EXPOSURE TO SOLUBLE NICKEL IN ELECTROLYTIC NICKEL REFINING

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Abstract—Past and present exposure to nickel was studied in an electrolytic nickel refinery, where an increased incidence of nasal cancer had been reported, using nickel analyses in air, blood and urine. Genotoxic effects were studied using analysis of micronuclei from acridine orange-stained smears from the buccal mucosa of the workers. Workers used respirators or masks in tasks where the exposure was expected to be high. Inside the mask, nickel concentrations were 0.9–2.4 μg m⁻³ in such tasks. In those tasks where masks were not used, nickel concentrations in the breathing zone were 1.3–21 μg m⁻³. Air-borne nickel concentrations (stationary sampling) varied between 230 and 800 μg m⁻³ in 1966–1988 with no systematic change; thereafter lower concentrations (170–460 μg m⁻³) have been observed. After-shift urinary concentrations of nickel were 0.1–2 μmol l⁻¹; they showed no correlation with nickel concentrations in the air. Concentrations of nickel in the urine were still elevated after a 2–4 week vacation. The frequency of micronucleated epithelial cells in the buccal mucosa of nickel refinery workers was not significantly elevated by comparison with referents. No relationship was observed between micronucleus frequencies and levels of nickel in air, urine or blood. © 1997 British Occupational Hygiene Society. Published by Elsevier Science Ltd.

INTRODUCTION

With the recent reanalysis of the cancer mortality of nickel refinery worker cohorts (Doll et al., 1990), the views of the carcinogenicity of different nickel species have profoundly changed: the most potent nickel species in the induction of lung and nasal cancer in humans now seem to be the water-soluble nickel salts (Doll et al., 1990; IARC, 1990; IPCS, 1991). However, few data exist on the levels of exposure to soluble nickel in nickel refining both in the past and in the present, which makes reliable risk assessments difficult. In this study, we have perused past nickel exposure data and analysed the present exposure situation in a nickel refinery, where an excess incidence of nasal cancer was recently reported (Karjalainen et al., 1992). For this purpose, we used both area and personal air sampling for air nickel measurement, as well as biological monitoring by means of blood and urinary nickel analyses. The biological analyses have been shown to be useful to estimate the exposure to soluble nickel salts (Aitio, 1984, 1995; Sunderman et al., 1986; Sunderman, 1988;
We also studied the genotoxic effects of the present nickel exposures by the analysis of micronuclei in buccal mucosal cells as a biomarker of biological response near the target site of nickel-induced cancer.

MATERIALS AND METHODS

Process

The nickel refining process at the Outokumpu Harjavalta facility, located in south-western Finland, can be divided into the following main stages: grinding of high-grade matte (not included in this study), leaching, solution purification, electrowinning of nickel, and cutting and packing (not included in this study).

The coarse matte is wet ground in ball mills, from where it is fed to leaching reactors. The fine matte is leached at atmospheric pressure at +90°C in three counter current stages in stainless steel reactors. Insoluble materials are fed to pressure leaching, which takes place in two autoclaves at 7–8 bar and at 150°C. The leaching is carried out with the spent electrolyte and thus the acids are constantly circulated at the nickel plant. About 98% of nickel is leached into the solution. The leaching is carried out in a building separate from the electrowinning.

Impurities such as cobalt and iron are dissolved with nickel during leaching. The main impurity is cobalt, which is removed during solution purification by precipitation as cobalt hydroxide. The purified solution is pumped to the nickel electrowinning cells. Electrowinning takes place in a building (150x60 m), which contains three tank houses (electrolysis halls) beside each other, without separating walls between them. The production capacity of pure nickel is 16000 tons a year.

A lead sheet, as an insoluble anode, and a 1 mm thick nickel cathode—as a starting sheet (produced on cathode preforms in separate starting cathode cells where nickel is electrolytically precipitated onto titanium plates)—is placed in the cell. There are 50 cathode sheets in each cell. The total number of electrolytic cells is 126. An electric current (density 230 A m⁻², cell voltage 3.7 V) is used to separate nickel from the solution onto nickel cathodes. In a week the nickel cathodes grow to 10 mm thickness and are lifted from the cells. Thereafter the nickel sheets are cut and packed. Electrowinning also proceeds on a smaller scale in small cells in tank house 2.

Subjects

The total number of employees at the facility is approximately 100, 50 of whom work in the tank houses. The total number of workers studied was 34. They were volunteers, and chosen so that all the main tasks in the plant were represented. The same worker performed at least two different tasks during the study period. All results are reported for a given task, not for an individual worker.

The tasks studied were:

1. Leaching (adjacent to solution purification, in a separate building),
2. Solution purification (at one end of tank house 1),
3. Hoisting of cathodes from the electrolytic cells (in all tank houses),
4. Handling of produced cathodes (floor below tank house 1),
5. Manufacturing of starting sheets (in a wing of tank houses 1 and 2),
6. Stripping of the mother sheets (floor below tank house 3),
Exposure to soluble nickel

(7) Works at mother sheet cells (in tank house 3),
(8) Crane operators in air-conditioned cabs in the tank houses,
(9) Other process work in the tank houses such as work at small cells (in tank house 2), cell maintenance and changes of bags (in the side wings of tank house 2),
(10) Maintenance work and cleaning of the tank houses,
(11) Maintenance work in the side wings of the tank houses and in the floor below the tank houses, including cleaning of equipment and washing the cloth bags of the cathodes,
(12) Repair work (including welding) in the tank houses (including the sites for leaching and solution purification).

In addition, exposure to nickel of one worker, designated as 'zero-man', who did not work but remained close to those working at the electrolytic cells and wore an air stream protection respirator (Clearflow-turbo), was followed during two workdays both with urinary samples and breathing zone air samples from inside and outside the mask.

For comparison, urinary nickel was analysed from a control group consisting of 30 office workers from the nickel refinery and 32 non-exposed persons from the Helsinki area.

Micronuclei in buccal mucosal cells were analysed from 25 male workers from the tank houses and 34 male controls working in construction, sulphuric acid production or production of aluminium salts.

**Sampling and analysis**

**Air measurements.** All air samples (both from stationary locations and breathing zone of workers) were collected on cellulose ester membrane filters (Millipore, AAAP, Ø37 mm for stationary locations and Ø25 mm for breathing zone specimens, pore size 0.8 μm) with stationary pumps (flow rate 20 l.min⁻¹) or personal sampling pumps (flow rate 2 l.min⁻¹).

The stationary samples were collected from areas where workers spent their time during the work shift (in process rooms) and where also the breathing zone samples were collected (both in process rooms and in resting room during the pauses). The collection was performed in 50 locations, and a total of 141 air specimens were collected. The collection time was approximately 6-8 h, which covered one work shift.

The air samples from the breathing zone of the workers were collected during four successive workdays. In the process areas the workers mostly used protective masks. When the worker used such a device, the sample was collected inside the mask. When the mask was taken off, the sample was collected from inside the mask hanging on the shoulder of the worker. When no respirator was used the sample was collected from the shoulder. In data analysis, the workers were grouped according to the task they performed, as well as to the type of the mask. A sample of 8 h was collected but when the worker switched from one task to another in the middle of a workday, two 4-h samples were collected. The masks used were Clearflow Turbo Protection Mask (Pulsafe Safety Ltd, U.K.), North half-mask (Siebe North Ltd, U.S.A.) and Silner half-mask (Kemira Safety Oy, Finland). From one tank house worker the breathing zone air samples were collected both from outside and inside the Clearflow Turbo mask during two workdays.
From the filters and their support pads, soluble nickel was dissolved in hot ion-exchanged water (1 h at 70°C). The water was decanted and the membrane was rinsed by water three times and dried at 100°C overnight. The dry filters and pads were dissolved in 5 ml concentrated nitric acid. After adding 5 ml hydrochloric acid the solution was evaporated to dryness. The residue was dissolved in 5% nitric acid and the solution was filtered through filter paper to a glass bottle, where water was added to give a final nitric acid concentration of 0.5%. From this solution nickel was analysed by electrothermal atomic absorption spectrophotometer (Varian SpectrAA 400 Zeeman) standardizing against AAS-nickel standards (Merck) diluted to 0.5% nitric acid. A spiked control was run in every series (Tossavainen, 1976).

Air samples (150–200 l.) were also collected on polycarbonate filters (Nuclepore, pore size 0.2 μm) for particle size and composition analyses. These samples were studied with scanning electron microscopy (JEOL 6400) and microanalysis (Tracor Northern TN5500). The membranes were covered with a gold layer (about 20 nm in thickness) in an ion-sputtering device (JEOL JFC 1100). The magnifications used were from 1000 to 100 000. The smallest detectable particles were about 0.1 μm in size and the detection limit was 1–10 wt% for the elements heavier than sodium. The factory records of previous industrial hygiene measurements on total nickel from stationary samplers were perused. These measurements had been performed for the purpose of routine monitoring of the working conditions.

**Biological measurements**

**Urine samples.** Special emphasis was put on contamination-free sample collection: during the working hours the biological specimens were collected at the occupational health centre located half a kilometre from the production site, after changing the overalls and washing before sample collection. Written instructions were given to the workers for the urine sample collection at home.

The workers were followed up for four successive workdays and one free day thereafter by collecting a spot urine sample every morning and after each workshift. An additional spot urine sample was collected at noon in case the workers switched from one task to another in the middle of the workday. In the evening of the last workday and the next day in the morning and afternoon, spot urine samples were also collected (Table 1).

Long-term clearance of nickel was followed from spot urine samples collected in the morning after a weekend and also after the summer vacation.

The nickel concentration in urine was measured by electrothermal atomic absorption spectrophotometry (Varian SpectrAA 400 Zeeman) (Kiilunen et al., 1987). The samples were diluted 1:5 and nitric acid was used as a modifier.

<table>
<thead>
<tr>
<th>Time</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>After weekend</th>
<th>After vacation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Noon*</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>After shift</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

*When worker moved from one task to another.*
Standards were made in the urine of a non-exposed person, in which a very low nickel concentration had been verified in advance. Commercial urine standards (Lyphochek 1 and 2, Bio-Rad, U.S.A. and Seronorm trace metal, Nycomed, Norway), a spiked control as well as two natural pooled urine controls (low and high nickel concentration) were used for internal quality assurance purposes.

From every urine sample the relative density was measured by a refractometer (Atago, Japan). Creatinine measurements were made by the picric acid colour reaction using a spectrometer (FP9, Labsystems, Finland). The nickel concentrations were corrected to both relative density (1.024) and creatinine excretion.

**Blood samples.** Blood samples were collected at the beginning of the study and at the end of the last workday at the occupational health centre of the plant. The first 5–10 ml of the blood were discarded before taking the sample for nickel analysis. The analyses were performed using a mild ashing method published earlier (Kiilunen et al., 1986).

**Micronucleus analysis.** Twenty five nickel-exposed men working in the tank houses and 34 male industrial referents were included in the micronucleus study, which was performed approx. 1 year after the assessment of the exposure described above. The 4-day time-weighted average level of nickel in the breathing zone for these workers was 5.7 μg m⁻³ (S.D. = 4.4, N = 21). Their mean urinary and blood nickel concentrations were 0.62 μmol l⁻¹ (S.D. = 0.48, N = 21) and 0.0318 μmol l⁻¹ (S.D. = 0.020, N = 17) in Friday afternoon specimens.

The referents were from the construction group (11 men) and sulphuric acid manufacturing department (11 men) of the same company and from an aluminium salt plant located in the same town (12 men). All subjects filled in a questionnaire inquiring details about their occupational history, health (including oral disorders) and medication, exposure to radiation (including oral) and life style (tobacco smoking, alcohol drinking, diets); except for occupational exposure to nickel, the tank house workers and the referents did not markedly differ from each other in these aspects. The referents were not notably exposed to known genotoxins, although low-level nickel exposure could not be excluded among the first two subgroups. The proportion of current tobacco smokers and the mean number of cigarettes smoked daily were similar among the exposed and the referents, but the smoking referents had, on an average, smoked longer than the smoking nickel workers (Table 8). Among current non-smokers, 58% of the exposed and 44% of the referents were ex-smokers; they had stopped smoking several years (4–29 years) earlier. The referents were older than the nickel workers (Table 8).

Buccal mucosa epithelial cells were collected from both sides of the oral cavity using a moistened wooden spatula. The cell material was transferred onto a microscopic slide which had been rinsed with aqueous 0.2 mol l⁻¹ sodium acetate solution. The samples were air-dried and fixed and stored thereafter in 80% methanol solution. After 2 weeks or more, the samples were dried and stained with acridine orange (0.005% w/v) for 4 min, rinsed with distilled water and dried. The slides were covered with a cover slip in a drop of sodium acetate buffer and were analysed by fluorescence microscopy; micronuclei in 1000 epithelial cells per person were counted by one technician on coded slides (Norppa et al., 1992).
The results were analysed statistically by using linear models and generalized additive models (S-Plus, version 3.2, MathSoft Inc.). The variables included in the models were exposure to Ni (expressed as concentration in air, blood or urine, or as years of exposure), cigarettes smoked daily, and age.

RESULTS

Air measurements

Stationary monitoring. On the basis of electron microscopic appearance, most of the airborne nickel was in the form of dry crystalline salt (Fig. 1a), and only to a very small extent, as an aqueous aerosol. The median count diameter of the particles was 12 μm; most particles were > 5 μm in diameter (Fig. 1b). Water-soluble nickel sulphate represented more than 95% of the total nickel everywhere in the facility, except at the leaching site, where the proportion of acid soluble (= water insoluble) nickel was 11%.

Concentrations of nickel in the air measured in the different measurement points of each working area were combined and are presented in Table 2. The collection time was almost 8 h and results are expected to be similar during the whole work shift. In each tank house—also in the solution purification—nickel exposure was quite uniform within each area: the ratio of the highest to lowest measuring point average was 3.0 in solution purification and 2.4, 3.0 and 1.9 in the three tank houses. Similarly, variation in air nickel concentration with time was rather small: the ratio of highest to lowest value at any single measurement point was ≤2.3. On the other hand, in leaching, the variation between individual measurement locations was more marked (13-fold difference between highest and lowest values). Even there, the variation with time was small: no more than 1.2-fold difference was observed for maximum and minimum values at any given measurement point.

In the nickel leaching department, average total nickel concentrations at different locations were 2.8–27 μg m⁻³ with an average for the whole department of 14 μg m⁻³; highest individual concentrations were observed in the vicinity of the filter presses. Disassembling and drying of the presses, which are short-duration operations, did not appreciably increase nickel concentrations in the air.

In solution purification, air-borne nickel concentrations were clearly higher: the concentration of total nickel in the air was 57–163 μg m⁻³. Nickel in the air was mostly water-soluble: the proportion of acid soluble (water insoluble) nickel was on average 4%. The concentrations of nickel in the air were similar in the vicinity of the cobalt filter (upper floor level) and at the site of cobalt removal (lower floor level).

Nickel concentrations in the air in the different tank houses varied greatly. In tank house 1 total nickel concentration varied from 69 to 162 μg m⁻³ in different measuring points with an average of 112 μg m⁻³. The highest single 8-TWA concentration (255 μg m⁻³) was observed between the electrolysis cells.

In tank house 2, the concentrations of nickel in the air were 187–560 μg m⁻³ with an average of 324 μg m⁻³. Highest 1-day average (560 μg m⁻³) was measured between two electrolysis cells.

In tank house 3, the range of air-borne nickel in different measuring points was 352–678 μg m⁻³ and the average 484 μg m⁻³. The highest individual 1-day average
Fig. 1. Nickel sulphate aerosol in the nickel refinery. (a) Magnification 1000×, (b) magnification 2000×.
Table 2. Air nickel concentrations at stationary sample collection points in different parts of the nickel refinery

<table>
<thead>
<tr>
<th></th>
<th>Leaching</th>
<th>Solution purification</th>
<th>Tank house 1</th>
<th>Tank house 2</th>
<th>Tank house 3</th>
<th>Small cells (tank house 2)</th>
<th>Other sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of measuring points</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>No. of samples</td>
<td>16</td>
<td>12</td>
<td>22</td>
<td>19</td>
<td>20</td>
<td>3</td>
<td>48</td>
</tr>
</tbody>
</table>

Arithmetic mean:
- Water-soluble nickel (μg m⁻³)
  - Leaching: 12
  - Solution purification: 103
  - Tank house 1: 111
  - Tank house 2: 323
  - Tank house 3: 483
  - Small cells (tank house 2): 482
  - Other sites: 11

Arithmetic S.D.:
- Water-soluble nickel (μg m⁻³)
  - Leaching: 8
  - Solution purification: 33
  - Tank house 1: 37
  - Tank house 2: 123
  - Tank house 3: 151
  - Small cells (tank house 2): 7.4
  - Other sites: 11

Geometric mean:
- Water-soluble nickel (μg m⁻³)
  - Leaching: 10
  - Solution purification: 94
  - Tank house 1: 110
  - Tank house 2: 281
  - Tank house 3: 451
  - Small cells (tank house 2): 7.4
  - Other sites: 11

Minimum:
- Water-soluble nickel (μg m⁻³)
  - Leaching: 1
  - Solution purification: 37
  - Tank house 1: 187
  - Tank house 2: 351
  - Tank house 3: 677
  - Small cells (tank house 2): 677
  - Other sites: 7.4

Maximum:
- Water-soluble nickel (μg m⁻³)
  - Leaching: 25
  - Solution purification: 157
  - Tank house 1: 161
  - Tank house 2: 559
  - Tank house 3: 677
  - Small cells (tank house 2): 161
  - Other sites: 34

Acid-soluble nickel (μg m⁻³):
- Leaching: 1.4
- Solution purification: 4.3
- Tank house 1: 0.6
- Tank house 2: 0.7
- Tank house 3: 1.0
- Small cells (tank house 2): 0.9
- Other sites: 0.5

Total nickel (μg m⁻³):
- Leaching: 14
- Solution purification: 107
- Tank house 1: 112
- Tank house 2: 324
- Tank house 3: 484
- Small cells (tank house 2): 483
- Other sites: 12

Arithmetic mean:
- Leaching: 7.4
- Solution purification: 33
- Tank house 1: 36
- Tank house 2: 123
- Tank house 3: 151
- Small cells (tank house 2): 7.6
- Other sites: 7.6

Geometric mean:
- Leaching: 12
- Solution purification: 98
- Tank house 1: 110
- Tank house 2: 281
- Tank house 3: 452
- Small cells (tank house 2): 7.6
- Other sites: 7.6

Minimum:
- Leaching: 2.8
- Solution purification: 57
- Tank house 1: 69
- Tank house 2: 187
- Tank house 3: 352
- Small cells (tank house 2): 1.0
- Other sites: 1.0

Maximum:
- Leaching: 27
- Solution purification: 163
- Tank house 1: 162
- Tank house 2: 560
- Tank house 3: 678
- Small cells (tank house 2): 35
- Other sites: 35
nickel concentration was 809 μg m⁻³ between two adjacent electrolysis cells. By the mother sheet cells the average air nickel concentration was 377 μg m⁻³.

The other working areas were located in the side wings of the tank houses or on the floor below the main process area. The concentrations of total nickel in these locations were quite low, not higher than 35 μg m⁻³ with an average of 12 μg m⁻³.

In the air-conditioned cab of the crane moving in all three tank houses the concentrations of nickel in the air varied from 5 to 57 μg m⁻³. The highest concentration was measured on the day when the cab door was open for an unusually long time. In the side wings of the tank houses, nickel concentrations were 3–21 μg m⁻³ and in the resting room for women on average 1 μg m⁻³ and for men 3 μg m⁻³. In the repair shop where also some welding was performed, total nickel concentration was 5 μg m⁻³.

**Breathing zone.** The breathing zone samples were recorded according to the different work tasks rather than the individual workers, because the workers could change their task daily, even at the midpoint of the work shift. Because 95% of nickel was water-soluble, the concentrations in breathing zone are presented in Table 3 as total nickel only.

Employees working solely in the leaching department (no mask in use) had 4.0–18.7 μg m⁻³ nickel in the breathing zone. One person who worked both in leaching and solution purification and did use the mask had an average exposure of 0.4 μg m⁻³.

During hoisting of the nickel cathodes at the cells all workers use protective masks and nickel concentrations were therefore measured from within the masks only. The nickel concentrations were generally low: in only one sample was the nickel concentration higher than 1 μg m⁻³ (8.6 μg m⁻³). On average it was 0.9 μg m⁻³.

In the manufacturing of starting sheets in the wing of the tank houses 1 and 2, the workers did not use protective masks and the average exposure was highest (21 μg m⁻³, range 4.6–40 μg m⁻³) within the whole refining process. Highest values

<table>
<thead>
<tr>
<th>Work task</th>
<th>Nickel in breathing zone air μg m⁻³</th>
<th>Arithmet/Geometric mean (N)</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inside mask No mask in use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaching</td>
<td></td>
<td>7.9/5.3 (8)</td>
<td>4.0</td>
<td>18.7</td>
</tr>
<tr>
<td>Solution purification</td>
<td></td>
<td>13.4</td>
<td>0.3</td>
<td>17.8</td>
</tr>
<tr>
<td>Hoisting of cathodes at the cells</td>
<td></td>
<td>0.9/0.3 (12)</td>
<td>0.1</td>
<td>8.6</td>
</tr>
<tr>
<td>Handling of produced cathodes</td>
<td></td>
<td>1.3/0.6 (7)</td>
<td>0.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Manufacturing of starting sheets</td>
<td></td>
<td>21.0/18.4 (6)</td>
<td>4.6</td>
<td>40.3</td>
</tr>
<tr>
<td>Stripping of mother sheets</td>
<td></td>
<td>1.8/1.3 (26)</td>
<td>0.1</td>
<td>7.5</td>
</tr>
<tr>
<td>Work at mother sheet cells</td>
<td></td>
<td>0.5/0.2 (25)</td>
<td>&lt;0.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Crane operators</td>
<td></td>
<td>3.1/1.6 (8)</td>
<td>0.5</td>
<td>12.2</td>
</tr>
<tr>
<td>Cleaning and maintenance in tank houses</td>
<td></td>
<td>0.8/0.4 (16)</td>
<td>0.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Other work in tank houses</td>
<td></td>
<td>2.4/0.7 (10)</td>
<td>0.1</td>
<td>16.1</td>
</tr>
<tr>
<td>Maintenance works (not in tank houses)</td>
<td></td>
<td>7.1/3.4 (15)</td>
<td>0.4</td>
<td>23.0</td>
</tr>
<tr>
<td>Repair work (not in tank houses)</td>
<td></td>
<td>6.2/4.4 (12)</td>
<td>0.4</td>
<td>18.2</td>
</tr>
<tr>
<td>Repair work (welding)</td>
<td></td>
<td>71.0/63.2 (4)</td>
<td>17.0</td>
<td>140.4</td>
</tr>
</tbody>
</table>
Exposure to soluble nickel were observed when the worker occasionally had to remove the bag around the cathode and did not wear the mask.

When handling produced cathodes and when stripping the mother sheets (on the floor below the tank houses), the workers did not use protective masks. In these tasks, breathing zone nickel concentrations were on average 1.3 \( \mu \text{g m}^{-3} \) (0.4–3.7 \( \mu \text{g m}^{-3} \)) and 1.8 \( \mu \text{g m}^{-3} \) (0.1–7.5 \( \mu \text{g m}^{-3} \)), respectively.

When working at the mother sheet baths the workers used protective masks. Individual half shift concentrations were in many cases below 0.1 \( \mu \text{g m}^{-3} \), their average was 0.5 \( \mu \text{g m}^{-3} \), and the highest measured value, 1.9 \( \mu \text{g m}^{-3} \).

Maintenance work in the tank houses consisted mainly of cleaning of equipment and the cathode bags in the sidewings of the tank houses and on the ground floor. The work was done without protective masks and the nickel content in the breathing zone was on average 7.1 \( \mu \text{g m}^{-3} \) (0.4–23.0 \( \mu \text{g m}^{-3} \)).

The crane operators worked in air-conditioned cabs and did not use protective masks. The nickel content in their breathing zone was on average 3.1 \( \mu \text{g m}^{-3} \) (0.5–12.2 \( \mu \text{g m}^{-3} \)). Crane operators performed cleaning and maintenance work (for example, cell washing) on alternate days and then used protective masks. In these tasks they had an average nickel content of 0.8 \( \mu \text{g m}^{-3} \) (0.1–5.4 \( \mu \text{g m}^{-3} \)) in their breathing zone.

Other work in the tank houses (Table 3) consisted of work at the small cells, different repair operations at the cells, and washing of the bags. During these tasks measurements were made inside the masks and nickel concentration was 0.1–16.1 \( \mu \text{g m}^{-3} \) with an average of 2.4 \( \mu \text{g m}^{-3} \). When the highest individual result is excluded, the average drops to 0.9 \( \mu \text{g m}^{-3} \).

The maintenance workers working outside the tank houses did not use protective masks; the nickel content in their breathing zone varied greatly depending on where they worked and how much they welded. Also the amount of acid soluble nickel (water-insoluble) varied from a quarter to two-thirds from total nickel and nickel content ranged from 0.4 to 18.2 \( \mu \text{g m}^{-3} \). The worker who welded (stainless steel, manual metal arc) mostly had 17–140 \( \mu \text{g m}^{-3} \) (mean 71 \( \mu \text{g m}^{-3} \)) of nickel in the breathing zone and about four-fifths of it was acid soluble.

**Historical data.** The operation of the nickel refinery commenced in 1960, and there are records on nickel exposure since 1966. The air nickel concentrations in the tank houses during previous years are collected in Table 4. In addition, data accumulated after the present study (1991–1992) are indicated. Until 1988, little change took place in the overall nickel concentrations. In the 1990s, a decrease could be observed in the nickel concentrations in tank house 1, and a smaller drop in tank house 2, while there was little change in tank house 3. The highest individual air nickel concentrations ever recorded have been 1.1 and 0.7 \( \mu \text{g m}^{-3} \).

Breathing zone concentrations of nickel were measured in 1979, 1980 and 1981. The average exposures were between 160 and 230 \( \mu \text{g m}^{-3} \); the highest individual result was 390 \( \mu \text{g m}^{-3} \) (Table 5). Respirators were not used.

**Blood nickel concentrations**

Average nickel concentrations in the morning blood of the second day in the work period (first research day) varied between 6 and 26 nmol l\(^{-1}\) in different work
Table 4. Historical data on the average nickel concentration (µg m⁻³) in the air of tank houses as measured by stationary samplers. Data for 1991–1992 come from the present measurements. Until 1983, there was only one tank house, which was expanded several times.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of measurements</th>
<th>Tank house 1</th>
<th>Tank house 2</th>
<th>Tank house 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966</td>
<td>11</td>
<td>480</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976</td>
<td>34</td>
<td>230</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1977</td>
<td>14</td>
<td>350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>21</td>
<td>260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>6</td>
<td>470±130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>27</td>
<td>520±310</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>12</td>
<td>670</td>
<td>630</td>
<td>590</td>
</tr>
<tr>
<td>1985</td>
<td>4</td>
<td>350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>3</td>
<td>800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>13</td>
<td>620</td>
<td>760</td>
<td>520</td>
</tr>
<tr>
<td>1991-2</td>
<td>141</td>
<td>112</td>
<td>324</td>
<td>484</td>
</tr>
<tr>
<td>1993</td>
<td>37</td>
<td>170</td>
<td>330</td>
<td>460</td>
</tr>
</tbody>
</table>

Table 5. Historical breathing zone nickel concentrations in tank houses (µg m⁻³)

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Mean (arithm.)</th>
<th>S.D.</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>17</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>6</td>
<td>230</td>
<td>110</td>
<td>100–390</td>
</tr>
<tr>
<td>1981</td>
<td>28</td>
<td>200</td>
<td>60</td>
<td>80–260</td>
</tr>
</tbody>
</table>

tasks. The highest measured individual concentration was 33 nmol l⁻¹. After the last workday blood nickel concentrations were 18–59 nmol l⁻¹ in different work tasks. The highest individual value, 77 nmol l⁻¹, was measured in a worker who was cleaning the equipment and washing the cloth bags of the electrolytic cathodes in the side wings of the tank houses and the floor below (Table 6).

Table 6. Blood nickel concentration in different worker groups at the beginning and end of the study period

<table>
<thead>
<tr>
<th>Work tasks</th>
<th>Blood nickel, µmol l⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tuesday morning mean, maximum (N)</td>
</tr>
<tr>
<td>Leaching</td>
<td>0.020, 0.025 (2)</td>
</tr>
<tr>
<td>Solution purification</td>
<td>0.018, 0.024 (2)</td>
</tr>
<tr>
<td>Hoisting of cathodes at the cells</td>
<td>0.019, 0.022 (5)</td>
</tr>
<tr>
<td>Handling of produced cathodes</td>
<td>0.006, 0.009 (3)</td>
</tr>
<tr>
<td>Manufacturing of starting sheets</td>
<td>0.016, 0.017 (3)</td>
</tr>
<tr>
<td>Stripping of mother sheets</td>
<td>0.012, 0.014 (2)</td>
</tr>
<tr>
<td>Works at mother sheet cells</td>
<td>0.019, 0.020 (2)</td>
</tr>
<tr>
<td>Crane operators</td>
<td>0.026, 0.033 (3)</td>
</tr>
<tr>
<td>Cleaning and maintenance in tank houses</td>
<td>0.009, 0.011 (2)</td>
</tr>
<tr>
<td>Other work in tank houses</td>
<td>0.013, 0.018 (3)</td>
</tr>
<tr>
<td>Maintenance works (not in tank houses)</td>
<td>0.026 (1)</td>
</tr>
<tr>
<td>Repair work (not in tank houses)</td>
<td>no samples</td>
</tr>
<tr>
<td>Repair work (welding)</td>
<td>0.017, 0.028 (4)</td>
</tr>
</tbody>
</table>
Exposure to soluble nickel

Fig. 2. Frequency distribution of urinary nickel concentrations in Finns not occupationally exposed to nickel. The concentrations have been corrected to a relative density of 1.024, \( N = 52 \). Samples with a relative density < 1.010 were excluded.

**Urine nickel concentrations**

Samples with a relative density below 1.010 were excluded from the analysis. There was no difference in the urinary nickel concentration between the office workers in the plant and the office workers from the Helsinki area and so the data were combined. The mean value for the pooled control group was 0.026 \( \mu \text{molL}^{-1} \) and median value 0.027 \( \mu \text{molL}^{-1} \) \( (N = 52) \), the 95th percentile was 0.060 \( \mu \text{molL}^{-1} \) (Fig. 2).

For most workers, a diurnal, exposure related fluctuation in the urinary nickel concentration was observed (Fig. 3). Average urinary nickel concentrations after shift in different tasks varied between 0.090 \( \mu \text{molL}^{-1} \) in solution purification and 1.28 \( \mu \text{molL}^{-1} \) in manufacturing of starting sheets (Table 7). Highest individual urinary nickel values were observed among crane operators (2.07 \( \mu \text{molL}^{-1} \)).

An additional urine sample was obtained from 25 workers after one weekend, and from 23 workers after the summer vacation (2–4 weeks). After the weekend, the urinary nickel concentration varied from 0.023 to 2.09 \( \mu \text{molL}^{-1} \) and 95% of the values were below 0.6 \( \mu \text{molL}^{-1} \). After the 2- and 4-week vacation the average concentrations were 0.26 and 0.11 \( \mu \text{molL}^{-1} \), respectively. In six samples collected after the vacation, the nickel concentration exceeded that immediately before the vacation.

**The effectiveness of the protective respirators**

From two workers in the tank house, breathing zone samples were collected both in- and outside of the protective mask. One performed the normal tasks in the tank
Fig. 3. Variation with time of urinary nickel concentration in nickel refinery workers, corrected to relative density (Z) or creatinine excretion (O). (a) Four tank house workers, (b) crane operator, (c) leaching worker, (d) solution purification worker, (e) maintenance worker.
Table 7. Urinary nickel concentrations in different work tasks at the end of the working day or at the noon, when worker changed his task

<table>
<thead>
<tr>
<th>Work tasks</th>
<th>Urinary nickel µmol.⁻¹</th>
<th>Arithmetic/geometric mean (N)</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mask in use</td>
<td>No mask in use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaching</td>
<td>0.63/0.60 (8)</td>
<td>0.14</td>
<td>1.29</td>
<td></td>
</tr>
<tr>
<td>Solution purification</td>
<td>0.09/0.07 (4)</td>
<td>0.55/0.49 (4)</td>
<td>0.36</td>
<td>0.85</td>
</tr>
<tr>
<td>Hoisting of cathodes at cells</td>
<td>0.69/0.69 (12)</td>
<td>0.09</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>Handling of produced cathodes</td>
<td>0.63/0.69 (7)</td>
<td>0.12</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Manufacturing of starting sheets</td>
<td>1.28/1.29 (6)</td>
<td>0.81</td>
<td>1.65</td>
<td></td>
</tr>
<tr>
<td>Stripping of mother sheets</td>
<td>0.78/0.84 (3)</td>
<td>0.13</td>
<td>1.37</td>
<td></td>
</tr>
<tr>
<td>Works at mother sheet cells</td>
<td>0.53/0.52 (24)</td>
<td>0.08</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>Crane operators</td>
<td>1.07/1.01 (7)</td>
<td>0.58</td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>Other work in tank houses</td>
<td>0.93/0.83 (10)</td>
<td>0.43</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td>Maintenance works (not in tank houses)</td>
<td>0.66/0.66 (1)</td>
<td>0.92/0.82 (14)</td>
<td>0.48</td>
<td>1.92</td>
</tr>
<tr>
<td>Cleaning and maintenance in tank houses</td>
<td>0.83/0.70 (15)</td>
<td>0.35</td>
<td>1.88</td>
<td></td>
</tr>
<tr>
<td>Repair work (not in tank houses)</td>
<td>0.44/0.39 (12)</td>
<td>0.25</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Repair work (welding)</td>
<td>1.83/1.66 (4)</td>
<td>1.09</td>
<td>2.91</td>
<td></td>
</tr>
</tbody>
</table>

house, while the other (so called 'zero-man') was only looking at his work. For the normal worker, the concentration of nickel within the mask was 0.3 µg m⁻³ and outside the mask 83.0 µg m⁻³, for the zero-man the figures were 0.01–0.02 µg m⁻³ inside and 173–183 µg m⁻³ outside the mask. The protection coefficients (based on one worker only) were thus 275 in work and 8000–18000 for the non-working person.

In the manufacturing of starting sheets, where masks were not used, the stationary to breathing zone nickel concentration ratio was 1.6. In those tasks where protective devices were used, the stationary/breathing zone (from within the mask) ratio of nickel concentrations was 630, 375, 330, 275 and 150 at different work sites.

When the workers were divided in two groups, those who used protective masks and those who did not, the average urinary nickel concentration was 0.67 µmol.l⁻¹ for the former and 0.78 µmol.l⁻¹ for the latter. The highest concentration measured with mask was 1.88 µmol.l⁻¹ and without the mask 2.91 µmol.l⁻¹. No major difference was observed between the urinary nickel concentrations among workers using different mask types (Fig. 4).

Relationship between air, blood and urinary nickel concentrations

No consistent correlation of breathing zone nickel concentrations was observed with nickel concentrations in the urine (with or without correction to common relative density or creatinine excretion) or in the blood. Similarly, no relationship was observed between the increase in the urinary nickel concentration during the working day, and the breathing zone nickel concentration. Two correlations emerged when the workers were grouped by their work tasks: in solution purification (U-Ni = 32.96×A-Ni + 0.089, N = 8, r = 0.883, P < 0.004) and in repair work including welding (U-Ni = 16.08×A-Ni + 0.43; N = 16, r = 0.869, P < 0.001).

If it is assumed that the volume of air inhaled during a half working day is 5 m³, pulmonary retention is 20% (most likely an overestimation for an average dust particle size of 12 µm), the weighted average breathing zone nickel concentration (from within the mask) for the electrolysis workers of 0.9 µg m⁻³ would lead to an
Fig. 4. Urinary nickel concentration of workers using different types of respirators. (1) Without mask, (2) Clearflow-turbo, (3) North half-mask, (4) Silner half-mask. The range, mean (○), median (—) and 25th and 75th percentiles (–) have been indicated.

absorption of 0.9 µg or 15 nmol of nickel in half a working day. If, as an upper bound, three-quarters of this amount were excreted within the first 4 h in a urine volume of 0.51., this would lead to a urinary nickel concentration of 23 nmol L⁻¹, which is less than 1/30 of the mean value actually observed.

Non-smokers had on average lower nickel concentrations in the urine than smokers (0.68 vs 0.74 µmol L⁻¹) but this difference was not significant.

Micronuclei

The results of the buccal mucosa micronucleus assay for both the nickel workers and the referents are presented in Table 8. The mean frequency of cells with micronuclei was marginally higher in the workers than in the controls, but the difference was not statistically significant. There was no association between the frequency of micronucleated cells and the concentration of nickel in breathing zone air samples, in Friday afternoon blood samples or urine samples collected in Friday afternoon, the morning after a weekend, or after a 2-4 week vacation.

Smokers had a slightly higher mean frequency of cells with micronuclei than non-smokers (Table 8). The difference was mainly due to heavy smokers [20 or more cigarettes per day or pipe, mean per 1000 cells 3.6 (S.D. = 2.6, N = 14) as compared with 2.5 in both non-smokers (S.D. = 1.5, N = 30) and those who smoked less than 20 cigarettes per day (S.D. = 2.0, N = 45)]. The frequency of micronucleated cells was five or more per 1000 cells in 29% of smokers, but only in 10% of non-smokers. The effect of smoking was not statistically significant when studied using linear models. However, the additive model (including cigarettes smoked daily, age, and years of nickel exposure) indicated that smoking influences the frequency of micronucleated cells (P < 0.001). The additive model (cigarettes smoked daily, age, urinary nickel, blood nickel) also suggested a non-linear dependence of micronucleus rate on age (P < 0.001), characterized by a lowering of micronucleus counts in older subjects (for example, mean = 3.0, S.D. = 2.4 for 41 subjects over 45 years; mean = 2.3, S.D. = 1.7
Table 8. Frequency of micronucleated buccal epithelial cells in nickel workers and referents; 1000 cells were scored per person for the presence of micronuclei

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (S.D.) age, years</th>
<th>Mean (S.D.) years of exposure</th>
<th>Mean (S.D.) No. cigarettes/day</th>
<th>Mean (S.D.) years of smoking</th>
<th>Micronucleated cells in 1000 cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>38.0 (9.7)</td>
<td>16.5 (10.3)</td>
<td>NA</td>
<td>NA</td>
<td>2.6 (2.0)</td>
</tr>
<tr>
<td>Referents</td>
<td>45.1 (8.3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.4 (1.2)</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>30.9 (8.5)</td>
<td>9.6 (8.1)</td>
<td>14.9 (7.9)</td>
<td>12.7 (8.1)</td>
<td>3.3 (2.4)</td>
</tr>
<tr>
<td>Referents</td>
<td>40.4 (9.8)</td>
<td>NA</td>
<td>16.0 (8.1)</td>
<td>20.3 (8.8)</td>
<td>2.9 (3.0)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>34.3 (9.6)</td>
<td>12.9 (9.7)</td>
<td>NA</td>
<td>NA</td>
<td>3.0 (2.2)</td>
</tr>
<tr>
<td>Referents</td>
<td>42.9 (9.2)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.7 (2.2)</td>
</tr>
</tbody>
</table>

* Includes seven ex-smokers who had stopped smoking 4-18 (mean 12.9) years earlier.

b Includes eight ex-smokers who had stopped smoking 7-29 (mean 17.5) years earlier.

c One subject who smoked 20 g of pipe tobacco a day is not included in this figure.

d Two of the subjects also smoked a pipe, one of them also cigars.
for 18 subjects 45 years or less). The age-effect was not statistically significant in linear models.

DISCUSSION

Exposure to nickel in the Outokumpu Harjavalta electrolytic nickel refinery has been followed unusually well during the whole production time: records exist on exposure levels since 1966, while the process started in 1960. The historical data show that the exposure has been quite stable until about 1988, with nickel concentrations measured at stationary sites between 230 and 800 $\mu g\cdot m^{-3}$. When protective masks were not in use, the breathing zone nickel concentrations have been in the range of 150–250 $\mu g\cdot m^{-3}$. During the early years apparently the use of masks was not insisted upon, and even more recently it was difficult to convince the workers of the importance of the masks; until 1981, the occupational exposure limit (guideline) for nickel and nickel compounds was 1 $mg\cdot m^{-3}$ in Finland. It is likely that at that time the nickel exposure of the workers may have been, at most, in the order of 250 $\mu g\cdot m^{-3}$. Recently an excess of nasal cancer was reported in this facility (Karjalainen et al., 1992). Nasal cancer was observed in three workers, one of these workers worked mainly in maintenance, one was a cleaning woman, and the third was a process worker. These workers had stopped working in the facility in 1977, 1982 and 1983, respectively. Thus they had worked in the facility when leaching, solution purification and precipitate removal were still performed within the tank house (until 1982). It is thus not clear that the exposure measurements reported here are fully representative of the exposure of these three workers. However, it seems that the conclusion of the Doll Committee (Doll et al., 1990) that nickel-induced cancer is only to be expected at soluble nickel concentrations exceeding 1 $mg\cdot m^{-3}$ may be too optimistic.

The breathing zone nickel concentrations in the absence of a protecting device (Table 3) were much lower (in the order of 10 $\mu g\cdot m^{-3}$) than the breathing zone nickel concentrations measured in the traditional way, as reported for earlier years (Table 5); the latter were approximately 200 $\mu g\cdot m^{-3}$. This is not due to a dramatic decrease of exposure, but rather to the fact that the samples for these low values were collected—as described in the Methods section—to reflect the true exposure in different work tasks: nickel was analysed outside the mask only when the worker did not use the mask, when the exposure was expected to be low, while only nickel concentrations inside the mask were analysed when the nickel concentration was expected to be high. For the same reason, the data in Table 3 cannot be used to assess the protective efficacy of the mask/respirator: values observed inside the mask were from samples collected in high exposure tasks, while those observed outside the mask were from samples collected in low exposure tasks.

During the last few years, improved ventilation and use of styrox balls floating on the electrolysis fluid have decreased the air-borne concentrations of nickel. Airborne nickel levels in the tank houses, however, still exceed 100 $\mu g\cdot m^{-3}$ outside respirators. On the other hand, exposure to nickel is quite low when the mask is used. Therefore, it seems that the use of masks, independent of the mask type, provides good protection, and is the only way an efficient protection can at present be achieved. It seems that masks are very diligently worn by the employees now.
Exposure to soluble nickel

Airborne nickel in the refinery occurred in the form of crystalline nickel sulphate dust, which was practically completely water soluble. The average particle size was 12 µm; it is thus expected that most of the inhaled nickel remains in the upper respiratory pathways. Thus the absence of a significant lung cancer excess (two cases, SIR = 2.0, 95% confidence interval 0.3–7.4) while there was an excess of nasal cancer, is not a surprise.

The 95th percentile of the urine nickel concentration in the controls was 0.06 µmol.l\(^{-1}\) and quite similar to values recently reported in Italy (Sabbioni et al., 1992), Belgium (Roels et al., 1993) and elsewhere (Templeton et al., 1994).

Average blood nickel values were elevated among electrolysis workers, and the reference limit of urinary nickel was exceeded in all samples from workers in the tank houses. High urinary/plasma nickel concentrations have frequently been reported in earlier studies in nickel electrolytic refineries (Høgetveit et al., 1978), in the U.S.A. (Bernacki et al., 1978) and Czechoslovakia (Rigaut, 1983), while markedly lower exposure levels have been observed in Norway (Torjussen and Andersen, 1979) and Germany (Raithel, 1987).

No correlation was observed between airborne nickel concentration and urinary nickel concentrations in the electrolytic refining of nickel. This was unexpected since several studies have shown that with exposure to soluble nickel salts (in nickel electroplating), such a correlation exists, although the slope of the regression lines is somewhat different in different studies (Ghezzi et al., 1989; Norseth, 1984; Tola et al., 1979; Ulrich et al., 1991; White and Boran, 1992). In addition, the concentration of nickel in inhaled air could explain only less than 10% of the nickel in the urine. This indicates that nickel was absorbed through routes other than respiration. This is in line with the findings of Bavazzano et al. (1994) among electroplaters. In order to further clarify this point, we studied the urinary excretion of nickel among crane operators, and noted that when they used gloves throughout the working day, their urinary nickel remained low. It seems likely that nickel dust contaminates the skin, notably the hands, and is from there ingested. Thus the urinary nickel concentrations reflect not only the nickel that is absorbed via the respiratory tract—which is probably toxicologically the most important route—but rather, the total nickel uptake.

The effectiveness of the protective masks was 150–630-fold for normal workers, as estimated on the difference between nickel concentrations in the stationary locations and inside the protective mask correlated to the time spent in the tank houses. The protection factor of the mask increased dramatically to 8000–18 000 when the workers only stayed in the tank house without doing any work. Like many earlier studies, our study found that the data from stationary sample collectors differ from those of breathing zone measurements—although even the former were planned in a way that was supposed to reflect worker exposure.

In only nine urine samples taken after the 2–4-week vacation and in one sample taken after the weekend was the nickel concentration within the Finnish reference limits. This indicates that a part of soluble nickel salt accumulates in the body, with a long half life. No clear increase was observed in blood nickel level during the four study days and it seems that blood nickel concentration is determined mainly by long-term exposure to nickel.
Although the mechanism of nickel carcinogenity is not fully elucidated, it is most likely that it involves genetic damage. Therefore, several studies have tried to assess genetic and chromosomal damage in nickel-exposed workers as well as in experimental animals. Several experiments conducted in mammalian cells in vitro have shown that soluble nickel salts produce chromosome breakage, although both positive and negative results have been reported in experimental animals in vivo (IARC, 1990). No previous studies are available on nickel exposure and micronuclei in humans exposed to nickel compounds. Workers of a nickel refinery, including those employed in electrolysis, were reported to show elevated frequencies of chromatid gaps but not of sister chromatid exchanges (SCEs) in their peripheral lymphocytes (Waksvik and Boysen, 1982). Retired workers from the same plant, showing nasal epithelial dysplasia, also had an elevated level of lymphocyte chromatid gaps and breaks, with no effect in SCEs (Waksvik et al., 1984). Electroplating workers exposed to nickel had an increase in both chromosomal aberrations and SCEs in their peripheral lymphocytes (Deng et al., 1988), and high rates of chromosomal aberrations were also observed in workers employed in the production of NiO and NiSO\textsubscript{4} (Senf et al., 1992); in the latter study, also control subjects from the same plant, without direct nickel exposure, were reported to have elevated frequencies of chromosomal aberrations, which the authors explained as an effect of general nickel pollution of the workplace. Gennart et al. (1993) observed that workers exposed to chromium, cobalt and nickel dust in metal powder production have a higher mean frequency of SCEs than unexposed controls. However, Decheng et al. (1987) saw no differences in chromosomal aberrations or SCEs in lymphocytes of workers exposed to nickel carbonyl.

In the present study, oral mucosa epithelial cells were chosen for examination, since their exposure to soluble nickel was supposed to be similar to that of nasal cells, a target tissue of nickel carcinogenesis. Recent studies of formaldehyde-exposed workers (Ballarin et al., 1992; Norppa et al., 1992; Suruda et al., 1993) have indicated that micronuclei in either buccal or nasal mucosa could be used to show the genotoxic effects of upper respiratory tract carcinogens. Our results suggest that the present low nickel exposure in electrolytic refining does not result in measurable clastogenic or aneuploidogenic effects in buccal mucosa.

In accordance with earlier results (Rosin, 1992), tobacco smoking increased the frequency of micronuclei. Ageing was associated with a decreasing micronucleus rate. This kind of age-effect has not earlier been described in the buccal mucosa micronucleus assay and will need confirmation from further studies. The mechanisms involved are unknown; micronuclei are formed only in dividing cells, and if mitotic activity is reduced in mucosa of ageing individuals, micronucleus formation in response to, for example, mutagens in food may be decreased.

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