The Russian nickel refineries located in the cities of Nikel and Zapolyarny close to the Norwegian border are responsible for extensive sulfur dioxide and nickel pollution, as well as severe ecological damage in both countries. The aim of our study was to investigate human nickel exposure in the populations living on both sides of the Norwegian–Russian border. The design was a cross-sectional population-based study of adults aged 18–69 years residing in Sor-Varanger municipality, Norway, and Nikel and Zapolyarny, Russia, during 1994 and 1995. Individual exposure to nickel was assessed by measurements of nickel in urine using electrothermal atomic absorption spectrometry. For controls, urine was collected from adults in the Russian cities of Apatity and Umba (Kola Peninsula) and the Norwegian city of Tromsø, all of which are locations without nearby point sources of nickel. Altogether, 2,233 urine specimens were analysed for nickel. People living in Nikel had the highest concentrations (median 3.4 µg/l), followed by Umba (median 2.7 µg/l), Zapolyarny (median 2.0 µg/l), Apatity (median 1.9 µg/l), Tromsø (median 1.2 µg/l), and Sor-Varanger (median 0.6 µg/l). Regardless of geographical location, the Russian study groups all had a higher urinary-nickel average than those in Norway (p<0.001). With the exception of nickel, neither the Russian nor the Norwegian urinary-nickel levels were associated with residence location near a Russian nickel refinery. We concluded that industrial nickel pollution alone cannot explain the observed discrepancy between Norway and Russia; we also discuss other possible nickel exposure sources that may account for the high urinary levels found in Russia. Key words: air pollution, environmental epidemiology, exposure assessment, industrial emissions, nickel, Norway, occupational exposure, Russia, smoking, urine. Environ Health Perspect 106:503-511 (1998). [Online 14 July 1998] http://ehpnet1.niehs.nih.gov/docs/1998/106p503-511smith-sivertsen/abstract.html

During the last decade, much attention has been allotted to the industrial air pollution in the Northern–Russian border area. The Kola Peninsula, Russia, features an extensive metal-refining industry, with nickel being the metal of greatest importance. Large nickel ore processing plants and refineries have been built up in the cities of Nikel, Zapolyarny, and Monchegorsk (Fig. 1), and this activity causes extensive environmental sulfur dioxide (SO₂) and metal pollution. In Sor-Varanger, a municipality on the Norwegian side of the border, pollution from the neighboring plants in Nikel and Zapolyarny has been a subject of great public and political concern. According to the official Russian emission data, 297 tons of nickel and 198,368 tons of SO₂ were discharged from the operations in Nikel and Zapolyarny in 1994 (7).

In 1988, a comprehensive research program on environmental pollution effects in the border area was initiated as a Russian–Norwegian collaborative project. Monitoring of air quality showed that for SO₂, the World Health Organization (WHO) Air Quality Guidelines were frequently exceeded, especially on the Russian side of the border, while levels of suspended particles were below current guidelines (2.3). Serious damage to the vegetation due to SO₂ effects was evident in an area of 3,000 km² around the emission sources (4), most conspicuous being the dead forest in close proximity to the refineries. The deposition patterns of nickel showed an increasing gradient toward the emission sources (Fig. 2). Increased nickel levels were found in parenchymal organs of caribou and moose in Sor-Varanger (5), as well as in cloudberry, mosses, and lichens (6). Rivers in the area have also been contaminated by nickel (7). To date, few studies have focused on human exposure and possible health effects in relation to the industrial pollution described.

The overall objective of our Norwegian–Russian cooperative study was to investigate both the exposure of selected populations and possible health effects from the nickel and SO₂ pollution in the border area. For this study, our purpose was to collect data on urinary levels of nickel as a measure of exposure to assess the importance of the local nickel industry as an exposure source for people in the border area. To do this, we not only analyzed urine collected from inhabitants of Nikel, Zapolyarny, and Sor-Varanger but also from individuals living more remotely from the Kola Peninsula nickel-producing centers. Nickel in urine is a valid index of nickel exposure, providing that the chemical identity and physiochemical properties of the nickel compounds are taken into consideration (8).

Materials and Methods
The study consists of separate cross-sectional population-based studies following a common protocol conducted on both sides of the Norwegian–Russian border. In Norway, the population of Sor-Varanger municipality was studied; in Russia, the study areas were the cities of Nikel and Zapolyarny. Comparison groups were sampled in Tromsø, Norway, and in Apatity, Kirovsk, and Umba, Russia. The study was steered by a joint Norwegian–Russian health group established in 1992.

Study areas and study populations. Sor-Varanger municipality in Finnmark county is situated in the northeastern part of Norway, north of the Arctic circle around the 70th parallel. In 1994, about 9,800 people lived in Sor-Varanger, half of them in the administrative center of Kirkenes (Fig. 2). Apart from Kirkenes and Bjarnevarn, the population is spread among minor settlements. The local iron smelting industry in Kirkenes, which was closed down in 1997, did not emit nickel. The eastern part of the municipality shares a border with Russia, which follows a river along the majority of its stretch. The Russian nickel industrial city of Nikel lies only about 10 km east of this river, at the same latitude and altitude as Svanvik (Fig. 2).

The Sor-Varanger study was conducted from May to October 1994. All adults between 18 and 69 years of age were invited to participate. After one reminder, 3,671 people (59.4%) joined the study (Table 1). The relatively low attendance rate was in part explained by low participation among young males. A written informed consent form was signed by all participants. The invitation procedure and enrollment

Address correspondence to T. Smith-Sivertsen, Institute of Community Medicine, University of Tromsø, N-9037 Tromsø, Norway.

We thank Per Einar Fiskebeek for his indispensable help throughout the study period, Evert Nieboer for his useful suggestions during the writing of the manuscript, and Natalya Romanova, Alexej Parias, and Gunhild Sand for performing the urinary analyses.

This study was funded by the Norwegian Ministries of the Environment, Health and Social Affairs and Foreign Affairs, the Russian Ministry of Health, and the Murmansk Regional Health Care Committee.

Received 5 January 1998; accepted 24 March 1998.
have previously been described in more detail (9).

Nikel and Zapolyarny are situated at the Kola Peninsula, about 10 and 40 km from the Norwegian border, respectively (Figs. 1,2). Nickel refining constitutes the major industry in both cities. The cities are densely built, and very few of the 23,000 (Nikel) and 25,000 (Zapolyarny) inhabitants live outside the city centers. Most people live and work locally. In Nikel, the refinery is situated in the northern part of the city, whereas the Zapolyarny plant lies about 1 km east of the city houses.

In these cities, the study was conducted from November 1994 to April 1995, after the Sør-Varanger study. Samples of adults 18–69 years of age were invited in each place: 4,000 out of 15,065 eligible persons in Nikel and 4,026 out of 16,542 in Zapolyarny. After three reminders, 1,788 (44.7%) and 1,941 (48.2%) participated, respectively (Table 1). As in Sør-Varanger, participation was highest among women and in the older age groups. The sampling and invitation procedure on the Russian side had to be adjusted to local Russian conditions because the local registers for these cities were not properly updated for effective use. It was therefore decided to sample on the basis of residency. Thus, a certain number of preexisting city zones were selected, and all inhabitants of these zones living in five- and nine-story buildings were invited. These buildings consist of one, two, and three living room flats of equal standard; almost all inhabitants, regardless of socioeconomic status, live in buildings such as these. In Nikel, four out of seven city zones were selected, corresponding to 58 apartment buildings. In Zapolyarny, residents of 54 buildings were invited from four out of eight zones. This method of sampling was judged as not giving any selection bias because housing conditions are very homogenous throughout both cities and the city areas are too small to be subject to any important concentration gradient for pollution. Because of previous Russian experiences that yielded low response rates when invitations were given by mail, all participants were invited personally by two trained field workers. In this way, all residents of each sampled apartment building were registered; thus, it was possible to calculate correct response rates. A written informed consent form was signed by the Russian participants prior to screening.

The Russian comparison cities of Apatity (70,000 inhabitants) and Kirovsk (35,000 inhabitants) are situated very close to each other in the center of the western section of the Kola Peninsula and can almost be regarded as one entity (Fig. 1). The cities have no nickel industry, but are industrial cities featuring apatite mining and production. The sampling strategy in these cities was the same as for Nikel and Zapolyarny; participation rates are given in Table 1. Surveys were performed April and May 1995 in Apatity and October and November 1995 in Kirovsk.

The nickel refinery of Monchegorsk lies about 25 km north of Apatity and Kirovsk, hence they cannot be regarded as free from environmental nickel pollution. For the nickel measurements, we decided to include an additional comparison group from the village of Umba (about 3,700 inhabitants), which is located 120 km southeast of Monchegorsk and is spared from any industrial pollution. In February 1996, urine specimens were collected from 20 adults randomly picked from a building identical to those canvassed in Nikel and Zapolyarny.

The Norwegian comparison city of Tromsø has approximately 55,000 inhabitants and is situated in northern Norway at about the same latitude as Sør-Varanger; it has no nickel-emitting industry. Participants from Tromsø were drawn from a large population-based follow-up study, referred to as
the Tromso Study (10). A random sample of 337 persons 25–69 years of age who attended the fourth follow-up in March 1995 were asked to give urine specimens for nickel determination. Urine was obtained from 302 of these persons.

Health screening procedure. We screened the three study populations (Sør-Varanger, Nikel, and Zapolyarny) and Apatity to map exposure and possible health effects from the SO₃ and nickel pollution. In Kirovsk, the screening excluded urinary nickel measurements, hence no data from Kirovsk are presented here. In Tromsø and Umba, the screening was limited to urine sampling for nickel determination.

To be able to use the same equipment (i.e., spirometers, computers) in both countries, the fieldwork in Russia was initiated after the Sør-Varanger study had ended. The fieldwork was conducted by different teams in Norway and Russia. The co-workers in Nikel and Zapolyarny went through a 1-week training course in Sør-Varanger where they participated in the actual survey there. Moreover, the researcher who was in charge of the fieldwork in Sør-Varanger carefully supervised the field workers in the initial phase of the Russian survey and also visited the Russian teams regularly during the whole study period to ensure that the protocols were strictly followed. All disposable equipment (i.e., syringes, needles, containers for urine samples) was supplied by the Norwegian team.

Information about lung diseases, allergies, pregnancy outcomes, work place, housing conditions, smoking habits, and social conditions was obtained from a four-page questionnaire with Norwegian and Russian versions. In Norway, the questionnaire, which was sent by mail, was completed by the participants and brought to the screening. In Russia, the participants were asked the same questions in an interview because self-administered questionnaires are of limited reliability in Russia. Apart from this, the screening procedure was identical in Sør-Varanger and Russia: weight and height were measured, the participants went through spirometry testing to determine lung function, blood was drawn to screen for IgE-mediated allergy (total-IgE and Phadiatop); and a subsample underwent nickel allergy testing. Finally, a spot urine specimen was collected from all subjects at the screening to measure nickel concentrations.

Urine sampling. The urine was collected in a disposable plastic cup, and a subsample (5–20 ml) was poured into a screw-capped 25-ml plastic container (Universal Container; NUNC, Denmark). We tested the plastic cups and containers for nickel leakage by leaching with 0.5% nitric acid; no detectable nickel contamination occurred (detection limit <0.2 pg/I). After sampling, the urine specimens were kept frozen at -20°C until analysis.

As a result of limited analytical capacity, not all urine samples could be analyzed. In Sør-Varanger, a total of 902 urine specimens were selected for nickel measurements. All specimens collected from individuals living adjacent to the Russian border were analyzed (Fig. 2), while the numbers included from other settlements were restricted, although randomly selected. In Nikel, Zapolyarny, and Apatity, about 25% of the urine specimens were randomly selected for analysis (Table 2); in Tromsø and Umba, all specimens (302 and 20, respectively) were analyzed. Altogether, nickel was determined in 2,233 urine samples.

Tap water sampling. To evaluate drinking water as a source of nickel, tap water samples were taken from all study areas. We collected samples from private homes of people we judged to be representative of the participants in the screening. After 5 min of flushing, cold water samples were collected in screw-capped nickel-free polyethylene bottles (Zinszer; Nalge Company, Rochester, NY) without nitric acid preservation. The bottles were kept unfrozen until analysis.

Analysis of urine and tap water. To prevent any risk of laboratory-acquired infection and to redissolve urine precipitates, all urine samples were heated for 1 hr at 95°C in a laboratory oven prior to analysis. To recover any nickel adsorbed to the inner

| Study population | Invited | Participation n (%) | Female n (%) | Male n (%) |
|-----------------|---------|----------------------|--------------|------------|
| Norway          |         |                      |              |            |
| Sør-Varanger    | 6,177   | 3,671 (59.4)         | 1,978 (53.9) | 1,693 (46.1) |
| Tromsø (control) | 346     | 302 (87.3)          | 150 (43.7)   | 152 (56.3)  |
| Russia          |         |                      |              |            |
| Nikel           | 4,000   | 1,788 (44.7)        | 1,193 (66.7) | 595 (33.3)  |
| Zapolyarny      | 4,826   | 1,481 (48.2)        | 1,304 (67.2) | 637 (32.8)  |
| Apatity (control) | 1,813  | 682 (42.3)         | 512 (75.1)   | 170 (24.9)  |
| Kirovsk (control) | 508    | 229 (45.1)         | 142 (62.0)   | 87 (38.0)   |
| Umba (control)  | 20      | 20 (100.0)          | 8 (40.0)     | 12 (60.0)   |

*Attendance rate at the Tromsø Study IV was 77% (49).

| Study population | n | Median (pg/I) | Mean (pg/I) | Range (pg/I) | Percent with nickel concentration ≥25 pg/I | Relative risk* | CI* |
|-----------------|---|--------------|-------------|--------------|------------------------------------------|----------------|-----|
| Norway          |   |              |             |              |                                          |                |     |
| Sør-Varanger    | 902| 0.6          | 0.9         | 0.3–11.0     | 5.9                                      | 1.0            |     |
| Tromsø (control city)* | 302| 1.2          | 1.4         | 0.3–6.0      | 8.9                                      | 1.5            | 1.0–2.3 |
| Russia          |   |              |             |              |                                          |                |     |
| Nikel**         | 371| 3.4          | 4.9         | 0.3–61.9     | 66.0                                     | 11.3           | 9.2–14.0 |
| Zapolyarny      | 418| 2.0          | 2.8         | 0.3–24.2     | 39.9                                     | 6.6            | 5.2–8.5 |
| Apatity (control city) | 220| 1.9          | 2.6         | 0.3–17.0     | 38.6                                     | 5.9            | 4.4–8.0 |
| Umba (control city) | 20 | 2.7          | 4.0         | 1.0–17.0     | 60.0                                     | 8.9            | 5.4–14.7 |

Relative risks and 95% confidence intervals (CI) of concentration ≥25 pg/I, with Sør-Varanger as the reference population.

*Relative risk and CI of nickel concentration ≥25 pg/I, adjusted for sex and age.
**Significantly higher urinary nickel concentrations in Nikel than in both Zapolyarny (p<0.001) and Apatity (p<0.001; Wilcoxon rank sum test).
surface of the sample containers, we added 0.5 ml 65% ultrapure nitric acid to each 25-ml tap water sample 24 hr before the nickel measurement was performed.

Nickel in urine and drinking water was measured by electrothermal atomic absorption spectrometry employing Perkin-Elmer Model 5100 PC/HGA-600 and Model SIMAA 6000/THGA atomic absorption spectrometers equipped with Zeeman-based background correction systems (Bodenseewerk Perkin-Elmer GmbH, Überlingen, Germany). All analyses were conducted in the analytical laboratory of the National Institute of Occupational Health in Oslo. Calibrations (4-point calibration curves) were made using aqueous standard solutions (water) and urinematched standard solutions. Surface water (SPS-SW Level 1; Spectrapure Standards Ltd., Oslo, Norway) and human urine Seronorm (Nycomed Ltd., Oslo, Norway) trace element quality control materials were used throughout the study to monitor the accuracy and the reproducibility of the measurements. The day-to-day variations of the nickel measurements in these reference materials were typically 5 and 15%, respectively. The mean nickel concentrations measured in SPS-SW1, batch 102, and Seronorm STE 101021 were 9.6 ± 0.3 [standard deviation (SD)] and 2.4 ± 0.3 µg/l, respectively. This is in good agreement with the recommended values of 10.0 and 2.5 µg/l of nickel given by the producers. The detection limit (2 standard deviations) of the method used was 0.5 µg/l of nickel.

To enable dilution corrections, creatinine content was measured in all urine specimens employing a Beckman Creatinine Analyser (Beckman, Brea, CA) based on Jaffe’s method.

Occupational exposure group classification. The Russian questionnaire provided information about current work in the nickel industry. All participants reporting current employment in the industry were classified into one of four major categories: 1) major refining plants with smelting and ore roasting; 2) supporting plants with maintenance and service functions; 3) mining; or 4) ore milling, concentration, and flotation. Different occupational groups were identified within these categories but, unfortunately, occupational groups could not be further defined for the individual worker with the coding system used. The nickel content in ore is low; thus, mining does not add significantly to the nickel exposure in workers. Participants from the other three categories were included in the survey as being occupationally exposed to nickel, although the exposure may have varied considerably between the subgroups, with a subsequent dilution of a possible high-exposure group.

Statistical analysis. We used the SAS statistical software package (11). The nickel concentration was skewed to the right and was not suited for analytic methods that assume a normal distribution. Values below the detection limit of 0.5 µg/l were found in 22.2% of the samples, and they were assigned the nominal value 0.3 µg/l. Means are presented despite the skewed distribution, as is common in literature on nickel in biologic fluids. We also present the median, which is a more proper way to give the average nickel value. We compared nickel levels between study areas, sexes, and age groups with frequency analysis grouping the subjects according to whether their urinary nickel concentrations were above or below a certain cut-off value. Stratified analyses comparing all areas with Ser-Varanger were done according to the Mantel-Haenszel method (12). The relative risks obtained were defined as the probability of having an elevated nickel concentration in the actual population divided by the same probability in the Ser-Varanger population. The differences between the study groups were statistically significant if the 95% confidence limits did not include the number 1. We also used the nonparametric Wilcoxon rank sum test to compare groups with regard to urinary nickel and tap water nickel.

Results

Urinary nickel concentrations differed greatly between the Norwegian and Russian populations, although the differences were far less pronounced within each country (Table 2). Residents of Nikel had the highest concentrations, with a mean and median of 4.9 µg/l and 3.4 µg/l, respectively, followed by Umba, Zapolyarny, and Aparty. The lowest concentrations were found in Ser-Varanger, with a mean and median of 0.9 µg/l and 0.6 µg/l, respectively.

Because of the skewed nickel distribution, frequency analysis was employed using a cut-off value of 2.5 µg/l. While only 5.9% of the Ser-Varanger samples had values above this cut-off, 66% of Nikel residents had urinary concentrations above 2.5 µg/l (Table 2). The urinary nickel distribution of each study population is shown in Figure 3A. In the following text, we use “elevated nickel concentration” to refer to urinary concentrations above the cut-off value of 2.5 µg/l. There is no obvious best choice for a cut-off value in this setting because there are striking differences in nickel distributions between the study populations. The selection of 2.5 µg/l, however, provides us with a sufficient number of cases in Ser-Varanger for meaningful comparative analyses.

With Ser-Varanger as the reference population, relative risks of elevated nickel concentrations adjusted for sex and age were calculated for each of the other populations (Table 2). All the Russian populations had markedly higher risks than the Ser-Varanger population. Living in Nikel, for instance, implied an 11-fold excess risk of elevated urinary nickel. The Norwegian Tromsø comparison group also exhibited a higher risk than Ser-Varanger residents (relative risk 1.5), although this difference was not significant. Using the Wilcoxon rank sum
content compared to nonexposed people in that city (medians 4.6 μg/l vs. 2.1 μg/l, respectively) (Table 3). In workers dealing with ore milling, concentration, and flotation in the ore beneficiation plant in Zapolyarny, the median concentration was not increased (2.4 μg/l), but the high mean value (6.2 μg/l) and the significant χ² test indicated some considerably higher single values among these workers (Table 3). Work with maintenance and services did not increase the urinary concentrations either in Nikel or Zapolyarny (medians 3.2 μg/l and 1.6 μg/l, respectively).

*Exposure from tobacco smoke.* Smokers and nonsmokers were compared separately for each place with the Wilcoxon rank sum test, and no statistically significant differences were found.

**Nickel in tap water.** Tap water analysis showed large differences in nickel levels between the different study areas (Fig. 5). Nikel had significantly raised nickel content in tap water compared with the other areas (median 68 μg/l), followed by Zapolyarny (median 34 μg/l). Apatity (median 5.6 μg/l) had intermediate levels, and the lowest nickel concentrations were encountered in Tromsø, Sør-Varanger, and Umba (medians 0.2, 1.0, and 0.8 μg/l, respectively).

**Discussion**

We found large differences in urinary nickel concentrations between the Norwegian and Russian populations; however, within-country differences were less pronounced. Except for the population of Nikel, vicinity to a Russian nickel refinery could not explain the observed contents of nickel in urine in either country. The Norwegian comparison group (Tromsø) had higher levels than people of Sør-Varanger, and the Russian comparison groups (Apatity and Umba) did not have lower nickel excretion than the residents of Zapolyarny.

**Strengths and limitations of the study.** The population-based study design and the

---

**Table 3. Urinary nickel concentrations in Nikel and Zapolyarny according to occupational exposure**

| City            | Occupational exposure | n   | Mean (μg/l) | Median (μg/l) | Percent with ≥10 μg/l | p-Value* |
|-----------------|-----------------------|-----|-------------|---------------|-----------------------|----------|
| Nikel           | Nonexposed            | 321 | 4.7         | 3.4           | 10.0                  | Reference |
|                 | Exposed               | 14  | 10.3        | 5.6           | 28.6                  | 0.03     |
|                 | Maintenance and services | 36 | 4.7         | 3.2           | 8.3                   | NS       |
| Zapolyarny      | Nonexposed            | 375 | 2.7         | 2.1           | 2.1                   | Reference |
|                 | Exposed               | 11  | 5.5         | 4.6           | 18.2                  | <0.001   |
|                 | Ore milling, concentration, and flotation | 8 | 6.2 | 2.4 | 25.0 | <0.001 |
|                 | Maintenance and services | 24 | 2.1 | 1.6 | 0.0 | NS     |

NS, not statistically significant.

*For the χ² test, a cut-off value for urinary-nickel of 10 μg/l was used.
large number of people examined allows us to draw conclusions about nickel levels in the general populations that we have studied. Our data may be subject to selection bias due to the relatively low participation rate, especially on the Russian side. In Russia, fewer men than women participated, which might point toward an under-representation of certain occupational groups at the nickel refineries in Nikel and Zapolyarny. However, the method used to recruit people to the study in Russia was not likely to have influenced the results because there is no reason to suspect significant differences in exposure status by residence location within each city. In Sør-Varanger, the settlements in the border area were overrepresented as a result of the way urine specimens were selected for analysis. Thus, the results do not reflect the true population average. Subanalyses from Sør-Varanger showed that the rural areas closest to the border had lower nickel levels than the urban area of Kirkenes (9). For our purposes, however, this heterogeneity was not of importance because the difference across the border was of a much greater magnitude.

Some nickel contamination from clothes and skin during specimen collection cannot be ruled out, and although identical instructions were given to all participants, differential contributions from this source may have occurred as a result of different nickel contents in ambient air. Differential nickel contamination from storage and analysis of urine, however, is not likely to have occurred because the same kind of plastic containers were used for sample collection and storage, and one laboratory was responsible for all nickel measurements.

Another possible source of bias is the influence of urine-dilution effects on nickel concentration when spot samples are taken. Different methods for dilution adjustments exist, the most common being normalization by specific gravity or by urinary creatinine (16). In our study we measured urinary creatinine concentrations to allow dilution adjustments. However, such normalization introduces new bias to the results because the elimination of creatinine is dependent on factors such as age, sex, muscular mass, pregnancy, exercise, diet, and various diseases (17). Moreover, normalization based on urinary creatinine may overestimate nickel concentrations in dilute urine specimens; Sunderman et al. (18) recommended that for random urine specimens, creatinine-adjusted nickel concentrations should only be reported as a supplement to unadjusted nickel values. We found it appropriate to present both sets of values to demonstrate that, like the unadjusted nickel values, the adjusted values did not correlate well with the industrial pollution levels (Fig. 3).

The age trend that we observed in Sør-Varanger, Tromsø, and Nikel might well be explained by age-dependent physiologic changes in the kidney rather than differences in nickel exposure since the glomerular filtration rate is known to decrease significantly with age (19). This assumption was supported by two facts: 1) because there were fewer individuals currently employed in the nickel industry among those aged 18–29 years than among those aged 30–49 years, occupational exposure was unlikely to explain the age trend; and 2) no significant age trend appeared in either study population after adjustments were made for urinary creatinine.

Industrial pollution in the study areas. The Geologic Survey of Norway (NGU) has estimated annual nickel deposition in three catchments in the Kola Peninsula, namely, in the vicinity of Zapolyarny, Monchegorsk, and Kirovsk; one catchment in Sør-Varanger 35 km southwest (offwind) of the smelter in Nikel was also surveyed (20). The estimates were based on nickel concentrations in samples of rainwater and meltwater during the year 1993–1994. The annual deposition was estimated to be 5.3 g/m² in the Norwegian catchment, 434 g/m² in Zapolyarny, 845 g/m² in Monchegorsk, and 4.7 g/m² in Kirovsk. Apatity is situated close to Kirovsk. It is evident from these numbers that the Kirovsk deposition is considerably lower than in Zapolyarny, closely resembling the deposition in the Norwegian catchment. According to a map of nickel concentrations from the same NGU Kola project, the mean annual deposition in Umba was approximately 1 g/m² (21). In summary, industrial nickel emissions are high in Zapolyarny and Monchegorsk due to the local nickel refineries; the same is implied for Nikel. The deposition of nickel is far less pronounced in Apatity and Sør-Varanger and even lower in Umba. This pollution pattern appears to be roughly reflected in our tap water samples (Fig. 5).

Evaluation of nickel exposure sources. Our objective was to assess the impact of the nickel refineries near the Norwegian–Russian border as a human nickel exposure source. On the Norwegian side, the finding of higher nickel concentrations in Tromsø than in Sør-Varanger virtually rules out the industry as an important source. On the Russian side, the industrial exposure is likely to account for a part of the high urinary nickel levels encountered in Nikel because both the urinary and the tap water nickel are significantly higher in that city. The distribution among the other settlements is, however, more difficult to explain. Although there were few specimens from Umba, they clearly indicate that nickel concentrations were high in the Russian populations, regardless of location in relation to nickel industrial sites. The Russian study groups all had increased urinary nickel compared to those in Norway, and it seems reasonable to search for a
nonindustrial country factor to explain this national difference.

When evaluating exposure sources, the different bioavailability of the specific nickel compounds must be considered (22). In the occupational context, it has been shown that exposure to soluble nickel compounds yields urinary nickel concentrations that are generally proportional to levels in ambient air. For the relatively insoluble nickel compounds, the air–urine relationship is less strong (8,16,23). Unfortunately, no chemical speciation of nickel compounds in the Nikel and Zapolyarny emissions has been undertaken. Recent studies of occupational exposure in the nickel refineries at Monchegorsk concluded that relatively insoluble nickel oxides and sulfides are dominant species (24). However, the specific departments surveyed featured secondary nickel refining, but in Nikel and Zapolyarny, primary refining is common with nickel mainly as the end product. Nevertheless, it is likely that nickel sulfate, nickel oxides, and nickel sulfides, in combination with non-nickel particles, are represented in the smaller emissions at Nikel and Zapolyarny, although their relative proportions cannot be predicted.

During the winter of 1994/1995, the mean PM$_{10}$ (particulate matter ≤10 μm in aerodynamic diameter) levels of nickel in ambient air at two Norwegian monitoring stations located close to the border were 22.5 ng/m$^3$ and 10 ng/m$^3$, whereas in Nikel the level was 53.5 ng/m$^3$ (25). The levels recorded at these stations did not show consistent seasonal variations during the years 1990–1995 (25). Occupational, environmental, and biological monitoring studies suggest that the slope value for plots of urinary nickel versus ambient nickel have values around 0.10 (μg/l)/(μg/m$^3$) for relatively water-insoluble nickel compounds and 1.0 (μg/l)/(μg/m$^3$) for water-soluble compounds (16,22,24,26). Consequently, ambient nickel concentrations of the order of 51 μg/m$^3$ might be expected to make only a minor contribution to urinary nickel levels. Indirect contributions through ingestion of dust and tap water are likely to constitute more meaningful environmental nickel sources, at least for residents of Nikel.

In searching for a country factor that could explain the different nickel levels in Norway and Russia, we have considered various possible nickel sources that may be differently distributed in the two countries. Drinking water and foodstuffs are both important exposure sources for nickel (3), although nickel in water is absorbed to a greater extent than nickel in food (27). Despite water being a good index for industrial pollution in our study, the observed drinking water concentrations could not explain the urinary concentrations. An exception to this was Nikel, where both tap water and urinary nickel concentrations were high. We also measured nickel in tap water boiled in private Russian homes with private cooking utensils. The nickel distribution between the study areas was the same as for the unboiled water (unpublished data); hence, nickel released from cooking utensils was not important. No association was found between consumption of locally produced food (i.e., domestic animals, game, berries, and fish) and urinary nickel levels in Sor-Varanger (9); in Russia, this information was not requested. Most of the food consumed on both sides of the border is, however, imported from elsewhere. Trade of food across the border has been very limited. We do not have sufficient information about dietary habits in either study population. This is unfortunate because it may well explain some of the national differences in urinary nickel excretion. In addition, the way food is preserved may also play a role.

We have already suggested an effect of urbanization and traffic on urinary nickel concentrations in Sor-Varanger (9). In the Russian cities in our study, all participants were urban dwellers; thus, on the Russian side, the possible effect of urbanization could not be properly studied. Urban residency may account for some of the national differences, given the fact that the Russian cities have larger population density than the city of Tromsø. Interestingly, the difference between Tromsø levels and Russian levels was reduced somewhat after the urinary nickel concentrations were adjusted for creatinine (Fig. 3).

Tobacco smoking has been regarded by some authors as an important source of human nickel exposure (28,29) although the amount of nickel in mainstream smoke has been a topic of some controversy (30). The association between nickel in urine and smoking habits in Sor-Varanger has been studied (9), and no significant relationship was revealed. Analyses from Nikel, Zapolyarny, and Apatity yielded negative results as well, and we question the significance of tobacco smoke as a source of nickel uptake.

In the search for exposure sources that might explain the discrepancy between Norway and Russia, we propose that dental implants may play a role. Most Russian dental implants are made from nickel-containing metal alloys (31), and corrosion with subsequent leakage of nickel to the saliva is possible (32). In several studies, leakage from stainless steel surgical implants (i.e., hip prostheses) caused increased serum and urinary nickel levels in individuals (33–35) although a study by Sunderman et al. (36) did not confirm this. It was evident from these studies that the degree of nickel leakage depended on the quality of the stainless steel.

Ocational exposure. As expected, occupational nickel exposure increased urinary nickel excretion in current workers. Because these workers constituted only a small fraction of the population, this did not seem to influence the results of the general population in Nikel and Zapolyarny. Considerably higher urinary levels have been reported in occupationally exposed workers from other nickel refineries, such as the Falconbridge nickel refinery in Kristiansand, Norway (13,14), and more recently at the refinery at Monchegorsk (24). Several factors may account for the difference observed: 1) different chemical species of nickel; 2) different stages in the refining process—workers employed in secondary refining are known to experience higher exposures; and 3) possible dilution of existing differences between exposed and nonexposed individuals in our study because of misclassification of the workers occupationally exposed to nickel.

Former studies of nonoccupationally exposed subjects. No other study has, to our knowledge, included a comparatively high number of urine specimens for nickel measurements. According to the TRACY-project, an international project for identifying reference intervals for concentrations of trace elements in human blood and urine (37), the largest study conducted so far was Italian and included 878 adults (38). Six

| Authors          | Reference | Country      | n   | Mean ± SD | Range | Units |
|------------------|-----------|--------------|-----|-----------|-------|-------|
| Sunderman et al. | (46)      | United States| 34  | 2.0 ± 1.5 | 0.5–6.0 | μg/l  |
| Kiljunen et al.  | (47)      | Finland      | 299 | 4.1± 1    |       | 10.0  | μg/l  |
| Elias et al.     | (48)      | France       | 55  | 1.59 ± 1.87 |       | NS    | μg/g creatinine |
| Minisia et al.   | (50)      | Italy        | 878 | 0.9 ± 0.2 | <0.5–4.6 | μg/g creatinine |
| Lin et al.       | (49)      | Taiwan       | 30  | 3.2 ± 1.7 | 1.2–7.8 | μg/l  |

Abbreviations: SD, standard deviation; NS, not stated. Modified from Templeton et al. (37).

*Geometric mean.

**95th percentile.
studies aiming to provide reference values on urinary nickel were referred in the TRACY protocol (Table 4). The Ser-Varanger nickel levels were, in general, lower than the proposed reference values, and the Russian levels exceeded them. To date, few studies have focused on urinary nickel concentrations in environmentally exposed populations. A study by Hopfer et al. (39), from the Canadian nickel refining town of Sudbury, focused on the effects of environmental pollution on urinary nickel excretion. In spot urine samples from 22 healthy hospital workers, the adjusted nickel levels averaged 2.4 ± 2.1 µg/g creatinine, whereas the mean ± SD for a control group of 43 hospital workers in Hartford, Connecticut, was 1.5 ± 1.5 µg/g creatinine. This slight difference, which was not statistically significant, contrasted sharply with the great difference found in tap water samples from Sudbury and Hartford; 109 ± 46 µg/l and 0.4 ± 0.2 µg/l, respectively. It was evident that nickel from the local tap water did not add much to the urinary nickel levels in Sudbury. In our study, tap water levels seemed to be closely related to air pollution levels. Although Russian urinary nickel levels were high regardless of nickel content in drinking water, in Nickel, tap water levels seemed to reflect an environmental effect superimposed on the country factor, since both tap water and urinary levels were higher in this city.

Odland et al. (40) studied urinary nickel concentrations, as well as levels of several other metals, in pregnant women and newborns living in Nickel and Ser-Varanger in 1991–1994. Controls were taken from the cities of Arkhangelsk, Russia, and Bergen, Norway. Their results were consistent with ours; the Russian urine samples had much nickel higher contents than the Norwegian samples, while the within-country differences were less pronounced.

Assessment of health effects. An excess risk of respiratory cancer has been shown for employees in the nickel refining industry (16,41). In nickel-exposed workers, however, most studies have demonstrated urinary nickel levels considerably higher than those we observed in our study populations (13–15). An increased cancer risk is very unlikely on both sides of the Norwegian–Russian border at the recorded environmental exposure levels. Actually, cancer incidence was studied in the Norwegian settlements closest to the border (Fig. 2), based on data from the Norwegian Cancer Registry from 1970 to 1989 (42,43). No conclusions could be made about any increased cancer risk. In Russia, no sufficiently updated cancer registry exists; thus, cancer incidence is difficult to study. Nickel allergy, which is another important clinical effect of nickel (44), was also evaluated in the present project and will be reported in a separate publication.

Conclusions

Urinary nickel levels in our Norwegian and Russian study populations were poorly associated with the proximity of residence to the Russian nickel refining industry. Regardless of location, the Russian populations all had significantly higher urinary nickel concentrations than the Norwegian groups, indicating that unidentified nonindustrial exposures are of importance. Although the populations living in the border area are very close geographically, they have been almost totally isolated from one another until the recent collapse of the Soviet Union. The existing differences in lifestyle, dietary habits, and socioeconomic conditions should be studied when searching for exposure sources that may explain the different nickel levels in these two countries.

References and Notes

1. Reimann C, de Caritat P, Halleraker J, Volden T, Ayras M, Niskavaara H, Chekushin VA, Pavlov VA. Rainwater composition in eight arctic catchments in Northern Europe (Finland, Norway, and Russia). Atmos Environ 31:159–170 (1997).
2. Sivertsen B, Baklanov A, Hagen LD, Makarova T. Air Pollution in the Border Areas of Norway and Russia. Summary Report April 1991–March 1993. OR 56/94. Lillestrøm, Norway/Norwegian Institute for Air Research, 1994.
3. WHO. Air Quality Guidelines for Europe. European Series No. 23. Copenhagen:World Health Organization, WHO Regional Publications 1987.
4. Temmerink H, Johansen S. Effects of air pollution on terrestrial ecosystems by means of remote sensing analysis. In: Effects of Air Pollutants on Terrestrial Ecosystems in the Border Area between Russia and Norway. Proceedings from the First Symposium, 18–28 March 1992, Svanvik, Norway. Rpt no 92/04. Oslo:State Admin for Nature:Norwegian Institute for Air Research, 1992.
5. Sivertsen T. Uptake of heavy metals in animals in Ser-Varanger [in Norwegian]. DN-notat 1991-15. Trondheim, Norway:Directorate for Nature Management, 1991.
6. Scholzberg J, Samb A, Bruteig IE, Hansen JE, Rambuk JM. Contents of Elements in Moss and Lichen, Eastern Finnmark 1981 [in Norwegian]. OR 55/93. Lillestrøm, Norway/Norwegian Institute for Air Research, 1983.
7. Traasen TS, Henriksson A, Kallqvist T, Wright RR. Acidification and Heavy Metal Pollution in the Border Area between Norway and Russia. Investigations on Water Chemistry 1986–1992 [in Norwegian]. Oslo: Norwegian Institute for Water Research, 1993.
8. Sundersen FW. Biological monitoring of nickel in humans. Scand J Work Environ Health 19 (suppl 1):34–38 (1983).
9. Smith-Sivertsen T, Lund E, Thomsen M, Norseth T. Human nickel exposure in an area polluted by nickel refining. The Sar-Varanger study. Arch Environ Health 52:464–471 (1997).
10. Thelle DS, Farde OH, Lahmann EH. The Tromsø Heart Study. Methods and main results of the cross-sectional study. Acta Med Scand 200:107–116 (1979).
11. SAS Institute. SAS/STAT Guide for Personal Computers. Cary, NC:SAS Institute, 1992.
12. Rothman KJ. Modern Epidemiology. 1st ed. Boston, MA:Little, Brown, 1986.
13. Hegeveit AC, Barton RT, Kostel CD. Plasma nickel as primary index of exposure in nickel refining. Ann Occup Hyg 21:113–120 (1978).
14. Torjussen W, Andersen A. Nickel concentrations in nasal mucosa, plasma nickel, and urine in active and retired nickel workers. Ann Clin Lab Sci 9:289–298 (1979).
15. Bernacki EJ, Parsons GE, Roy BR, Mikac-Devic M, Kennedy CD, Sundersen FW. Nickel urine concentrations in nickel-exposed workers. Ann Clin Lab Sci 8:184–198 (1978).
16. Nieboer E, Sanford WE, Stace BC. Absorption, distribution and excretion of nickel. In: Nickel and Human Health:Current Perspectives (Boeniger E, Niskavaara H, eds). New York:John Wiley & Sons, 1992:49–68.
17. Boeniger MF, Lowy LK. Rosenberg J. Interpretation of urine results used to assess chemical exposure with emphasis on creatinine adjustments: a review. Am Ind Hyg Assoc J 54:615–627 (1993).
18. Sundersen FW, Hopfer SM, Crisostomo MC. Stoeppler M. Rapid analysis of nickel in urine by electrothermal atomic absorption spectrophotometry. Ann Clin Lab Sci 16:219–230 (1986).
19. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. Age-adjusted standards for creatinine clearance. Am Ind Med 5458–5509 (1979).
20. Chekushin VA, Bogatyryev IV, de Caritat P, Niskavaara H, Reimann C. Annual atmospheric deposition of 16 elements in eight catchments of the central Barents region (unpublished data).
21. Chekushin VA, Bogatyryev IV, Pavlov VA, Ayras M, Niskavaara H, Halleraker JH. Annual technogenic depositions during the last 4 years in the Barents Region, based on regional moss sampling 1990 (Abstract). Presented at the Third International Barents Symposium: Environment in the Barents Region, 12–15 September, 1996, Kirkenes, Norway.
22. Sundersen FW, Aitto A, Morgan LG, Norseth T. Biological monitoring of nickel. Toxicol Ind Health 21:7–78 (1986).
23. Morgan LG, Rouge PJ. A study into the correlation between atmospheric and biological monitoring of nickel in nickel refinery workers. Ann Occup Hyg 22:311–317 (1978).
24. Nieboer E, Tachtachine VP, Odland JB, Thomassen Y. Reproductive and Developmental Health in Relation to Occupational Exposure to Nickel in the Kola Peninsula of Russia: A Feasibility Study, Final Report. Hamilton, Ontario, Canada:McMaster University,1997.
25. Hagen LO, Sivertsen B, Johnsrudd M. Monitoring of Air and Precipitation Quality in the Border Areas of Norway and Russia. Health Effects of Atmospheric Deposition during the Last 40 Years 1955–1995 [in Norwegian]. OR 28/96. Kjeller, Norway/Norwegian Institute for Air Research, 1996.
26. Schaller KH, Rachel HJ, Angerer J. Nickel. In: Handbook on Metals and Non-metallic Chemistry (Seiler HG, Sigel A, Sigel H, eds). New York:Marcel Dekker, 1994:505–518.
27. Sundersen FW, Hopfer SM, Sweeney KR, Marcus AH, Most BM, Creasan J. Nickel absorption and kinetics in human volunteers. Proc Soc Exp Biol Med 191:1–11 (1988).
28. Grandjean P, Nielsen GD, Andersen O. Human nickel exposure and biomarkers. In: Nickel and the Skin: Immunology and Toxicology (Maibach HI, Menne T, eds). Boca Raton, FL:CRC Press, 1992:9–34.
29. IPCS Environmental Programmes on Chemical Safety. Nickel. Environmental Criteria 108. Geneva: World Health Organization, 1991.
30. U.S. EPA. Health Assessment Document for Nickel and Nickel Compounds. EPA/800/8–83/017F:4–9.3. Research Triangle Park, NC:U.S. Environmental Protection Agency, 1986.
31. Selketski A, personal communication, 1997.
32. Mulders C, Darwish M, Holte R. The influence of alloy composition and casting procedure upon the corrosion behaviour of dental alloys: an in vitro study. J Oral Rehabil 23:825–831 (1996).
33. Black J, Maudsley EC, Gelman J, Morris DM. Serum concentrations of cobalt, nickel and total hip replacement: a six month study. Biomaterials 4:160–164 (1983).
34. Hennig F, Rothfelth JJ. Schaller KH, Döhler JR, Nickel, chromium and cobalt-concentrations in human tissue.
and body fluids of hip prosthesis patients. J Trace Elem Electrolytes Health Dis 8:239–243 (1992).

35. Pazzaglia UC, Minioa C, Ceciliani L, Riccardi C. Metal determination in organic fluids of patients with stainless steel hip arthroplasty. Acta Orthop Scand 54:574–579 (1983).

36. Sunderman FW, Hopfer SM, Swift T, Rezuke WN, Ziebka L, Highman P, Edwards B, Folcik M, Goasling HR. Cobalt, chromium and nickel concentrations in body fluids of patients with porous-coated knee or hip prostheses. J Orthop Res 7:307–315 (1989).

37. Templeton DM, Sunderman FW, Herber RFM. Tentative reference values for nickel concentrations in human serum, plasma, blood, and urine: evaluation according to the TRACY protocol. Sci Total Environ 148:243–251 (1994).

38. Minoia C, Sabbioni E, Apostoli P, Pietra R, Pozzoli L, Gallorini M, Nicolaou G, Alessio L, Capodaglio E. Trace element reference values in tissues from inhabitants of the European Community I. A study of 46 elements in urine, blood and serum of Italian subjects. Sci Total Environ 95:89–105 (1990).

39. Hopfer SM, Fay WP, Sunderman FW. Serum nickel concentrations in hemodialysis patients with environmental exposure. Ann Clin Lab Sci 19:161–167 (1989).

40. Olland JB, Romanova N, Sand G, Thomassen Y, Salbu B, Lund E, Nieboer E. Cadmium, lead, mercury, nickel, and cesium-137 concentrations in blood, urine, or placentas from mothers and newborns living in arctic areas of Russia and Norway. In: Environmental Biomonitoring: Exposure Assessment and Specimen Banking (Subramanian KS, Iyengar GV eds). Washington, DC:American Chemical Society, 1997:135–150.

41. Doll R, ed. Report of the International Committee on Nickel Carcinogenesis in Man. Scand J Work Environ Health 16:1–82 (1990).

42. Sunde HG, Haldorsen T. Cancer in the Pasvik Valley. Pollution from Nickel. A connection? (in Norwegian). Tidsskr Nor Laegeforen 109:1762–1764 (1989).

43. Sunde HG, Alexander J. Cancer in the Pasvik Valley II. Pollution from Nickel—no relationship after all? (in Norwegian). Tidsskr Nor Laegeforen 112:2384–2386 (1992).

44. Norseth T. Clinical effects of nickel. In: Nickel in the Human Environment (Sunderman FW Jr, ed). IARC Scientific Publications No. 53. Lyon:International Agency for Research on Cancer, 1984:295–401.

45. Stensland-Buggle E, Banas KH, Joakimsen O. Reproducibility of ultrasonographically determined intima-media thickness is dependent on arterial wall thickness. The Tromso Study. Stroke 28:1972–1980 (1997).

46. Sunderman FW, Hopfer SM, Crisostomo MC, Steeppler M. Rapid analysis of nickel in urine by electrothermal atomic absorption spectrophotometry. Ann Clin Lab Sci 16:219–220 (1986).

47. Kilunen M, Järvisalo J, Mäkitie O, Aitio A. Analysis, storage stability and reference values for urinary chromium and nickel. Int Arch Occup Environ Health 59:43–50 (1987).

48. Elias Z, Mur JM, Pierre F, Gilgenkrantz S, Schneider O, Baruthio F, Daniere MC, Fontana JM. Chromosome aberrations in peripheral blood lymphocytes of welders and characterization of their exposure by biological samples analysis. J Occup Med 31:477–483 (1989).

49. Lin SM. Optimization of graphite furnace atomic absorption spectrophotometry for determination of trace cadmium, lead and nickel in urine. Anal Sci 7:155–158 (1991).

A workshop hosted by The National Institute of Environmental Health Sciences Research Triangle Park, North Carolina

Linking Environmental Agents and Autoimmune Diseases

1–3 September 1998

The purpose of this workshop is to bring together immunologists, developmental biologists, autoimmune specialists, epidemiologists, molecular biologists, and toxicologists in order to define the state of the art, data gaps, and future directions and research needed to understand the mechanistic link and importance of environmental agents in the initiation and exacerbation of the various forms of autoimmune disease.

Topics to be addressed include:

- Epidemiology of autoimmune diseases
- Immunology of autoimmune diseases
- Overview of the role of environmental agents in autoimmune diseases
- Sensitive subpopulations
- Role of gender and hormones
- Developmental vs. adult exposure to environmental agents
- Autoimmune models
- Interaction of genetics and environment in autoimmune diseases
- Search for environmental links to autoimmune diseases
- Defining research needs and future directions

http://www.niehs.nih.gov/dert/linkmtg.htm