In 1996, a citizens group in Nogales, Arizona, reported to the Arizona Department of Health their concerns about a possible excess prevalence of systemic lupus erythematosus (SLE) due to exposure to environmental contamination in the area. The authors conducted a two-phase study in which the objectives of phase I were to identify potential SLE cases and to determine the prevalence of SLE and the objectives of phase II were to identify potential risk factors associated with the development of SLE and to evaluate the possible association between SLE and environmental exposure to pesticides and inorganic compounds. Participants included 20 confirmed cases and 36 controls. The authors found the prevalence of SLE to be 103 cases per 100,000 population (95 percent confidence interval: 56, 149), two to seven times higher than the prevalence in the US population. They detected elevated levels of 1,1-dichloro-2,2-bis-(p-chlorophenyl)ethylene and organophosphate metabolites among cases and controls. In both, levels were higher than the reference mean for the US population. The authors found no statistical association between elevated levels of pesticides and disease status. Their results show that the prevalence of SLE in Nogales is higher than the reported prevalence in the US population and that both cases and controls had past exposure to chlorinated pesticides and have ongoing exposure to organophosphates. Am J Epidemiol 2001;154:1029–36.

Nogales, Arizona (population 19,489) is adjacent to Nogales, Sonora, Mexico, a rapidly growing city with an official census population of 107,000. According to the 1990 Census, the population of Nogales, Arizona, was 92 percent Hispanic. The international border, marked in most places by a fence, is all that separates the two communities. Nogales, Arizona, is downwind and downriver from Nogales, Sonora. During the winter rainy season, Nogales, Arizona, is subject to episodes of surface water pollution from surface water runoff that flows north from industrial areas in Mexico into the Nogales River. Air pollution originating from industries in Mexico is also a concern. Because of the potential for exposure to environmental agents in Nogales, Arizona, the community was concerned about possible relation of these agents to an apparent increase in systemic lupus erythematosus (SLE) in the area. The possibility of an excess prevalence of SLE in Nogales, Arizona, was first brought to the attention of the Arizona Department of Health in the fall of 1996 by a local citizens group.

SLE is a multisystem disease caused by tissue damage resulting from antibody and complement-fixing immune complex deposition (1). Although there is a substantial body of literature regarding possible etiologic agents for SLE, it has not been possible to assign a definite cause to this disease. SLE is one of many complex autoimmune diseases thought to have a multifactorial etiology. Researchers believe that a combination of genetic and environmental factors is most likely responsible for this disease (2). Evidence that suggests a genetic predisposition to SLE includes the increased risk of the disease affecting first-degree relatives (3–5) and the known higher risk of SLE in Black Americans and Asians (6). Although certain genetic markers are associated with an increased risk of developing SLE, this susceptibility may also be influenced by environmental factors, including dietary factors, stress, ultraviolet light, and chemicals such as aromatic amines, hydrocarbon solvents, and inorganic agents such as cadmium and mercury (7). The specific metabolites that react with specific cells have been well demonstrated for certain drugs (8, 9). Other proposed mechanisms for the induction of an autoimmune response by a number of different compounds includes the possibility of cross-reactive antigens, interference with tolerance mechanisms, the potential alteration of...
DNA, and the role of the genetics of the various metabolic pathways of the compounds (7). There have been several studies of air and water quality in the border area, but none has specifically assessed the potential links between biomarkers of environmental exposures and patterns of disease.

In March 1997, the Arizona Department of Health requested assistance from the Centers for Disease Control and Prevention (CDC) to conduct a two-phase study to address the citizens’ concerns. The main objectives of our study were to conduct active case finding for SLE patients in Nogales, Arizona, to determine the prevalence of SLE to conduct a case-control study to identify potential risk factors associated with the development of SLE, and to evaluate the possible association between SLE and environmental exposure to pesticides in Nogales, Arizona.

MATERIALS AND METHODS

Data collection was performed in two phases (phases I and II).

Phase I

In phase I, people who had been diagnosed with SLE or who believed they might have SLE were recruited for the study through notification by a community representative; by using local mass media; and by case finding through all local physicians, clinics, and hospitals. All potential cases were asked to sign a consent form if they decided to participate in this phase. We conducted interviews in person at a local health clinic participating in the study. We administered a brief questionnaire that solicited the participants' names and addresses, how long they had lived in Nogales before diagnosis, whether they had a home telephone, if they had experienced any of a series of symptoms characteristic of SLE, whether their SLE symptoms had improved or worsened over each of the preceding 24 months, and whether they had a relative who has been diagnosed by a physician with SLE. If a relative was identified and lived within the city limits of Nogales, he or she was contacted by telephone and asked to be interviewed as part of the study.

Phase II

We used a case-control study design. Similar to a study conducted by Freni-Titulaer et al. (10), a definite case of SLE in our study was defined as a person identified in phase I who, after a physical examination by the board-certified rheumatologist participating in this study, was found to fulfill at least four of the 1982 revised American College of Rheumatology (ACR) criteria for SLE (11), one of which was required by our protocol to be a positive laboratory test for SLE, i.e., a positive antinuclear antibody (ANA) test. While the ACR criteria allow the clinical diagnosis of SLE without a positive ANA, for this study, we applied a stricter case definition. A probable case was a participant who had undifferentiated connective tissue disease, that is, one who clinically suffered from three or more typical SLE symptoms but failed to fulfill the case criteria for SLE given above and for whom the clinical testing did not support SLE (negative ANA test).

Participants enrolled as controls must have reported being free of signs or symptoms of SLE and must not meet any of the criteria for the definite case or probable case definition. They were selected by random digit dialing from the areas where SLE cases are identified. They were matched to cases by age (≥5 years), sex, race, length of residence, and telephone prefix. For each confirmed case, two controls were selected by random digit dialing using all residential telephone prefix areas in Nogales.

All study participants were interviewed in person at a local health clinic participating in the study. The questionnaire included questions about gynecologic and obstetric histories for women, a detailed family history of autoimmune rheumatologic disease, occupational and environmental exposure histories, residential history, medication use, hair dye use, breast implants, and some dietary factors.

In addition, cases and probable cases completed a medical examination consisting of a complete history and physical examination by a board-certified rheumatologist, with special attention to signs and symptoms of SLE and other connective tissue diseases. All potential cases were asked to give blood specimens for determining ANA levels. We did not perform ANA blood tests for the controls.

Eligibility

All eligible subjects were adults who lived within the city limits of Nogales, Arizona, and who were required to have resided in Nogales for at least 1 year prior to the onset of the first SLE symptoms in the case. Participating subjects were asked to sign a consent form that described the study. All phases of the study, including the medical examination and tests, were described to the participants. Potential controls were contacted by telephone.

Toxicologic examination

Serum and urine samples for biomarker analysis were collected from all study participants. All samples were sent to the Division of Laboratory Sciences at the National Center for Environmental Health, CDC, for analysis for cadmium, mercury, and arsenic; organophosphate pesticides; and chlorinated pesticides. We chose the three inorganics and the two families of pesticides because of a known history of community exposure to these potential toxics specifically during the rainy season.

Urine samples collected from the cases were analyzed for inorganic cadmium, mercury, and arsenic by using atomic absorption spectrometry. Urine samples were analyzed for the following organophosphate metabolites by using gas chromatography-tandem mass spectrometry: dimethylphosphates, dimethyldithiophosphates, dimethylphosphonate, diethylphosphate (DEP), diethylthiophosphate, and diethyl-dithiophosphate. Serum samples were analyzed for B-hexachlorocyclohex, dieldrin, hexachlorobenzene, heptachlor epoxide, mirex, oxychlordane, polychlorinated biphenyl congeners, 1,1,1-trichloro-2,2-bis-(p-chlorophenyl)-
ethane (DDT), and its metabolites, in particular, 1,1-dichloro-2,2-bis-(\(p\)-chlorophenyl)ethylene (DDE), and trans-nonachlor by using twin column gas chromatography with electron capture detection (12).

Data analysis

We hypothesized that there is an association between environmental exposure to pesticides and the risk of developing SLE in Nogales, Arizona. Statistical analysis was performed by using SAS Version 8.0 (SAS Institute, Inc., Cary, North Carolina). All odds ratios are reported with a 95 percent confidence interval.

For this report, we performed a matched analysis of the data in two ways: All confirmed cases were analyzed together and compared with the controls, and then all probable and confirmed cases were combined and this group was compared with the controls as well. Conditional logistic regression was used to generate odds ratios and confidence intervals.

RESULTS

Thirty-six potential cases of SLE were identified in phase I of the study. Of those 36 potential cases, 20 met the case definition and were confirmed as having SLE by the rheumatologist’s physical examination. Therefore, we estimated the prevalence of SLE in Nogales, Arizona, to be 103 cases per 100,000 population (95 percent confidence interval (CI): 56, 149). We also identified seven probable cases; four participants reported three or more symptoms but had a negative ANA on clinical laboratory testing, and for the other three, a positive ANA was present, but only two other symptoms were found. Of the 20 confirmed cases, only one person refused to participate in phase II of the study; thus, 19 cases are included in the analyses presented here. We were able to match two controls to each case with the exception of two cases who were matched to only one control each. Thus, 19 cases and 36 controls were included in the final analysis. The distribution of demographics and employment did not differ significantly between cases and controls except for educational level, where 31.6 percent of the cases reported an educational level greater than high school compared with 8.3 percent of the controls (table 1).

All 19 cases were female, Hispanic, and of Mexican origin. Symptoms reported by cases included painful swollen joints reported by 17 (89.5 percent), mouth ulcers reported by 12 (63.2 percent), low blood counts reported by 14 (73.7 percent), malar (cheek) rash reported by 11 (57.9 percent), development of malar rash in the sun reported by 14 (73.7 percent), pleurisy reported by 13 (68.4 percent), protein in the urine reported by six (31.6 percent), hair loss reported by eight (42.1 percent), and seizure reported by five (26.3 percent).

Risk factor analysis

Potential risk factors were categorized into demographic, behavioral, medical, and environmental factors. A univariate analysis of the risk factors in each category did not show a statistically significant association with SLE (table 2).

Of the 19 cases, 17 (89.5 percent) were using medications regularly compared with 17 of 36 controls (47.2 percent). However, when we excluded medications used to treat SLE and hypertension (a frequent sequela of SLE) from the analysis, we found no statistical association between use of medications and SLE (odds ratio (OR) = 3.0, 95 percent CI: 0.8, 11.8). We also considered the sources of medications, that is, whether they were purchased in the United States or Mexico. We found that 95 percent of both cases and controls reported purchasing their medications in the United States. Approximately 54 percent of our participants used city water supplies and bottled water combined as their source for drinking water, and 33.3 percent used only bottled water. Only one case and one control reported using private wells. No statistical association was found between the use of city water (OR = 5.3, 95 percent CI: 0.9, 31.6) or private well water (OR = 0.9, 95 percent CI: 0.1, 11.7) and disease status compared with bottled water. Risk factors that were not included further in the analysis were birth control pills, breast implants, and swimming in the Nogales River. Only one case reported using birth control pills, none of the cases reported having breast implants, and neither the cases nor the controls reported that they swam in the wash.

When we repeated the risk factor analysis including all seven probable cases (for a total of 26 probable and definite cases) and the corresponding controls, the results were similar to the analysis that used only definite cases.

Toxicologic analysis

Eighteen of the 19 cases and 34 of 36 controls gave blood and urine samples for analysis. DDE, a metabolite of DDT, and organophosphate metabolites were detected at elevated levels among both cases and controls; however, the mean, median, and frequency distributions for both groups were remarkably similar, indicating that there was no association between SLE and these chemical exposures (table 3). In addition, the univariate analysis indicated that there was no statistical association between the elevated levels of pesticides and the disease status. Toxicologic analysis for the other chemicals such as polychlorinated biphenyls and inorganics were below the detection limit.

<table>
<thead>
<tr>
<th>TABLE 1. Comparison of demographic characteristics between definite cases and controls, study of systemic lupus erythematosus, Nogales, Arizona, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Family origin Mexico</td>
</tr>
<tr>
<td>Born in Mexico</td>
</tr>
<tr>
<td>Employed</td>
</tr>
<tr>
<td>Educational level (more than high school)</td>
</tr>
</tbody>
</table>

Am J Epidemiol  Vol. 154, No. 11, 2001
Although we found no differences between cases and controls, the mean or median of each of the metabolites analyzed in both groups was higher than the reference mean or medians for the US population, with the exception of DEP. Unlike the cases, the median level of DEP detected in the controls was lower than the reference median for the US population as provided by the Division of Laboratory Sciences at National Center for Environmental Health/CDC. Because reference ranges for exposure to organophosphates and chlorinated pesticides among Hispanics are unavailable, we used available reference ranges for US adults for comparison purposes.

**DISCUSSION**

Our study has two major findings. First, we found the prevalence of SLE in Nogales, Arizona, to be 20 cases per 19,489 people (95 percent CI: 11, 29), or 103 cases per 100,000 population (95 percent CI: 56, 149), approximately two to seven times higher than prevalence estimates reported for the US population, which range from 14.6 to 50.8 cases per 100,000 (13–16). When we compare the prevalence of SLE among ethnic groups, the prevalence of SLE among Hispanic women in Nogales, Arizona (208/100,000) (17) is also higher than that among Caucasian women (54/100,000) (17) and the SLE prevalence among Alaskan Native-American women (165/100,000) (18). Second, we found both cases and controls to have elevated levels of DDE, a DDT metabolite, as well as elevated levels of organophosphate metabolites.

The high prevalence estimate we found could be either an under- or an overestimate. Since this study was conducted in a relatively small geographic area with a small population, we believe that we included all or nearly all cases of SLE in the area. Extensive case finding was done by using community meetings, local physicians and clinics, and widespread media publicity. Additionally, cases who voluntarily participated in the study were specifically asked to tell us of relatives who might also have SLE. Therefore, the principal cases we may have missed would have been those who

### Table 2. Relations of risk factors obtained by the questionnaire to the study of systemic lupus erythematosus, Nogales, Arizona, 1997

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR*</th>
<th>95% CI*</th>
<th>p value</th>
<th>Cases No.</th>
<th>Cases %</th>
<th>Controls No.</th>
<th>Controls %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>0.7</td>
<td>0.2, 2.7</td>
<td>0.66</td>
<td>12</td>
<td>67</td>
<td>27</td>
<td>75</td>
</tr>
<tr>
<td>United States</td>
<td>1.0</td>
<td></td>
<td></td>
<td>6</td>
<td>33</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>1.5</td>
<td>0.4, 5.2</td>
<td>0.52</td>
<td>10</td>
<td>53</td>
<td>23</td>
<td>64</td>
</tr>
<tr>
<td>Not married</td>
<td>1.0</td>
<td></td>
<td></td>
<td>9</td>
<td>47</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>2.0</td>
<td>0.2, 17.9</td>
<td>0.54</td>
<td>18</td>
<td>95</td>
<td>32</td>
<td>89</td>
</tr>
<tr>
<td>Unemployed</td>
<td>1.0</td>
<td></td>
<td></td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td><strong>Behavioral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of border crossing</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily or weekly</td>
<td>0.4</td>
<td>0.1, 1.6</td>
<td>0.22</td>
<td>6</td>
<td>32</td>
<td>17</td>
<td>47</td>
</tr>
<tr>
<td>Less than weekly</td>
<td>1.0</td>
<td></td>
<td></td>
<td>13</td>
<td>68</td>
<td>19</td>
<td>53</td>
</tr>
<tr>
<td>Smoke more than 100 cigarettes in a lifetime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.2</td>
<td>0.4, 4.2</td>
<td>0.75</td>
<td>7</td>
<td>37</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td>12</td>
<td>63</td>
<td>24</td>
<td>67</td>
</tr>
<tr>
<td>Current smoker</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.8</td>
<td>0.3, 2.7</td>
<td>0.77</td>
<td>7</td>
<td>39</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td>11</td>
<td>61</td>
<td>22</td>
<td>61</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular use of medications (excluding SLE*-specific medications and antihypertensives)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.0</td>
<td>0.8, 11.8</td>
<td>0.12</td>
<td>13</td>
<td>68</td>
<td>17</td>
<td>47</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td>6</td>
<td>32</td>
<td>19</td>
<td>53</td>
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<tr>
<td>Gone through menopause</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>1.4</td>
<td>0.4, 4.9</td>
<td>0.59</td>
<td>11</td>
<td>58</td>
<td>19</td>
<td>53</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td>8</td>
<td>42</td>
<td>17</td>
<td>47</td>
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<tr>
<td>Taking hormone replacement therapy</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>1.5</td>
<td>0.5, 5.1</td>
<td>0.47</td>
<td>7</td>
<td>37</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td>12</td>
<td>63</td>
<td>25</td>
<td>71</td>
</tr>
</tbody>
</table>

Table continues
decided not to participate or possibly those cases who were so severely affected that they were referred to specialty clinics or were physically unable to participate. In addition, people who were clinically diagnosed with SLE but who did not meet our selection criteria would have been excluded from our study. Thus, an underestimate of the prevalence of SLE as defined for our study is possible, but unlikely. An overestimate might have occurred if the data for the population of Nogales have increased substantially since the census data we used were obtained or if people who were not genuinely affected with SLE were included in the study. We believe that the latter is very unlikely, since the case criteria we used were stricter than those used by the ACR and since all participants who were potential cases for the study were thoroughly examined by a board-certified rheumatologist. We also do not believe that any cases were from the sister city, Nogales, Sonora. All participants were required to provide local addresses, and all reported having lived in Nogales, Arizona, for an average of 28 years. Additionally, residents of Mexico are covered by a national health program that provides care at little or no cost, including access to specialists, and it is unlikely that any SLE patients from Mexico sought care in Nogales, Arizona, for which they would have to pay.

In addition, the prominent toxicologic finding of elevated levels of DDE, a DDT metabolite, in both cases and controls, indicates past exposure to DDT. Although DDT use was banned in the United States in 1972, some exposure might have continued through either unauthorized use in the United States or from sources in Mexico (19). We also found levels of organophosphate metabolites in both cases and controls that were elevated when compared with the reference ranges for the US population. This finding suggests exposure to organophosphate pesticides within the previous week and most likely within the previous 48 hours. While the present level of organophosphate metabolites cannot be associated with SLE that developed in the past, it could indicate ongoing pesticide exposure. Values above the reference range most likely indicate recent exposure from a source or sources greater than the average person might have.

### TABLE 2. Continued

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. %</td>
<td>No. %</td>
</tr>
</tbody>
</table>

**Ever breastfeed**
- Yes: 5.4 (0.6, 45.9) 0.11 (15, 88) 25 (76)
- No: 1.0 (0.6, 45.9) 0.11 (2, 12) 8 (24)

**No. of pregnancies**
- ≥1: 0.9 (0.1, 5.2) 0.87 (17, 89) 33 (92)
- None: 1.0 (0.6, 45.9) 0.11 (2, 12) 8 (24)

**No. of miscarriages**
- ≥1: 3.0 (0.7, 12.1) 0.13 (8, 47) 9 (28)
- None: 1.0 (0.6, 45.9) 0.11 (2, 12) 8 (24)

**Currently taking natural medicines**
- Yes: 1.2 (0.4, 4.3) 0.75 (9, 47) 16 (44)
- No: 1.0 (0.6, 45.9) 0.11 (10, 53) 20 (56)

**Environmental**
- Ever lived on a farm
  - Yes: 1.0 (0.3, 3.9) 0.98 (3, 16) 6 (17)
  - No: 1.0 (0.6, 45.9) 0.11 (16, 84) 30 (83)

- Used a hair dye in the previous 5–10 years
  - Yes: 2.0 (0.4, 11.2) 0.43 (17, 89) 29 (81)
  - No: 1.0 (0.6, 45.9) 0.11 (2, 11) 7 (19)

- Pesticides applied in/around home in the previous 12 months
  - Yes: 1.3 (0.1, 14.6) 0.84 (14, 93) 30 (94)
  - No: 1.0 (0.6, 45.9) 0.11 (1, 7) 2 (6)

- Lawn treatments for weeds or insects applied
  - Yes: 1.2 (0.3, 5.1) 0.81 (4, 27) 8 (25)
  - No: 1.0 (0.6, 45.9) 0.11 (11, 73) 24 (75)

- Water source
  - City: 5.3 (0.9, 31.6) 0.06 (14, 74) 15 (43)
  - Private well/filtered: 0.9 (0.1, 11.7) 0.96 (1, 5) 6 (17)
  - Bottled: 1.0 (0.6, 45.9) 0.11 (4, 21) 14 (40)

* OR, odds ratio; CI, confidence interval; SLE, systemic lupus erythematosus.
have on a daily basis. This finding implies that both cases and controls have or have had similar exposures to these chemicals. Approximately 45–84 percent of the levels detected exceeded the reference range for the US population. Nevertheless, we found no statistical association between any of the pesticide metabolites detected and SLE.

In this study, a genetic predisposition to SLE is probably the main contributing factor for development of SLE, since 37 percent of our cases reported that they have a family member diagnosed with SLE. While, to our knowledge, this is the first study of SLE conducted in a Hispanic population of primarily Mexican descent, other studies have examined Puerto Rican, African-American, and Latin-American populations (20, 21). The prevalence of SLE in Puerto Ricans has been reported to be 35.9/100,000 females and, for African Americans, 49.2/100,000 females (14). These populations have been shown to have an elevated prevalence of SLE when compared with Caucasians in the United States (22, 23). The overall US prevalence of SLE represents rough estimates, since the data available are limited to regional studies that not only varied over time and place but also used different methods of case ascertainment (14, 16, 24).

There are no established criteria for the definition of environmentally associated autoimmune disease, including SLE. Ideally, for an environmental agent to be considered a possible cause of an environmental autoimmune disease, there should be 1) absence of symptoms prior to exposure, 2) no other known or likely cause to explain the disease, 3) no family history of a similar disease, and 4) improvement of symptoms when the environmental agent is removed (25). Nevertheless, exceptions to the last two criteria have been documented in the past, in particular toxic oil syndrome, in which many relatives were affected in whom the disease did not remit on removal of the causative agent (26).

Drug-induced SLE is a well-documented syndrome known to be induced by medications that have aromatic amine moities in their structures, such as hydralazine and procainamide (27). Drugs that contain chemicals with structural similarities to these medications may also induce SLE. Persons who are slow acetylators are predisposed to development of lupus from using drugs that have aromatic amine moities in their structures, such as hydralazine and procainamide (27). In our study, cases used multiple medications as compared with controls, but these were mainly antihypertensives and antacids. The most likely explanation for the higher medication use is that SLE patients in general are sicker than controls. While some of these medications may not have been specific treatment for SLE, they could be treatment for some of the long-term consequences of SLE, such as hypertension. This supports our results that showed no statistical association between medication use and the

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**TABLE 3. Distribution of metabolites of 1,1-dichloro-2,2'-bis(p-chlorophenyl)ethylene and organophosphate pesticides in biological samples collected from case and control participants, study of systemic lupus erythematosus, Nogales, Arizona, 1997**

<table>
<thead>
<tr>
<th>Metabolites and participants</th>
<th>Mean (SD)†</th>
<th>Median</th>
<th>Percentile</th>
<th>Reference for US population</th>
<th>OR*</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>75th</td>
<td>95th</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Organochlorine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDE*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>10.8 (7.7)</td>
<td>10.1</td>
<td>15.2</td>
<td>27.9</td>
<td>1.1–37.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Cases</td>
<td>10.5 (8.0)</td>
<td>9.51</td>
<td>14.08</td>
<td>32.3</td>
<td>1.6–32.3</td>
<td></td>
</tr>
<tr>
<td>Organophosphates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFP*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>6.2 (7.5)</td>
<td>3.5</td>
<td>8.4</td>
<td>18.0</td>
<td>0.4–37.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Cases</td>
<td>12.2 (22.8)</td>
<td>6.6</td>
<td>13.0</td>
<td>98.0</td>
<td>0.5–98.0</td>
<td></td>
</tr>
<tr>
<td>DMP*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>8.0 (6.9)</td>
<td>4.9</td>
<td>13.0</td>
<td>24.0</td>
<td>0.5–25</td>
<td>1.5</td>
</tr>
<tr>
<td>Cases</td>
<td>5.9 (9.8)</td>
<td>2.0</td>
<td>6.30</td>
<td>41.0</td>
<td>0.6–41</td>
<td></td>
</tr>
<tr>
<td>DMTP*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>8.7 (8.3)</td>
<td>6.0</td>
<td>14.0</td>
<td>25.0</td>
<td>0.19–31</td>
<td>6.1</td>
</tr>
<tr>
<td>Cases</td>
<td>10.2 (11.5)</td>
<td>6.3</td>
<td>14.0</td>
<td>47.0</td>
<td>0.73–47</td>
<td></td>
</tr>
<tr>
<td>DETHP*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>2.9 (3.4)</td>
<td>2.0</td>
<td>3.3</td>
<td>12.0</td>
<td>0.35–17</td>
<td>0.7</td>
</tr>
<tr>
<td>Cases</td>
<td>5.9 (12.9)</td>
<td>1.5</td>
<td>5.6</td>
<td>53.0</td>
<td>0.03–53</td>
<td></td>
</tr>
<tr>
<td>DMDETP*</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1.8 (1.8)</td>
<td>1.5</td>
<td>2.2</td>
<td>5.4</td>
<td>0.04–17</td>
<td>0.7</td>
</tr>
<tr>
<td>Cases</td>
<td>3.7 (3.9)</td>
<td>2.5</td>
<td>3.3</td>
<td>13</td>
<td>0.21–13</td>
<td></td>
</tr>
<tr>
<td>DEDTP*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1.0 (0.9)</td>
<td>0.6</td>
<td>1.5</td>
<td>2.3</td>
<td>0.1–4.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Cases</td>
<td>0.3 (0.2)</td>
<td>0.3</td>
<td>0.5</td>
<td>0.6</td>
<td>0.1–0.6</td>
<td></td>
</tr>
</tbody>
</table>

† All DDE units are in ppb; all organophosphate metabolite units are in μg/g creatinine.
risk for SLE after exclusion of medications potentially used to treat SLE.

Our study has several limitations. These include 1) the small sample size that limited our statistical power to examine the association between SLE and the risk factors presented, 2) the restricted geographic location from which the sample was drawn, which could raise concerns about the generalizability of our results, 3) possible recall bias, in particular for variables related to time, and 4) possible selection bias when choosing controls since we did not recruit people who did not have telephones.

Other studies that have attempted to examine the association of environmental exposures and SLE have used exposure indices based on questionnaire and history information rather than direct measurement of the biomarkers of an exposure (28). In our study, we used a combination of clinical, toxicologic, and risk factor data to examine whether an association exists between the development of SLE and exposure to certain environmental contaminants. We were unable to document an association between selected environmental exposures in Nogales, Arizona, and the development of SLE. We did, however, find the prevalence of SLE in Nogales to be much higher than the overall reported prevalence in the US population. Although we were unable to determine a cause for this increase in SLE prevalence, our study was able to address several shortcomings of previous studies. Unlike those previous studies, we obtained biologic samples from the participants to document levels of environmental exposure to selected pesticides and metals, and we demonstrated that there was no correlation between exposure levels and disease status in a nonoccupational setting. We also used a very strict case definition and applied it rigorously. All SLE patients were required to undergo physical examination and clinical testing by a rheumatologist to confirm the illness, thus excluding participants who might have had milder disease or other rheumatic diseases. Finally, we collected the same biological samples and questionnaire data from local matched controls.

While, in this instance, we were not able to show a clear association between an environmental contaminant and disease, we believe that the results of this study will serve to suggest directions for future research into the association of environmental contaminants and autoimmune diseases such as SLE. Future research may focus on establishing criteria for the definition of environmentally associated autoimmune diseases, documenting exposure information by developing useful biomarkers, and initiating population-based registries that will help identify clusters of cases potentially associated with environmental exposures.

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REFERENCES


