Little is known on environmental risk factors for cryptorchidism and hypospadias, which are among the most frequent congenital abnormalities in male births. Cryptorchidism (maldescent of the testis) is observed in 1–5% of full-term male births (Toppari et al. 1996) and is a risk factor for subfertility and testicular cancer. Hypospadias (abnormal location of the orifice of the urethra) is observed in 0.3–0.7% of male births and requires surgical treatment in most cases (Pierik et al. 2002).

In the past two decades, concern has been raised over a possible increase in disorders of the male reproductive tract, including cryptorchidism, hypospadias, testicular cancer, and impaired semen quality. It has been suggested that these disorders are interrelated and share a common etiology during fetal life, described by Skakkebaek and colleagues as the testicular dysgenesis syndrome (TDS) (Sharpe and Skakkebaek 1993; Skakkebaek et al. 2001). Fetal exposure to endocrine disruptors (EDs) with estrogen-like or antiandrogen-like activity has been suggested as a cause for TDS (Sharpe 2003; Sharpe and Skakkebaek 1993). Various groups of chemicals, including pesticides and phthalate esters, have been identified as being weakly estrogenic or antiandrogenic (Sharpe 2003). These chemicals may occur in working environments, drinking water, and food (Toppari et al. 1996). Humans can also be exposed to natural phytoestrogens, through consumption of food products derived from plants (Toppari et al. 1996).

There is only limited evidence that the suggested increase in male urogenital abnormalities in humans can be attributed to exposure to EDs (Sharpe 2003) or environmental chemicals in general. An excess of hypospadias has been reported among newborns in populations living within 2–3 km of landfill sites (Dolk et al. 1998; Elliott et al. 2001). These findings may indicate an effect of chemical wastes, but exposure classification was too crude to differentiate this exposure from confounding factors (Dolk et al. 1998; Elliott et al. 2001). In contrast, no association was observed between hypospadias and occupational exposure to EDs by the mother during pregnancy (Vrijheid et al. 2003). A maternal vegetarian diet during pregnancy has been associated with hypospadias in the offspring, suggesting a role of a higher intake of phytoestrogens (North and Goldberg 2000). Although several studies have demonstrated male-mediated developmental effects of environmental exposure (Davis et al. 1992; Robaire and Hales 2003), its role in the etiology of cryptorchidism and hypospadias remains unclear.

The aim of the present study was to evaluate the role of maternal and paternal occupational and dietary exposures to potential EDs in the occurrence of cryptorchidism and hypospadias.
both abnormalities. We selected controls from the 8,541 boys without cryptorchidism or hypospadias if their age was compatible with the observed age range of cases. For statistical power, three times more controls than cases were approached for participation.

Parents of cases and controls were invited to participate in the study, and after written informed consent a research nurse interviewed the mother with a structured questionnaire during a home visit approximately 11 weeks (median) after giving birth (5th and 95th percentiles, 6 and 27 weeks). If present, the father was also interviewed. This study was approved by the institutional review board. The participation rate among mothers was 86% (78 of 91) for cryptorchidism cases, 84% (56 of 67) for hypospadias cases, and 68% (313 of 462) for controls. This participation produced 443 mother–child pairs, including the four boys with both abnormalities. Paternal information was available for 326 of the 443 subjects (74%), in which the paternal information was provided by the biologic father in 91 subjects (28% overall, and 24 and 38% for controls and cases, respectively) and was filled out by the mother because of the father’s absence in 235 subjects (72%). The paternal questionnaire was considered a nonresponse when mothers could not provide core information on the biologic father regarding the country of origin of his

Self-perceived general health was measured with a four-point ordinal scale and dichotomized into good health versus less than good health (Ware et al. 1996). Information was also collected on time to pregnancy (in months), parity, weeks of gestation, birth weight (grams), folic acid supplements, contraceptive pill use before the last pregnancy, and whether the pregnancy was induced by assisted reproduction technologies (ART). Infants were defined as small for gestational age (SGA) when their birth weight was more than two standard deviations below the reference value for their gestational age (Usher and McLean 1969). Preterm delivery was defined as a birth before 35 weeks of gestation (10th percentile).

We ascertained dietary patterns during the first 6 months of pregnancy. One general question distinguished vegetarian diets and diets rich in vegetables, fruits, meat, or fish. A phytoestrogen-specific food questionnaire was developed to differentiate categories of exposure based on a semi-quantitative estimation of the intake of food products containing isoflavonoids and lignans, which are considered the most important naturally occurring phytoestrogens. The questionnaire was developed for this study by TNO Food and Nutrition Research (Zeist, the Netherlands; Brants 1999). For the questionnaire, food products were selected that may contribute to isoflavonoid or lignan intake based on previous research (Brants 1999). For soy consumption, all known soy products were selected except soy oil and soy sauce, because they contain little or no biologically active isoflavonoids. Lignan-containing products were selected for their contribution to the total lignan intake, which was estimated on the basis of their lignan contents (according to food-constituent tables) and the use of the product in the general population (including nonusers) or in the group of users (Brants 1999). We also considered the feeding patterns in Surinam, Turkish, or Moroccan culture (the main groups of immigrants in Rotterdam). We quantified the average daily intake of phytoestrogens (based on consumption per week) by multiplying frequency of use by portion size by the concentration of phytoestrogens according to food-constituent tables (Brants 1999). The intakes per product were added up to the total intake of lignans and isoflavonoids to allow differentiation of subjects with high, intermediate, and low intake, based on tertiles.

We derived occupational exposure from generic questions on paid employment (yes/no) and jobs held in the year before delivery. The focus was on chemicals that may have endocrine activity (Van Tongeren et al. 2002) or that have previously been described as male reproductive toxins (Tielemans et al. 1999a). For the few parents with multiple jobs, the job with most working hours was selected at the time of the first trimester (for mothers) or around fertilization (for fathers). Parents without a job were considered as having no occupational exposures. Additional questions were asked about job title, type of business, name of employer, and activities in the job. A checklist was used for self-reported exposure (yes/no) to ionizing radiation, physical exposures, and classes of chemical substances that have been linked to human reproductive impairment, such as solvents, pesticides, and heavy metals (Tielemans et al. 1999a). Subjects were classified as being exposed to solvents when reporting contact in their job to industrial cleaning products (degreasers), paints, printing inks, glues, or industrial cleaning products (Tielemans et al. 1999b).

We also assessed occupational exposure by applying a job-exposure matrix (JEM) for potential EDs (Van Tongeren et al. 2002). The JEM was based on the judgment of occupational hygienists who estimated for particular jobs the exposure to seven categories of potential EDs (e.g., pesticides and polychlorinated organic compounds) (Van Tongeren et al. 2002). A person in a particular job was assigned “probable exposure = yes” if the experts judged that it was probable that a reasonable proportion of workers had some exposure. An overall classification of “probable exposure to potential EDs = yes” was given to a job if at least one of the seven exposure categories was scored as “yes.”

Statistics. The agreement between self-reported exposure and exposure classification derived from the JEM was determined by the weighted Cohen’s κ. A κ value < 0.4 was considered poor agreement, 0.4–0.6 moderate agreement, and > 0.6 good agreement (Landis and Koch 1977).

We computed frequency counts, crude odds ratios (ORs), and 95% confidence intervals (95% CIs) for all potential risk factors. Continuous risk factors were categorized into three or four categories for ease of interpretation. Trends were assessed by a chi-square test for trends in 2 × 3 or 2 × 4 tables. Logistic regression analysis with stepwise forward selection on univariate risk factors was used to arrive at a multivariable model for either outcome, with a significance level of 0.05 for retained variables. In addition, exposure variables of interest were also included in a multivariable model when this factor was statistically significantly associated with either cryptorchidism or hypospadias in the univariate analysis and the factor caused a change by ≥ 15% in the coefficient of other risk factors in the model. Interactions of all variables were also tested for significance. The 95% CIs around the ORs were derived from the individual Wald’s statistics, except for variables with cell frequencies of five or fewer, in which case likelihood-based confidence intervals are given. Because information on fathers was not
collected on all children, we performed separate analyses for those with mother information and those with mother and father information. Regression analyses were performed using PROC LOGISTIC in SAS (version 8.2; SAS Institute, Cary, NC, USA).

Results

The general characteristics of the study population are shown in Tables 1 and 2. Table 1 presents the risk factors for cryptorchidism and hypospadias related to the mother and pregnancy. Significant risk factors were related to intrauterine growth (low birth weight and SGA for hypospadias, preterm delivery for cryptorchidism). Mothers with better general health, higher education, and larger height showed less risk of having offspring with either abnormality. These individual characteristics were strongly interrelated. Boys born from mothers of Turkish origin had increased risks for cryptorchidism and hypospadias. Compared with a Dutch origin, a Turkish origin was strongly associated with suboptimal health, a lower education level, and lower maternal height. Dietary phytoestrogens and maternal occupational exposure to potential EDs did not significantly alter the risk of either abnormality.

Table 2 presents paternal risk factors. Paternal age, education, and country of origin were associated with cryptorchidism and hypospadias. Smoking among fathers was associated with hypospadias (OR = 3.4). ORs for cryptorchidism in offspring were elevated for self-reported solvent exposure (OR = 2.0) and pesticide exposure according to the JEM (OR = 4.5). Self-reported exposure to pesticides also gave an increased risk (OR = 2.8) of borderline significance (p = 0.08). Paternal self-reported solvent exposure (OR = 2.4) was also associated with hypospadias. Self-reported exposure to heavy metals, anesthetics, and other JEM categories was not significantly associated with the outcomes.

The exposure prevalence in men was significantly higher than in women. Among men, the prevalence of self-reported exposure was 23.0% (n = 75) for solvents, 10.2% (n = 33) for heavy metals, 4.6% (n = 15) for pesticides, and 1.9% (n = 6) for anesthetics, and 31% were exposed to at least one of these categories. The single largest group reporting pesticide exposure was workers in greenhouses involved in cultivation of vegetables (n = 3) or flowers (n = 3). The JEM identified paternal ED exposure in 12.0% of the fathers. In the JEM, pesticide exposure (n = 14) was assigned primarily to greenhouse workers in flowers (n = 7) or vegetables (n = 6). Among couples, maternal and paternal exposures to pesticides were associated for self-reports and the JEM (Spearman rank correlation, 0.18 and 0.21, respectively). The agreement between pesticide exposures based on self-reports and the JEM was moderate (k = 0.54; 95% CI, 0.36–0.71). Age, education level, smoking, and country of origin within couples were strongly correlated (Spearman correlation coefficients > 0.50).

Tables 3 and 4 present the multivariate models with maternal and paternal risk factors for cryptorchidism and hypospadias, respectively. The final models on maternal risk factors (Tables 3 and 4) provide no evidence for an association between maternal dietary and environmental exposure and the occurrence of both outcomes while adjusting for other risk factors. When manually added to the final multivariate models, the risk estimates for occupational exposures and dietary phytoestrogens were very similar to their effects in the univariate analyses in Table 1 (< 15% change in coefficient), although the confidence intervals were somewhat larger.

A preterm delivery and a low education level were the strongest risk factors for cryptorchidism in the maternal multivariate model, together with an interaction between country of origin and mother’s age at delivery. Among Turkish mothers ≥ 30 years of age, an increased risk of cryptorchidism in newborns was observed compared with younger Turkish and with Dutch mothers. When taking into account also the characteristics of the father (Table 3), the only paternal risk factor associated with cryptorchidism was probable occupational exposure to pesticides (OR = 3.8). Although not selected by the stepwise forward selection, manual addition of self-reported exposure to solvents produced a similar effect as in the univariate analysis (OR = 1.9; 95% CI, 0.9–3.9), but the influence of probable exposure to EDs was substantially smaller (OR = 1.3; 95% CI, 0.5–3.3) than when analyzed univariately.

The important maternal risk factors for hypospadias were SGA birth and health status of the mother (Table 4). Again, Turkish origin was associated with an increased risk for hypospadias. The important paternal risk factors were maternal weight during pregnancy and preterm delivery; in the final model, together with an interaction between maternal age and smoking level were the strongest risk factors for hypospadias. When manually added to the final multivariate models, the risk estimates were not significantly altered.
hypospadias (OR = 3.0), but no interaction with age was identified. When also taking into account the characteristics of the father, current smoking of the father was a strong risk factor (OR = 3.8). The risk for self-reported exposure to solvents among fathers was elevated (OR = 2.0) but of borderline significance ($p = 0.09$). This risk factor was included because it influenced the risk estimates of time to pregnancy, because of the moderate association between time to pregnancy and solvent exposure. When manually entered into the multivariate model, the risk estimates for maternal and paternal occupational exposures and dietary phytoestrogens (that were not selected by the stepwise procedure) were very similar to their univariate accuracy (88% verification) of the hypospadias diagnosis by CHC physicians has been demonstrated previously (Pierik et al. 2002), whereas the accuracy of cryptorchidism diagnosis was not assessed. Because the case status was assessed prospectively before data on determinants were collected, the misclassification by CHC physicians is probably nondifferential, which would bias the results toward unity in our analyses. Resources were insufficient to have CHC physicians report the exact location of the urethral opening and the left and right tests for the nearly 9,000 subjects. Another strength of the present study is that both maternal and paternal determinants were included. A weakness of the study is that the paternal determinants were missing for 26% ($n = 116$) of the subjects, and in the subjects with paternal information, the paternal determinants were presented by the fathers themselves only 28% ($n = 91$). Differential misclassification between mothers and fathers on self-reported paternal exposure to solvents cannot be ruled out because fathers and mothers reported a paternal exposure prevalence of 31 and 20%, respectively. However, the hypospadias risk for paternal solvent exposure reported by the father (OR = 1.9; 95% CI, 0.6–6.2) or mother (OR = 2.5; 95% CI, 1.0–6.2) was comparable in size, although the 95% CI was wider in these smaller subsets. For other paternal occupational exposures and lifestyle factors, such as smoking and alcohol use, no differences were observed between reporting mothers and fathers.

The multivariate analyses suggest an important role of paternal smoking and occupational exposures. Paternal smoking was significantly associated with hypospadias (OR = 3.8; Table 4). Paternal smoking has previously been associated with the occurrence of single and multiple birth defects (Zhang et al. 1992), but not specifically with hypospadias. Paternal smoking could have an effect through passive exposure of the mother, but this is unlikely because active smoking by the mother was not a risk factor. We cannot exclude that mothers have underreported their smoking. When mothers of cases underreport their own smoking more than that of their partner, paternal smoking may partly be a spurious risk factor.

After correction for other significant risk factors, paternal pesticide exposure based on the JEM was significantly associated with cryptorchidism (OR = 3.8; Table 3), and self-reported paternal solvent exposure was borderline associated with hypospadias (OR = 2.0; Table 4). The exposure classifications of solvents and pesticides were too broad to allow identification of specific (groups of) chemical agents to be held responsible for the increased risks of either anomaly. Because parents of cryptorchidism and hypospadias cases may have been more concerned with and knowledgeable about environmental risk factors than were

### Table 4. Continued

| Variable                      | Controls | Cryptorchidism (n = 78) | Hypospadias (n = 56) |
|------------------------------|----------|-------------------------|----------------------|
|                              | Cases    | OR (95% CI)             | Cases               | OR (95% CI)         |
| Prematurity birth            |          |                        |                      |
| Yes                          | 25       | 14                      | 2.5* (1.2–5.1)       | 8                    | 1.9 (0.8–4.5) |
| No                           | 288      | 64                      | 1.0                  | 48                   | 1.0           |
| Primiparaous                 |          |                        |                      |
| Yes                          | 162      | 44                      | 1.2 (0.7–2.0)        | 25                   | 0.8 (0.4–1.3) |
| No                           | 151      | 34                      | 1.0                  | 31                   | 1.0           |
| Folic acid supplements in pregnancy |          |                        |                      |
| Yes                          | 179      | 35                      | 0.6 (0.4–1.0)        | 32                   | 1.0 (0.6–1.8) |
| No                           | 134      | 43                      | 1.0                  | 24                   | 1.0           |
| Vegetable-rich diet          |          |                        |                      |
| Yes                          | 125      | 24                      | 0.7 (0.4–1.1)        | 17                   | 0.7 (0.4–1.2) |
| No                           | 186      | 54                      | 1.0                  | 39                   | 1.0           |
| Soy protein intake           |          |                        |                      |
| ≥ 20 g/day                   | 51       | 8                       | 0.6 (0.3–1.3)        | 9                    | 1.0 (0.5–2.2) |
| > 0–20 g/day                 | 41       | 12                      | 1.1 (0.6–2.3)        | 8                    | 1.1 (0.5–2.5) |
| 0 g/day                      | 221      | 58                      | 1.0                  | 39                   | 1.0           |
| Lignan intake                |          |                        |                      |
| ≥ 6 g/day                    | 115      | 23                      | 0.7 (0.4–1.3)        | 22                   | 1.0 (0.5–2.1) |
| 4–6 g/day                    | 119      | 31                      | 0.9 (0.5–1.6)        | 19                   | 0.8 (0.4–1.8) |
| < 4 g/day                    | 79       | 24                      | 1.0                  | 15                   | 1.0           |
| Paid employment              |          |                        |                      |
| Yes                          | 213      | 46                      | 0.7 (0.4–1.1)        | 31                   | 0.6 (0.3–1.0) |
| No                           | 100      | 32                      | 1.0                  | 25                   | 1.0           |
| Probable exposure to EDs (JEM) |          |                        |                      |
| Yes                          | 24       | 6                       | 1.0 (0.4–2.6)        | 3                    | 0.7 (0.2–2.0) |
| No                           | 289      | 72                      | 1.0                  | 53                   | 1.0           |
| Probable exposure to pesticides (JEM) |          |                        |                      |
| Yes                          | 7        | 2                       | 1.2 (0.2–4.9)        | 2                    | 1.6 (0.2–6.9) |
| No                           | 306      | 76                      | 1.0                  | 54                   | 1.0           |
| Self-reported exposure to pesticides |          |                        |                      |
| Yes                          | 4        | 2                       | 2.0 (0.3–10.6)       | 1                    | 1.4 (0.1–9.7) |
| No                           | 309      | 76                      | 1.0                  | 55                   | 1.0           |
| Self reported exposure to solvents |          |                        |                      |
| Yes                          | 32       | 6                       | 0.7 (0.3–1.8)        | 9                    | 1.7 (0.8–3.8) |
| No                           | 281      | 72                      | 1.0                  | 47                   | 1.0           |
Animal studies provide evidence that exposure to pesticides, solvents, and other chemicals can mediate adverse reproductive outcomes. More than 100 chemicals, including pesticides and solvents, have been related to male reproductive health outcomes such as cryptorchidism and hypospadias. The role of specific occupational exposures, such as exposure to environmental pollutants (EDs), has also been studied. Occupational exposure to EDs during fetal life could be a causal pathway leading to cryptorchidism and hypospadias. However, further research is needed to confirm or refute this hypothesis. We did not find an association between maternal occupational exposure and either abnormality, perhaps due to the small proportion of exposed mothers. A previous study reported a maternal vegetarian diet as a risk factor for hypospadias and suggested a higher phytoestrogen intake as explanation. We specifically assessed dietary phytoestrogen intake, which was not a significant risk factor for hypospadias or cryptorchidism. The nutrition data may suffer from inaccuracies because nutrition was assessed only once, whereas considerable individual variation has been described with food-frequency questionnaires. We anticipated that maternal smoking and occupational exposure may mediate the observed effects of paternal risk factors.

Table 2. Univariate analysis of the association between paternal risk factors and the occurrence of cryptorchidism and hypospadias in a case–control study among 326 father–child pairs.

| Variable                          | Controls | Cryptorchidism (n = 50) | Hypospadias (n = 41) |
|----------------------------------|----------|-------------------------|----------------------|
|                                  |          | Cases | OR (95% CI) | Cases | OR (95% CI) |
| Age (years)                      |          |       |             |       |             |
| < 25                             | 19       | 10    | 1.0         | 5     | 1.0         |
| 25–30                            | 43       | 6     | 0.3* (0.1–0.8) | 12 | 1.1 (0.3–3.4) |
| 30–35                            | 64       | 19    | 0.6 (0.2–1.4) | 8     | 0.5 (0.1–1.6) |
| > 35                             | 109      | 15    | 0.3* (0.1–0.7) | 16 | 0.6 (0.2–1.7) |
| Height (cm)                      |          |       |             |       |             |
| < 175                            | 59       | 14    | 1.0         | 12    | 1.0         |
| 175–180                          | 42       | 9     | 0.9 (0.4–2.3) | 5    | 0.6 (0.1–1.8) |
| 180–185                          | 48       | 12    | 1.1 (0.5–2.5) | 11    | 1.1 (0.5–2.8) |
| > 185                            | 82       | 15    | 0.8 (0.4–1.7) | 14    | 0.8 (0.4–2.0) |
| Educational level                |          |       |             |       |             |
| Low                              | 59       | 19    | 1.0         | 12    | 1.0         |
| Intermediate                     | 89       | 13    | 0.5* (0.2–1.0) | 25 | 1.4 (0.6–4.0) |
| High                             | 86       | 18    | 0.7 (0.3–1.4) | 5     | 0.3* (0.1–0.9) |
| Country of origin                |          |       |             |       |             |
| Netherlands                      | 127      | 26    | 1.0         | 25    | 1.0         |
| Morocco                          | 16       | 6     | 1.8 (0.6–4.9) | 2    | 0.6 (0.1–2.4) |
| Turkey                           | 16       | 11    | 3.4* (1.4–8.1) | 7    | 2.2 (0.8–5.8) |
| Surinam                          | 31       | 2     | 0.3 (0.1–1.1) | 3    | 0.5 (0.1–1.5) |
| Other                            | 46       | 5     | 0.5 (0.2–1.4) | 5    | 0.6 (0.2–1.4) |
| Good general health              |          |       |             |       |             |
| Yes                              | 205      | 39    | 1.0         | 34    | 1.0         |
| No                               | 30       | 10    | 1.8 (0.8–3.9) | 7    | 1.4 (0.6–3.5) |
| Current smoker                   |          |       |             |       |             |
| Yes                              | 98       | 22    | 1.2 (0.6–2.1) | 29    | 3.4* (1.7–7.0) |
| No                               | 138      | 27    | 1.0         | 12    | 1.0         |
| Paid employment                  |          |       |             |       |             |
| Yes                              | 209      | 41    | 0.7 (0.3–1.6) | 37    | 1.0 (0.3–3.6) |
| No                               | 27       | 8     | 1.0         | 5     | 1.0         |
| Probable exposure to potential EDs (JEM) |          |       |             |       |             |
| Yes                              | 38       | 13    | 1.8 (0.9–3.8) | 10    | 1.6 (0.7–3.8) |
| No                               | 198      | 37    | 1.0         | 32    | 1.0         |
| Probable exposure to pesticides (JEM) |          |       |             |       |             |
| Yes                              | 7        | 6     | 4.5* (1.4–13.9) | 1    | 0.8 (0.3–3.6) |
| No                               | 229      | 44    | 1.0         | 41    | 1.0         |
| Self-reported exposure to pesticides |          |       |             |       |             |
| Yes                              | 9        | 5     | 2.9 (0.8–8.5) | 1    | 0.6 (0.0–3.4) |
| No                               | 227      | 45    | 1.0         | 41    | 1.0         |
| Self-reported exposure to solvents |          |       |             |       |             |
| Yes                              | 45       | 16    | 2.0* (1.0–3.9) | 15    | 2.4* (1.2–4.8) |
| No                               | 191      | 34    | 1.0         | 27    | 1.0         |

*p < 0.05.
The findings in our case–control study suggest an association between cryptorchidism and hypospadias and lower socioeconomic status, as reflected in low education level and suboptimal general health status of both parents. The effect of socioeconomic status may be confounded by selection bias, especially because of differential response between cases and controls. For the impact of education to be spurious, this would require approximately a 2-fold higher response among parents of cases than of controls in subjects with a low education.

A similar differential response bias may have contributed to the observed effect of Turkish origin on cryptorchidism and hypospadias. Based on the nationalities of all 8,695 examined boys, Moroccan, Turkish, and other minorities were underrepresented by about 40–50% among controls. To exclude confounding by country of origin, we repeated the regression analysis in Dutch subjects only, which did not yield significantly different results, although standard errors increased because of a smaller sample. Among Dutch subjects paternal exposure to pesticides has a similar effect (OR = 3.4; 95% CI, 0.3–43.0) on cryptorchidism but failed to reach the level of conventional significance. Paternal smoking (OR = 6.5; 95% CI, 2.0–21.7) and self-reported paternal exposure to solvents (OR = 3.3; 95% CI, 1.2–9.5) remained significant risk factors for hypospadias among Dutch subjects.

Previous studies have reported ethnic variations in the occurrence of cryptorchidism and hypospadias (Chia et al. 2003; Fredell et al. 2002). Familial aggregation has been described for both abnormalities, supporting the importance of genetic factors (Fredell et al. 2002; Weidner et al. 1999). The association between Turkish origin and cryptorchidism and hypospadias may be the result of a genetic or environmental factor among Turkish people that predisposes toward these abnormalities. A higher maternal age was a significant risk factor within the Turkish minority, but not in the overall group of non-Turkish origin. We cannot exclude the possibility that the response may have been different with age among Turks.

In the multifactorial models without adding paternal risk factors, preterm delivery was associated with cryptorchidism (OR = 3.1; Table 3), and being SGA was associated with hypospadias (OR = 7.3; Table 4). These associations are well known from previous studies (Weidner et al. 1999). Some authors point to reduced placental function as underlying etiology for low birth weight, cryptorchidism, and hypospadias (Fredell et al. 1998).

Some earlier studies looking at large groups of cases have reported ORs ranging from 1.1 to 1.9 for low birth order and a higher maternal age as risk factors for cryptorchidism or hypospadias cases (Akre et al. 1999; Biggs et al. 2002; Kallen 2002; Möller and Skakkebæk 1997), although others did not observe these excess risks (Berkowitz et al. 1995; Jones et al. 1998). Birth order and parental age were not significantly related to cryptorchidism or hypospadias in our study, which may be because of the relatively small effect and limited population size.

Our observation that a longer time to pregnancy was associated with hypospadias (Table 4) may be explained by familial aggregation of hypospadias (Fredell et al. 2002) and its association with subfertility (Skakkebæk et al. 2001). Previous studies have reported a higher incidence of hypospadias in boys born after intracytoplasmic sperm injection (Ericson and Kallen 2001; Wennerholm et al. 2000), which may be explained by a lower birth weight that occurs more frequently after ART. In our study, the frequency of ART was too low to evaluate its association with hypospadias or cryptorchidism.

This study suggests that paternal environmental exposures may increase the risk of cryptorchidism and hypospadias in newborn boys, which may indicate an effect on the paternal germline. Cryptorchidism was associated with paternal exposure to pesticides, and hypospadias was more frequent in fathers who were active smokers. The pregnancy-related risk factors of low birth weight and SGA birth for hypospadias and preterm delivery for cryptorchidism have consistently been found in previous studies (Weidner et al. 1999). Future studies on environmental risk factors for cryptorchidism and hypospadias should not only focus on maternal exposure during fetal life but also include the paternal pathway to substantiate whether the observed associations are causal.

### References

Akre O, Lipworth L, Cnattingius S, Sparen P, Ekborn A. 1999. Risk factor patterns for cryptorchidism and hypospadias. Epidemiology 10:364–369.

Berkowitz GS, Lapinski RH, Godbold JH, Dolgin SE, Holzman IR. 1995. Maternal and neonatal risk factors for cryptorchidism. Epidemiology 6:127–131.

Biggs ML, Baer A, Cricklow CW. 2002. Maternal, delivery, and perinatal characteristics associated with cryptorchidism: a population-based case–control study among births in Washington State. Epidemiology 13:197–204.

Brants HAM. 1999. Qualitative Questionnaire on Dietary Intake of Soy Products and Lignans (in Dutch). Zeist:TNIO.

Chen TT. 1989. A review of methods for misclassified categorical data in epidemiology. Stat Med 8:1095–1098.

Chia SE, Shi LM, Chan OY, Chew SK, Foong BH. 2003. Parental occupations and other risk factors associated with non-chromosomal single, chromosomal single, and multiple birth.
Kallen K. 2002. Role of maternal smoking and maternal reproductive effects: biologic and epidemiologic findings and a plea for clinical research. Reprod Toxicol 6:289–292.

de Muinck Keizer-Schrama SM. 1987. Consensus on management of the undescended testis. Ned Tijdschr Geneeskd 131:1817–1821.

Dolk H, Vrijheid M, Armstrong B, Abramsky L, Bianchi F, Garne E, et al. 1998. Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. Lancet 352:423–427.

Elliott P, Briggs D, Morris S, de Hoogh C, Hurt C, Jensen TK, et al. 2001. Risk of adverse birth outcomes in populations living near landfill sites. Br Med J 323:363–368.

Ericson A, Kallen B. 2001. Congenital malformations in infants born after IVF: a population-based study. Hum Reprod 16:504–509.

Fredell L, Kockum I, Hansson E, Holmer S, Lundquist I, Lackgren G, et al. 2002. Heredity of hypospadias and the significance of low birth weight. J Urol 167:1423–1427.

Fredell L, Lichtenstein P, Pedersen NL, Svensson J, Nordenskjold A. 1998. Hypospadias is related to birth weight in discordant monozygotic twins. J Urol 160:2197–2199.

Goldbohm RA, van’t Veer P, van den Brandt PA, van’t Hof MA, Brants HA, Sturmans F, et al. 1995. Reproducibility of a food frequency questionnaire and stability of dietary habits determined from five annually repeated measurements. Eur J Clin Nutr 49:420–429.

Greenland S. 1980. The effect of misclassification in the presence of covariates. Am J Epidemiol 112:564–569.

Jones ME, Svendsen AJ, Griffith M, Goldacre MJ. 1998. Prenatal risk factors for cryptorchidism: a record linkage study. Paediatr Perinat Epidemiol 12:383–396.

Kallen K. 2002. Role of maternal smoking and maternal reproductive history in the etiology of hypospadias in the offspring. Teratology 66:185–191.

Keij I. 2000. Numbers of foreigners according to various definitions [in Dutch, summary in English]. Maandstatistieke van de bevolking 49/3:14–17.

Kristensen P, Ingens LM, Andersen A, Bye AS, Sundheim L. 1997. Birth defects among offspring of Norwegian farmers, 1967–1991. Epidemiology 8:537–544.

Kristensen P, Ingens LM, Dalvæv AK, Andersen A. 1992. Perinatal outcome among children of men exposed to lead and organic solvents in the printing industry. Am J Epidemiol 134:134–144.

Landis JR, Koch GG. 1977. The measurement of observer agreement for categorical data. Biometrics 33:159–174.

Moller H, Skakkebaek NE. 1997. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. Cancer Causes Control 8:904–912.

North K, Golding J. 2000. A maternal vegetarian diet in pregnancy is associated with hypospadias. BJU Int 85:107–113.

Olshan AF, Teschke K, Baird PA. 1991. Paternal occupation and congenital anomalies in offspring. Am J Ind Med 20:447–475.

Pierik FH, Burdorf A, Nijman JM, de Muinck Keizer-Schrama SM, Juttmann RE, Weber RF. 2002. A high hypospadias rate in The Netherlands. Hum Reprod 17:1112–1115.

Robaire B, Hales BF. 2003. Mechanisms of action of cyclophosphamide as a male-mediated developmental toxicant. Adv Exp Med Biol 518:169–180.

Sharpe RM. 2003. The “oestrogen hypothesis”—where do we stand now? Int J Androl 26:2–15.

Sharpe RM, Skakkebaek NE. 1993. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 341:1392–1395.

Skakkebaek NE, Raepert-De Meyts E, Main KM. 2001. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 16:972–978.

Somers CM, Yauk CL, White PA, Parfett CL, Quinn JS. 2002. Air pollution induces heritable DNA mutations. Proc Natl Acad Sci USA 99:15904–15907.

Tielemans E, Burdorf A, de Velde ER, Weber RF, van Kooij RJ, Veulemans H, et al. 1999a. Occupationally related exposures and reduced semen quality: a case-control study. Fertil Steril 71:980–986.

Tielemans E, Heederik D, Burdorf A, Vermeulen R, Veulemans H, Kromhout H, et al. 1999b. Assessment of occupational exposures in a general population: comparison of different methods. Occup Environ Med 56:145–151.

Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillett LJ, et al. 1998. Male reproductive health and environmental xenosterogens. Environ Health Perspect 106:41–403.

Usher R, McLean F. 1989. Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr 74:901–910.

Van Tongeren M, Nieuwenhuijzen MJ, Gardiner K, Armstrong B, Vrijheid M, Dolk H, et al. 2002. A job-exposure matrix for potential endocrine-disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias. Am Occup Hyg 46:465–477.

Vrijheid M, Armstrong B, Dolk H, van Tongeren M, Botting B. 2003. Risk of hypospadias in relation to maternal occupational exposure to potential endocrine disrupting chemicals. Occup Environ Med 60:543–550.

Ware J Jr, Kosinski M, Keller SD. 1996. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 34:220–233.

Weidinger IS, Moller H, Jensen TK, Skakkebaek NE. 1998. Cryptorchidism and hypospadias in sons of gardeners and farmers. Environ Health Perspect 106:793–796.

Weidinger IS, Moller H, Jensen TK, Skakkebaek NE. 1999. Risk factors for cryptorchidism and hypospadias. J Urol 161:1606–1609.

Wennerholm UB, Bergh C, Hamberger L, Lundin K, Nilsson L, Wihlander M, et al. 2000. Incidence of congenital malformations in children born after ICSI. Hum Reprod 15:944–948.

Zhang J, Savitz DA, Schwingl PJ, Cai WW. 1992. A case-control study of paternal smoking and birth defects. Int J Epidemiol 21:273–278.