

*Short report***Non-Hodgkin's lymphoma and nitrate in drinking water: a study in Yorkshire, United Kingdom**

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Non-Hodgkin's lymphoma (NHL) is a haematological malignancy with a continuing rise in incidence in the United Kingdom.<sup>1</sup> The unknown cause may be attributable to changes in environmental risk factors. Various explanations have been proposed including a dysfunctioning immune system, occupational exposure to pesticides or rural residence,<sup>2</sup> but so far no clear causal factors are forthcoming.

Ingested nitrate produces N-nitroso compounds, after amination in the stomach, with known carcinogenic properties. Two recent American studies have shown a positive association between drinking water nitrate and NHL<sup>3,4</sup> and this study has investigated the association for the first time in the United Kingdom.

**Methods**

A population-based incidence register of NHL has been collected by the Leukaemia Research Fund since 1 January 1984, completing 160 million person years of surveillance for approximately 25% of the UK population.<sup>5</sup> This study included cases in 0-79 year olds, diagnosed during 1984-93, resident within the supply areas of Yorkshire Water plc or the York Water Company who distribute drinking water to West, South and North Yorkshire and North Humberside (population 3.06 million persons). All Kiel types were pooled and subdivided into nodal (lymph nodes, marrow, blood, tonsils) and extra-nodal disease.

Domestic water in England is regulated under the Water Industry Act 1991, and distribution networks must be divided into geographically distinct Water Supply Zones (WSZs) with less than 50 000 residents. Water supplied within a WSZ has the same chemical composition at any one time. A total of 9330 tap water measurements were available from 148 WSZs, covering six years (1990-95) (table 1). Nitrate was measured according to guide-

lines regulated by the Drinking Water Inspectorate, at a single laboratory where random samples from consumers taps are subject to mandatory quality control. Annually, nitrate levels oscillate around an average, because of seasonal factors, and therefore exposure was calculated as the mean of the monthly mean.

Age-sex specific population counts from the 1991 census (ESRC purchase, Crown Copyright) were linked to a WSZ using a Geographical Information System, as described elsewhere,<sup>6</sup> forming the underlying susceptible population. Poisson regression models were fitted to observed counts of cases within each WSZ using the log of the number of expected cases, derived from age-sex standardised incidence rates, as the offset. Population density (persons per hectare) and nitrate were assigned into three categories with approximately equal number of persons in each level (table 2). Population density was included as a proxy for urban/rural status, as previous research has shown rural habitation is a risk factor for NHL.<sup>7</sup> The effect of removing nitrate exposure from the model was tested using the likelihood ratio statistic and the simplest model was chosen based on significant improvement in model fit. The incidence rate ratio is reported as a measure of association and poor model fit caused by extra-Poisson variation was corrected using the method of Breslow. Modelling was repeated for nodal and extra-nodal sites, time period at diagnosis (1984-88, 1989-93) and age group (0-59, 60-79), as evidence suggests these subsets have potentially distinct aetiologies.

**Results**

There were no significant associations between NHL incidence and explanatory variables for all cases combined. For 1984-88, nitrate was retained in the model and had a significant positive association with the incidence of NHL at both the second and highest levels above baseline. In contrast, removing nitrate from the model for the second time period, 1989-93, did not significantly reduce model fit. There was no association between nitrate or population density and NHL in the two age groups or in extra-nodal cases. The rate ratio for level 2 of nitrate was significantly raised for nodal sites, however, that of the highest level of nitrate exposure was not significantly raised. Model

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*Table 1 Demographic characteristics of the Water Supply Zones (WSZ) in the study*

| WSZ (n=148)                   | Mean  | Minimum | Maximum |
|-------------------------------|-------|---------|---------|
| Area (hectares)               | 6780  | 91      | 61252   |
| Population*                   | 20702 | 61      | 51148   |
| Population density†           | 12.47 | 0.04    | 54.19   |
| Nitrate concentration (mg/l)‡ | 11.86 | 1.48    | 40.01   |

\*0-79 years of age. †Persons per hectare. ‡Mean of the monthly mean.

Table 2 Association of nitrate concentrations in drinking water and population density with NHL: incidence rate ratios (IRR) for chosen Poisson regression model (using likelihood ratio test to choose model)

| Group       | Incidence* (obs) | Variable            | Level | IRR          | 95% CI†           |
|-------------|------------------|---------------------|-------|--------------|-------------------|
| All         | 8.61 (2637)      | Population density‡ | 1     | 1            | —                 |
|             |                  |                     | 2     | 1.104        | 0.92, 1.17        |
|             |                  |                     | 3     | 0.943        | 0.84, 1.06        |
| 1984–88     | 7.76 (1188)      | Population density  | 1     | 1            | —                 |
|             |                  |                     | 2     | 1.106        | 0.96, 1.27        |
|             |                  |                     | 3     | <b>0.857</b> | <b>0.74, 0.99</b> |
|             |                  | Nitrate§            | 1     | 1            | —                 |
|             |                  |                     | 2     | <b>1.170</b> | <b>1.01, 1.35</b> |
|             |                  |                     | 3     | <b>1.210</b> | <b>1.04, 1.41</b> |
| 1988–93     | 9.46 (1449)      | Population density  | 1     | 1            | —                 |
|             |                  |                     | 2     | 1.000        | 0.86, 1.17        |
|             |                  |                     | 3     | 1.028        | 0.88, 1.21        |
|             |                  | Nitrate             | 1     | 1            | —                 |
|             |                  |                     | 2     | 1.069        | 0.92, 1.25        |
|             |                  |                     | 3     | 0.917        | 0.78, 1.08        |
| 0–59        | 4.19 (1048)      | Population density  | 1     | 1            | —                 |
|             |                  |                     | 2     | 1.138        | 0.98, 1.32        |
|             |                  |                     | 3     | 0.962        | 0.83, 1.12        |
| 60–79       | 28.37 (1589)     | Population density  | 1     | 1            | —                 |
|             |                  |                     | 2     | 0.987        | 0.85, 1.15        |
|             |                  |                     | 3     | 0.951        | 0.81, 1.11        |
|             |                  | Nitrate             | 1     | 1            | —                 |
|             |                  |                     | 2     | 1.137        | 0.98, 1.32        |
|             |                  |                     | 3     | 0.975        | 0.83, 1.15        |
| Nodal       | 5.10 (1561)      | Population density  | 1     | 1            | —                 |
|             |                  |                     | 2     | 1.046        | 0.91, 1.20        |
|             |                  |                     | 3     | 0.962        | 0.83, 1.11        |
|             |                  | Nitrate             | 1     | 1            | —                 |
|             |                  |                     | 2     | <b>1.254</b> | <b>1.09, 1.45</b> |
|             |                  |                     | 3     | 1.100        | 0.94, 1.28        |
| Extra-nodal | 2.95 (905)       | Population density  | 1     | 1            | —                 |
|             |                  |                     | 2     | 1.102        | 0.93, 1.30        |
|             |                  |                     | 3     | 0.927        | 0.78, 1.10        |

\*Internally standardised incidence rate per 100 000 persons per year. †Corrected for extra-Poisson variation; significant at  $p < 0.05$  in bold. ‡Persons per hectare; 1 >18.39, 2 6.91–18.39, 3 <6.91. §Mean of the monthly mean of nitrate in mg/l; 1 <3.24, 2 3.24–14.85, 3 >14.85.

residuals showed no systematic spatial pattern when mapped by WSZ or observable higher order interactions.

### Discussion

There was no evidence of an association between nitrate in drinking water and the incidence of NHL for the entire study period. Population density was retained throughout the model building as a control variable, but showed no significant association. These results contrast with previous studies in the US state of Nebraska where NHL was found to be associated with increased levels of nitrate.<sup>3,4</sup> A small ecological study of 195 cases<sup>3</sup> found increased incidence in “counties” with more than 20% of the water failing their statutory limit of 10 ppm nitrate-nitrogen (equivalent to 44 mg/l of nitrate). A case-control study in the same state used an imprecise estimate of nitrate exposure assessed from single annual measurements for a “city or town”; 26% of Yorkshire WSZs had average nitrate concentrations exceeding 18 mg/l, the level with reported statistically increased risk in Nebraska.<sup>4</sup>

Incidence during 1984–88 showed significant associations with nitrate, a pattern that did not persist to 1989–93. Data collection procedures and quality have remained consistent and differences cannot be explained by systematic change in practice. The other subgroups showed no association with nitrate with the exception of nodal disease. However, the lack

of dose response or significance of the highest category suggest confounding with a further unmeasured variable. Population density, always included during the modelling process, reduced the likelihood of observing nitrate as a confounder for factors associated with rural habitation.

Nitrate measurements represented a six year time period, during which 81% of all WSZs did not change.<sup>6</sup> Historical data before 1990 were not systematically collected, and analyses of these data would not be possible. However, systematic migration of those persons with NHL initiated, but not diagnosed, to a lower water nitrate region, which could account for the lack of consistent association, is unlikely.

Studies using areal units of analysis assign an exposure to all persons based on the properties of the area. However, despite heterogeneity across the study area each geographical unit of analysis (WSZ) was internally homogenous with respect to nitrate levels. The small geographical areas of the WSZs and homogeneity of water quality within a WSZ, lead to an accurate picture of the population structure and nitrate exposure from drinking water. Added to this, a survey reported 99% of all households in the United Kingdom drink tap water, and 77% of total liquid consumption is derived from tap water.<sup>7</sup> Measuring nitrate load using this method avoids reporting bias from people and inherent problems with dietary studies of people, particularly the evaluation of micronutrient ingestion.

Despite the observed association in the first time period between nitrate and incidence of NHL, the trend or significant associations do not persist into the second half of the data collection period and was not evident for the entire period. These results do not provide substantial evidence to support the hypothesis that nitrate in drinking water is an initiator or promoter of non-Hodgkin's lymphoma, in contrast with previous studies.

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