 1985 screening, while 46% participated in the 1981—1982 screening (24). The participants in the program have been found to be more likely to be older, to have never smoked, and to have worked with wood. How this history might influence the results of the study is unknown. However, it is important to note that this was a generally healthy working population and it seems unlikely that individual decisions to participate had any relationship with lymphocyte counts. Second, only total lymphocyte count was available for all of the participants. Subset counts, as well as other markers of immune impairment, would have been optimal but, given the expense, were not collected as part of the screening.

Differences types of epoxy resins, woods, and plastic dusts may have very different toxic effects. Another limitation of this study was that more specific information regarding exposure was not available. The drop in lymphocyte counts between the two screenings among the persons who subsequently became cases was substantially greater than that observed in relationship to any of the exposures examined. This result might indicate that the true agent responsible for the change in lymphocyte counts was either not measured or poorly measured. The lack of a dose-response relationship in this study may have been due to the fact that both the percentage of time and the duration were poor surrogates for true dose.

In conclusion, epoxy resins formed the exposure most consistent with lymphocytopenia among the pattern and model makers, while weaker evidence was found for exposure to plastic dusts and soft-wood dust. Because this effect has been observed in a group of workers with an elevated risk of cancer, future investigations will focus on assessing the relationship between these exposures and the risk of colon and rectal cancer.

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Received for publication: 6 April 1993