An increasing incidence of testicular cancer has been reported from several countries in the Western world during the last decades. According to current hypothesis, testicular cancer is initiated during the fetal period, and exposure to endocrine disruptors, i.e., xenoestrogens, has been of concern. In this investigation we studied the concentrations of the sum of 38 polychlorinated biphenyls (PCBs), p,p′-dichlorodiphenyl-dichloroethylene, hexachlorobenzene (HCB), and chlordanes, in 61 cases with testicular cancer and 58 age-matched controls. Furthermore, case and control mothers were also asked to participate, and 44 case mothers and 45 control mothers agreed. They were of similar age. In cases only the concentration on lipid basis of cis-nonachlordane was significantly increased, whereas case mothers showed significantly increased concentrations of the sum of PCBs, HCB, trans- and cis-nonachlordane, and the sum of chlordanes. Among case mothers the sum of PCBs yielded an odds ratio (OR) of 3.8; 95% confidence interval (CI), 1.4–10 was calculated using the median concentration for the control mothers as cutoff value. For HCB, OR = 4.4 (95% CI, 1.7–12); for trans-nonachlordane, OR = 4.1 (95% CI, 1.5–11); for cis-nonachlordane, OR = 3.1 (95% CI, 1.2–7.8); and for sum of chlordanes, OR = 1.9 (95% CI, 0.7–5.0). No consistent different risk pattern was found for seminoma or nonseminoma testicular cancer. Key words: chloroalanes, fetal period, hexachlorobenzene, persistent organic pollutants, polychlorinated biphenyls, testicular cancer.

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**Chemical analysis.** All blood samples were coded with an identification number that did not reveal sex or whether it was a case or a control. Approximately 20 mL of blood was used for analyses of 38 congeners of polychlorinated biphenyls (PCBs) most abundant in human samples. The sum of these 38 congeners is presented here in addition to \( p,p' \)-dichlorodiphenyl-dichloroethylene (\( p,p' \)-DDE), hexachlorobenzene (HCB), and six chlordane congeners (\( cis \)-heptachlordane, \( cis \)-chlordane, oxychlordane, MC6, \( trans \)-nonachlordane, \( cis \)-nonachlordane). The plasma samples were fortified with \( ^{13}C \)-labeled internal standards. The lipid fraction, containing the organochlorines, was first removed from blood by use of a Hydromatrix column (Varian, Palo Alto, CA, USA). The lipid content was then determined gravimetrically, and lipids and interferences were removed by multilayer silica chromatography. Congener-specific analyses and quantification of the organochlorines was done by high-resolution gas chromatography and coupled mass spectrometry running in electro impact (EI) and selected ion monitoring (SIM) mode. The two most abundant ions of the chlorine cluster of the molecular ion for each compound were measured in addition to the one ion for the 12 \( ^{13}C \)-labeled internal standards (IS) and the three recovery standards (RS). We used a quantification mix including all compounds in addition to the IS and RS to calculate relative response factors (RRFs), and then used these RRFs to calculate the levels in the samples. In addition, the recovery of the IS was calculated. All recoveries of the 12 different IS were between 50 and 120%. In addition, one laboratory blank sample was processed with each set of nine samples. All blank levels were <10% of the levels reported for all compounds. The methods detection level defined over the detection limit. However, for the sum of PCBs, chlordanes, HCB, and \( p,p' \)-DDE, all analytes were above detection limit.

**Table 1. Age distribution among cases, controls, and mothers of cases and controls.**

|                | No. | Mean | Median | Minimum | Maximum |
|----------------|-----|------|--------|---------|---------|
| Cases          | 58  | 31   | 30     | 18      | 45      |
| Seminoma       | 22  | 34   | 33     | 23      | 45      |
| Nonseminoma    | 36  | 29   | 29     | 18      | 42      |
| Controls       | 61  | 32   | 31     | 19      | 47      |
| Mothers of cases | 44 | 57   | 54     | 41      | 75      |
| Seminoma       | 14  | 60   | 61     | 48      | 75      |
| Nonseminoma    | 30  | 55   | 54     | 41      | 69      |
| Mothers of controls | 45 | 57   | 55     | 43      | 75      |

**Table 2. Concentrations of organochlorine compounds (nanograms per gram lipid) in cases with testicular cancer and controls.**

|                | No. | Mean | Median | Minimum | Maximum | \( p \)-Value* |
|----------------|-----|------|--------|---------|---------|---------------|
| Sum of PCBs    |     | 395  | 357    | 96      | 1,099   | 0.91          |
| Cases          | 58  | 394  | 364    | 110     | 1,083   |               |
| Controls       | 61  | 34   |        |         |         |               |
| HCB            |     | 24   | 22     | 8.8     | 47      | 0.33          |
| Cases          | 58  | 152  | 117    | 35      | 529     | 0.27          |
| Controls       | 61  | 140  | 98     | 29      | 601     |               |
| \( p,p' \)-DDE |     | 27   | 31     | 19      | 47      |               |
| Cases          | 58  | 13   | 11     | 13      | 13      | 0.30          |
| Controls       | 61  | 1.3  | 1.0    | 0.3     | 9.3     |               |
| \( cis \)-Heptachlordane |     | 2.1  | 1.2    | 0.2     | 13      | 0.71          |
| Cases          | 58  | 1.1  | 0.8    | 0.1     | 4.6     |               |
| Controls       | 61  | 1.0  | 0.9    | 0.2     | 2.6     |               |
| \( cis \)-Chlordane |    | 8.3  | 6.9    | 0.9     | 33      | 0.61          |
| Cases          | 59  | 7.5  | 6.5    | 2.0     | 32      |               |
| Controls       | 61  | 2.5  | 2.0    | 0.7     | 7.5     | 0.79          |
| MC6            |     | 2.3  | 1.9    | 0.5     | 7.0     |               |
| Cases          | 58  | 8.6  | 7.5    | 1.6     | 28      | 0.87          |
| Controls       | 61  | 8.5  | 7.9    | 0.9     | 26      |               |
| \( cis \)-Nonachlordane |    | 1.8  | 1.5    | 0.4     | 7.6     | 0.04          |
| Cases          | 58  | 1.4  | 1.1    | 0.3     | 7.8     |               |
| Controls       | 61  | 24   | 21     | 8.0     | 72      | 0.41          |

**Table 3. OR (95% CI) for cases with testicular cancer, all types combined.**

|                | Cases/controls | OR (95% CI) |
|----------------|---------------|-------------|
| Sum of PCBs    | 28/30         | 1.1 (0.5–2.6) |
| HCB            | 35/30         | 1.7 (0.8–3.6) |
| \( p,p' \)-DDE | 34/30         | 1.7 (0.8–3.7) |
| \( cis \)-Heptachlordane | 34/29 | 1.6 (0.6–3.4) |
| \( cis \)-Chlordane | 27/26 | 1.2 (0.6–2.6) |
| Oxychlordane   | 31/29         | 1.4 (0.7–2.9) |
| \( trans \)-Nonachlordane | 30/30 | 1.3 (0.6–2.9) |
| \( cis \)-Nonachlordane | 27/30 | 1.0 (0.4–2.1) |
| Sum of chlordanes | 31/30 | 1.3 (0.6–2.8) |

*Wilcoxon \( p \)-value.
analyzed blood from only 58 cases. Of the case mothers, 44 agreed to participate compared with 45 of the control mothers.

Cases and controls. The 58 cases with testicular cancer were of mean age 31 years (median 30, range 18–45), and the 61 controls were of mean age 32 years (median 31, range 19–47) (Table 1). Cases with seminoma were somewhat older than cases with nonseminoma cancer, as was expected according to the age distribution for these tumor types.

The median number of birth order was two for both the cases and controls (p = 0.27). Median breast-feeding for the cases was 4 months (range 0–13.5) and for the controls 3 months (range 0–12; p = 0.49).

Of the cases, 22 had seminoma and 36 had nonseminoma testicular cancer (28 embryonal cancer and 8 teratoma).

Table 2 displays results on concentrations of organochlorines for the sons. The only significant difference was an increased concentration of cis-nonachlordane in cases with testicular cancer. This yielded OR = 2.6 (95% CI, 1.2–5.7) if the median concentration among the controls was used as cutoff value (Table 3). Sum of PCBs did not differ between cases and controls. For other studied organochlorines, somewhat increased concentrations were found among the cases yielding increased ORs, although not significantly so.

Analysis according to histopathology gave only significantly increased risk for cis-nonachlordane among seminoma cases with OR = 4.8 (95% CI, 1.4–16) (Table 4).

Mothers to cases and controls. Both groups of mothers were of similar age overall, although mothers to seminoma cases tended to be somewhat older (Table 1). Median duration of breast-feeding in total before blood sampling (all children including the studied child) was 8 months both for case and control mothers (p = 0.91).

Table 5 displays the results of concentrations of organochlorines in mothers of cases and controls. Significantly increased concentrations were found for the sum of PCBs, HCB, trans-nonachlordane, cis-nonachlordane, and sum of chlordanes.

Table 6 shows results of calculations of OR and CI in the group of mothers. For sum of PCBs, OR = 3.8 (95% CI, 1.4–10); for HCB, OR = 4.4 (95% CI, 1.7–12); for trans-nonachlordane, OR = 4.1 (95% CI, 1.5–11); and for cis-nonachlordane, OR = 3.1 (95% CI, 1.2–7.8). For cis-chlordane, a borderline significant result was obtained with OR = 2.5 (95% CI, 0.99–6.1). The other organochlorines also yielded increased ORs, although not significantly so.

We made further calculations for mothers, separated according to histopathology type of the testicular cancer in the respective child (Table 7). The results were similar to the whole study group.

Discussion
The organochlorines studied are fat-soluble chemicals that bioaccumulate in the human body. The half-life for PCBs has been estimated to be between 7 and 30 years in human serum (Wolff et al. 1992). For p,p'-DDE, the half-life in plasma is approximately 10 years (Hunter et al. 1997), and for chlordanes, half-life is 10–20 years (Dearth and Hites 1991). For HCB, no half-life figure in humans is documented.

Because of the long half-life, it would be possible to estimate previous exposure by measurement of lipid-based concentrations of certain organochlorines. Because median time from the fetal period until blood sampling was similar for the cases (30 years) and for the controls (31 years) in the data presented here, previous differences in exposure may be reflected in current blood levels. Of course, there may be individual differences in exposure and metabolism patterns over the years, but we lack such data. The results certainly indicate that further studies are necessary, perhaps with a different design, use of early blood samples if existing, and the like. It cannot be completely excluded that the real etiologic agent is something unknown related to these factors. However, the results for control mothers seem to be in reasonable agreement with those found in another study in Sweden (Hardell et al. 2001).

Table 4. OR (95% CI) for cases with testicular cancer, seminoma, and nonseminoma, respectively.

|                | Seminoma | Nonseminoma |
|----------------|----------|-------------|
| Sum of PCBs    | 13/30    | 15/30       |
| HCB            | 14/30    | 21/30       |
| p,p'-DDE       | 14/30    | 20/30       |
| cis-Chlordane  | 12/29    | 22/29       |
| cis-Heptachlordane | 7/26     | 20/26       |
| cis-Chlordane  | 11/29    | 18/29       |
| trans-Nonachlordane | 11/30   | 16/30       |
| cis-Nonachlordane | 18/29 | 22/29       |
| Sum of chlordanes | 11/30 | 20/30       |

Table 5. Concentrations of organochlorine compounds (nanograms per gram lipid) in mothers of cases with testicular cancer and controls.

|                | No. | Mean | Median | Minimum | Maximum | p-Value* |
|----------------|-----|------|--------|---------|---------|----------|
| Case mothers   | Case mothers | | | | | |
| Control mothers| 43  | 859  | 792    | 236     | 2,114   | 0.0006   |
| Control mothers| 41  | 592  | 563    | 141     | 1,193   |          |
| HCB            | Case mothers | | | | | |
| Control mothers| 44  | 47   | 39     | 12      | 120     | 0.006    |
| Control mothers| 45  | 34   | 31     | 8.9     | 81      |          |
| p,p'-DDE       | Case mothers | | | | | |
| Control mothers| 44  | 566  | 315    | 109     | 3,339   | 0.48     |
| Control mothers| 45  | 428  | 324    | 51      | 1,431   |          |
| cis-Chlordane  | Case mothers | | | | | |
| Control mothers| 44  | 1.2  | 1.0    | 0.3     | 5.1     | 0.12     |
| Control mothers| 45  | 1.0  | 0.8    | 0.3     | 7.6     |          |
| cis-Heptachlordane | Case mothers | | | | | |
| Control mothers| 44  | 0.9  | 0.7    | 0.2     | 7.9     | 0.24     |
| Control mothers| 45  | 0.7  | 0.7    | 0.2     | 1.5     |          |
| Oxychlordane   | Case mothers | | | | | |
| Control mothers| 44  | 14   | 10     | 1.9     | 50      | 0.24     |
| Control mothers| 45  | 10   | 9.4    | 1.4     | 32      |          |
| MCB            | Case mothers | | | | | |
| Control mothers| 44  | 5.1  | 4.2    | 0.7     | 13      | 0.09     |
| Control mothers| 45  | 3.6  | 3.8    | 0.6     | 7.8     |          |
| trans-Nonachlordane | Case mothers | | | | | |
| Control mothers| 44  | 22   | 17     | 2.4     | 64      | 0.02     |
| Control mothers| 45  | 15   | 13     | 0.6     | 42      |          |
| cis-Nonachlordane | Case mothers | | | | | |
| Control mothers| 44  | 1.8  | 1.3    | 0.4     | 9.2     | 0.008    |
| Control mothers| 45  | 1.1  | 1.0    | 0.4     | 2.8     |          |
| Sum of chlordanes | Case mothers | | | | | |
| Control mothers| 44  | 46   | 34     | 14      | 131     | 0.04     |
| Control mothers| 45  | 32   | 31     | 5.8     | 76      |          |

*Wilcoxon p-value. *One case and four controls were not analyzed for certain PCB congeners because of technical reasons.
Collection of blood was made during the same period for cases and controls. In this way, any change over time of organochlorines in the population was eliminated. All blood was drawn before treatment of the cases with chemotherapy or radiotherapy to eliminate any potential influence of treatment on the results. When a case pair was recruited, a control subject was selected at random in the same age group (5-year intervals). Furthermore, as an inclusion criterion, the control mother was in the same age group as the respective case mother. The study was well balanced for age in the case and control series.

BMI might influence the concentration of organochlorines. Furthermore, the concentrations increase with age. All results were adjusted for BMI and age (Hardell et al. 2001).

No subject reported occupational exposure to the studied chemicals. In this study, only one type of chlordane, cis-nonachlordane, was significantly increased among the cases. Most other studied organochlorines showed some but not significant increases.

Interestingly, significantly increased concentrations were found among case mothers for the sum of PCBs, HCB, cis-nonachlordane, and the sum of chlordanes. Analysis according to the histopathology of the sons (seminoma or nonseminoma) yielded similar risk patterns. Seminoma and nonseminoma both start as carcinoma in situ (Skakkebæk et al. 1987). Epidemiological studies (Andersen et al. 1999; Möller 1988; Möller and Skakkebæk 1997; Skakkebæk 1987) and biological evidence (Jørgensen et al. 1995; Skakkebæk et al. 1987) indicate that carcinoma in situ starts during the fetal period. Thus, biologically it would be relevant to study concentrations of endocrine disruptors in the mothers.

The concentration of POPs in mothers’ milk reflects the body burden. Decreasing concentrations of certain organochlorines such as PCBs have been found in Swedish breast milk since the 1980s. The highest concentrations were found in early 1970s (Norström and Mörnryd 1998). Because the median age among the cases was 30 years, most of them were born during the period with high concentration in the population. Fetuses and nursing infants receive significant exposures to POPs as well as the largest body burdens (Hooper and McDonald 2000). Prenatal and lactation exposure appears to be an important source of the adverse health effects of POPs seen in infants, such as cognitive motor deficits (Patandin et al. 1999).

During lactation, the concentration of POPs decreases in the mother (Lindström and Lindström 1994), but the period when breast-feeding took place did not differ for cases and controls. Furthermore, total time of breast-feeding for all children was similar among case and control mothers. In contrast, higher concentrations of POPs give higher exposure during breast-feeding in spite of similar duration of breast-feeding. Because of the long half-life for the studied chemicals, it is postulated that the increased concentration among the case mothers indicates higher exposure during the fetal and postnatal period for cases than for controls. One explanation for the differences found would be if exposure to POPs, mainly through the food chain, differs later in life among case mothers.

In one study, neonates born to mothers who were active smokers had highest PCB and HCB concentrations compared with children of mothers exposed to second-hand smoke or nonsmoking mothers (Lackman et al. 2000). However, in our study, smoking habits in mothers did not change the results (data not shown).

Some POPs, such as PCBs, especially the hydroxylated metabolites, and chlordanes, have been postulated to be endocrine disruptors (Andersen et al. 1999; Andersson et al. 1999; Willingham and Crews 1999; Willingham et al. 2000). PCBs reverse gonadal sex in turtle (Bergeon et al. 1994), and abnormalities of reproductive development has been described in juvenile alligators living in a contaminated environment in Florida (Guillette et al. 1994, 1996); HCB has endocrine-disrupting properties (Colborn et al. 1993). In addition, p,p’-DDE has been postulated to be an environmental endocrine disruptor (Willingham and Crews 1999). In this study, no significant differences were found for p,p’-DDE.

In summary, according to current hypotheses, testicular cancer is initiated during the fetal period (Sharpe and Skakkebæk 1993; Skakkebæk et al. 1987, 2001). Our results show that the concentrations of certain POPs are higher in mothers to patients with testicular cancer, but the etiologic significance of this finding needs to be further explored.

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### Table 6. OR (95% CI) for mothers of cases with testicular cancer, all types combined.

| Compounds | Cases/controls | OR (95% CI) |
|-----------|---------------|-------------|
| Sum of PCBs | 34/20 | 3.8 (1.4–10) |
| HCB | 35/22 | 4.4 (1.7–12) |
| p,p’-DDE | 22/22 | 1.3 (0.5–3.0) |
| cis-Heptachlor | 27/21 | 2.1 (0.8–5.0) |
| cis-Chlordane | 22/15 | 2.5 (0.99–6.1) |
| Oxychlordane | 28/22 | 2.6 (0.9–7.1) |
| MCB | 25/22 | 1.3 (0.5–3.2) |
| trans-Nonachlordane | 34/41 | 4.1 (1.5–11) |
| cis-Nonachlordane | 32/22 | 3.1 (1.2–7.8) |
| Sum of chlordanes | 27/22 | 1.9 (0.7–5.0) |

### Table 7. OR and 95% CI for mothers of cases with testicular cancer, seminoma, and nonseminoma, respectively.

| Compounds | Seminoma (Cases/controls) | OR (95% CI) | Nonseminoma (Cases/controls) | OR (95% CI) |
|-----------|--------------------------|-------------|-----------------------------|-------------|
| Sum of PCBs | 11/20 | 3.1 (0.7–14) | 23/20 | 4.3 (1.3–14) |
| HCB | 10/22 | 2.1 (0.6–8.2) | 25/22 | 9.0 (2.4–33) |
| p,p’-DDE | 7/21 | 1.0 (0.3–3.4) | 15/22 | 1.4 (0.5–4.0) |
| cis-Heptachlor B | 9/21 | 3.2 (0.8–13) | 18/21 | 1.8 (0.7–4.7) |
| cis-Chlordane | 8/15 | 4.3 (1.1–17) | 14/15 | 2.1 (0.7–5.7) |
| Oxychlordane | 11/22 | 3.3 (0.7–16) | 17/22 | 2.5 (0.8–7.9) |
| MCB | 9/22 | 1.3 (0.4–5.0) | 16/22 | 1.3 (0.5–3.6) |
| trans-Nonachlordane | 10/22 | 1.9 (0.5–7.5) | 24/22 | 5.6 (1.7–19) |
| cis-Nonachlordane | 11/22 | 4.1 (0.9–18) | 21/22 | 2.8 (1.0–7.8) |
| Sum of chlordanes | 9/22 | 1.2 (0.3–4.8) | 17/22 | 0.9 (0.2–3.4) |

*All control mothers used for comparison. The median concentration of the chemicals in the mothers of controls was used as cutoff value; numbers greater than the median (expressed in nanograms per gram lipid) are shown for cases and controls, and adjustment was made for age and BMI. One case and four controls were not analyzed for certain PCB congeners because of technical reasons.
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