Urinary Porphyrin Excretion in Children is Associated with Exposure to Organochlorine Compounds

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BACKGROUND: Hexachlorobenzene (HCB) and other organochlorines induce porphyria cutanea tarda (PCT) in animal studies. Evidence in humans, however, is contradictory. In neonates and adults from a population historically highly exposed to HCB (Flix, Catalonia, Spain), no relation with PCT or with porphyrin excretion was found.

OBJECTIVES: We aimed to analyze the association between urinary porphyrin excretion and exposure to HCB and other organochlorinated compounds in children 4 years of age.

METHODS: Our birth cohort included all newborns from Flix and the five surrounding towns (where no airborne pollution occurred). Among the 68 children with porphyrins we measured in cord blood, 52 children 4 years of age provided blood to measure organochlorine compounds, hair for methylmercury, and urine for porphyrin excretion pattern.

RESULTS: Quantitative porphyrin excretion was within the normal values. However, total porphyrins, coproporphyrin I (CPI), and coproporphyrin III (CPIII) adjusted to creatinine excretion increased with increasing levels of HCB, 1,1-dichloro-2,2-bis(4-chlorophenyl)ethylene (p,p’-DDE), 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (p,p’-DDT), and polychlorinated biphenyl congener 153 (PCB-153). We found no association with methylmercury. When we fitted multiple pollutant models, p,p’-DDE had the strongest association. We found these associations in children from both Flix and other towns, and they were independent of breast-feeding and of organochlorine and porphyrin levels at birth.

CONCLUSION: HCB at current levels did not induce porphyria or increase uroporphyrins. However, the increase of urinary coproporphyrins suggests an incipient toxic effect of the organochlorines, especially for p,p’-DDE, on the hepatic heme-synthesis pathway that differs from the major effects seen in PCT.

KEY WORDS: coproporphyrins, DDE, DDT, HCB, methylmercury, PCB-153, porphyrina, uroporphyrins, Environ Health Perspect 116:1407–1410 (2008). doi:10.1289/ehp.11354 available via http://dx.doi.org/ [Online 5 June 2008]
liquid chromatography (Waters 474; Waters Corp., Milford, MA, USA) and fluorescence detection according to the method described elsewhere (To-Figuera et al. 2003). We quantified each porphyrin and isomer fraction (coproporphyrin I and III (CPI and CPIII), uroporphyrin I and III (UPI and UPIII), heptaporphyrin III (heptaIII), hexaporphyrin III (hexaIII), and pentaporphyrin III (pentaIII)) independently in urine and standardized to µmol/mol creatinine. We set a limit of detection (LOD) of 0.1 µmol/mol creatinine for each of the individual porphyrins in urine. We analyzed the creatinine concentration with a Bayer ADVIA 1650 analyzer (Bayer, Burladingen, Germany). We performed all porphyrin analyses at the Porphyria Unit, Biochemistry Service of the Hospital Clinic of Barcelona.

Analysis of organochlorine compounds. We extracted polychlorinated biphenyls (PCB congeners 118, 138, 153, and 180), HCB, β-hexachlorocyclohexane (β-HCH), 1-dichloro-2,2-bis(4-chlorophenyl)ethylene (p,p’-DDE), and 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (p,p’-DDT), in serum from blood collected both at 4 years of age and at birth, with n-hexane and blindly assayed the extracts with gas chromatography coupled to electron capture detection (Sala et al. 2001). We measured methylmercury using gas chromatography equipped with a cold-vapor atomic fluorescence spectrometry system (Montuori et al. 2006). We carried out all analyses at the Department of Environmental Chemistry at the Institute of Chemical and Environmental Research (IQAB-CSIC) in Barcelona.

Table 1. Urinary porphyrins, organochlorine compounds in serum, and methylmercury in hair of 4-year-old children from Ribera d’Ebre (n = 52).

| Compound | No. | Median (interquartile range) | Total porphyrins | UPI | CPI | CPIII |
|----------|-----|-----------------------------|------------------|-----|-----|-------|
| HCB (ng/mL) | 17 | 4.0 (2.5–8.1) | 2.2 (1.3–2.8) | 0.7 (0.2–1.1) | 1.7 (0.4–2.8) |
| < 0.78 | 17 | 4.0 (2.5–7.2) | 2.3 (1.3–2.7) | 0.5 (0.2–1.0) | 1.2 (0.5–2.7) |
| < 0.20 | 17 | 8.4 (3.4–23.3) | 1.7 (1.4–3.1) | 1.6 (0.7–3.5) | 3.8 (1.0–19.2)** |
| < 0.50 | 17 | 3.8 (2.2–5.7) | 1.6 (1.3–2.5) | 0.5 (0.2–1.5) | 1.2 (0.5–2.0) |
| < 0.01 (Kruskal–Wallis test). p = 52). | 17 | 18.8 (10.0–28.5) | 2.3 (1.5–3.0) | 1.5 (0.9–4.0) | 4.9 (1.0–18.2)* |
| > 0.10 | 17 | 13.7 (7.5–33.6)** | 2.2 (1.5–3.4) | 3.1 (0.9–5.6)** | 8.4 (2.6–23.8)** |
| > 0.50 | 17 | 4.0 (2.5–7.2) | 2.3 (1.3–2.7) | 0.5 (0.2–1.0) | 1.2 (0.5–2.7) |
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LOD: porphyrins, 0.1 µmol/mol creatinine; HCB, 0.3 ng/mL; PCBs, 0.1 ng/mL; HCB, p,p’-DDE, and p,p’-DDT, 0.001 ng/mL; methylmercury, 0.04 µg/g.

Table 2. Urinary UPI, CPI, and CPIII concentrations (µmol/mol creatinine) by organochlorine concentrations in serum and methylmercury in hair of 4-year-old children from Ribera d’Ebre.

| Compound | No. | Total porphyrins | UPI | CPI | CPIII |
|----------|-----|------------------|-----|-----|-------|
| HCB (ng/mL) | 17 | 4.0 (2.5–8.1) | 2.2 (1.3–2.8) | 0.7 (0.2–1.1) | 1.7 (0.4–2.8) |
| < 0.78 | 17 | 4.0 (2.5–7.2) | 2.3 (1.3–2.7) | 0.5 (0.2–1.0) | 1.2 (0.5–2.7) |
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Results

Table 1 summarizes the distribution for total porphyrins and the major individual excreted porphyrins. CPIII, UPI, and CPI were the major excreted porphyrins. We detected CPIII in all children, and UPI and CPI in 96%. We detected heptaIII in 25 children (48%) and pentaIII in two children (4%). All
values were within the normal range. Among the organochlorine compounds, HCB, \( p,p' \)-DDE, \( \beta \)-HCH, and PCB-153 showed the highest levels.

CPI and CPIII, as well as total porphyrins, increased with any increase of any organochlorine compound (Table 2). The association was statistically significant for the highest levels of \( p,p' \)-DDE, \( p,p' \)-DDT, and PCB-153 for CPI and CPIII, and \( \beta \)-HCH only for CPIII. UPI increased only with PCB-118. Methylmercury did not show any association.

In linear regression models, HCB, \( p,p' \)-DDE, \( p,p' \)-DDT, and PCB-153 also showed a statistically significant association with CPI and CPIII (Table 3). These associations remained unchanged after adjusting for the potential confounding variables in the -linear regression models, as well as after adjusting for organochlorine compounds at birth or porphyrins at birth (data not shown). Organochlorine compounds at birth were unrelated with the coproporphyrins measured at 4 years of age.

Table 3 also shows results from multi-pollutant models. These include more than one organochlorine compound, although organochlorine compounds showed high correlation coefficients among them (between 0.5 and 0.7). Nevertheless, the multi-pollutant models suggested a stronger association for total porphyrins (and for CPI and CPIII) with \( p,p' \)-DDE, after adjusting for HCB, \( \beta \)-HCH, and PCB-153. Adjustment for methylmercury did not show any change. The high collinearity between \( p,p' \)-DDE and \( p,p' \)-DDT (\( r = 0.89 \)) precluded any mutual adjustment.

Levels of porphyrins and HCB were higher in children from Flix than in children from the other towns, whereas levels of \( p,p' \)-DDE were slightly lower in the former. In addition, total porphyrin and \( p,p' \)-DDE levels were higher in breast-fed than in formula-fed children (Table 4). However, the association between \( p,p' \)-DDE and total porphyrins (as well as CPI and CPIII) was not influenced by location or breast-feeding (\( p \) for interaction > 0.30).

Discussion

The study concludes the research of the porphyrinogenic role of HCB in Flix, a village of 5,000 inhabitants with high atmospheric levels of HCB during the last decades of the 20th century (mean, 35 pg/m^3^ in 1991) (Grimalt et al. 1994). In 1994, a cross-sectional study in adults found high serum levels of HCB (mean, 36.7 ng/mL), the highest ever recorded in the general population (Sala et al. 1999a, 1999b). The evaluation of the urinary porphyrin excretion showed one case of subclinical PCT and five subjects with coproporphyrinuria among 604 subjects, exhibiting a prevalence that is close to expected (Herrero et al. 1999). The porphyrin profile of the highly exposed subjects (some with HCB levels > 1,000 ng/mL) was normal (Herrero et al. 1999). Thus, levels in adults were not high enough to trigger a significant alteration of the uroporphyrinogen decarboxylase activity. Two other findings were also observed among these subjects: a linear increase in \( \gamma \)-glutamyltransferase (Sala et al. 2001), and a decrease of coproporphyrins (Sunyer et al. 2002) with an increase in HCB levels. Both findings suggested a functional effect of HCB in the liver, although no mechanistic explanation for the latter finding could be established.

A further step was provided by the study of the effects of organochlorine compounds in all neonates born in 1997–1999. The neonate’s HCB burden depends on the mother’s level of contamination. In this cohort, the mothers from Flix had been living for a long time in this village, and the HCB concentrations found in neonatal cord blood and maternal serum from Flix subjects were still higher than for children and mothers from the surrounding towns. On the other hand, HCB for Flix subjects had decreased since 1994, probably because of an intervention in the factory (Ozalla et al. 2002). No major alteration in urinary porphyrin excretion was found, although infants were expected to be more susceptible, based on the observations of the Turkish epidemic. Thus, placental HCB transfer to the fetus may not reach the threshold for subclinical alteration in porphyrin excretion patterns.

The present study is the first assessing the porphyrinogenic effect of environmental chemicals in preschool children from the general population. HCB levels were much lower than in studies in adults carried out almost 10 years earlier. In general, all concentrations of organochlorine compounds were moderate. In fact, although HCB levels were still higher in children from Flix than in those from control towns, the levels were only 1.7 times higher, whereas 10 years before (in adults) the difference was 10 times. Again, no case of PCT was found. Levels and patterns of porphyrins were within the normal ranges (Minder and Schneider-Yin 1996), confirming that HCB concentrations at current levels are unable to inhibit uroporphyrinogen decarboxylase and cause clinical or subclinical porphyria.

However, coproporphyrin concentrations (and consequently total porphyrin levels) increased at higher levels of HCB, \( p,p' \)-DDE, \( p,p' \)-DDT, \( \beta \)-HCH, and PCB-153 (> 0.14 ng/mL) with an increase in HCB levels. This increase might be associated with the coexistence of high levels of HCB and \( p,p' \)-DDE, \( p,p' \)-DDT, and PCB-153 (> 0.14 ng/mL) in 2 of 5 neonates born in 1997–1999. The evaluation of the urinary porphyrin excretion showed one case of subclinical PCT and five subjects with coproporphyrinuria among 604 subjects, exhibiting a prevalence that is close to expected (Herrero et al. 1999). The porphyrin profile of the highly exposed subjects (some with HCB levels > 1,000 ng/mL) was normal (Herrero et al. 1999). Thus, levels in adults were not high enough to trigger a significant alteration of the uroporphyrinogen decarboxylase activity. Two other findings were also observed among these subjects: a linear increase in \( \gamma \)-glutamyltransferase (Sala et al. 2001), and a decrease of coproporphyrins (Sunyer et al. 2002) with an increase in HCB levels. Both findings suggested a functional effect of HCB in the liver, although no mechanistic explanation for the latter finding could be established.

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Although with a chelation agent that abated mercury phyrins were reduced after an intervention (Geier 2007). In the latter study, coproporphyrinogen oxidase inhibition (Doss et al. 2000; Horie et al. 1987). The analysis of multipollutant models suggests that the strongest association is with p,p'-DDE and PCB-153. These associations were not confounded by maternal smoking or alcohol intake during pregnancy, or by sex or body mass index. The increase of coproporphyrins, albeit without exceeding the normal urinary limits, suggests that the exposure to organochlorines may induce minor alterations in the heme-synthesis pathway, probably by mechanisms similar to those that lead to secondary coproporphyrinuria after exposure to chemicals such as vinyl chloride (Doss 1987) or alcohol (Doss et al. 2000). The mechanisms leading to secondary coproporphyrinuria associated with chemical exposure may involve different mechanisms, including increase of reactive oxygen species generation in the liver, prooxidation of coproporphyrinogens, and coproporphyrinogen oxidase inhibition (Doss et al. 2000; Horie et al. 1987).

Among the previous studies in human populations, only one shows an increase of coproporphyrins in workers highly exposed to HCB (Burns and Miller 1975), and two other studies show a relation with mercury. These last two concerned 38 dentists (Woods et al. 1993) and 71 autistic children (Geier and Geier 2007). In the latter study, coproporphyrins were reduced after an intervention with a chelation agent that abated mercury levels. The lack of association between mercury and porphyrins in the present cohort may be attributable to the moderate levels of this metal. Two older clinical studies in pediatric populations suggest a toxic effect of organochlorine compounds. One studied the survivors of the Taiwan maternal PCB contamination during pregnancy, in whom increased levels of total porphyrins were observed (Gladen et al. 1988), and the other studied children with diagnosed PCT who exhibited high levels of dioxins (Boyd et al. 1989). In contrast, no previous evidence of association between higher porphyrin levels and p,p'-DDE was reported. Furthermore, the increase of coproporphyrins in relation to childhood exposure but not in relation to in utero exposure probably reflects the short-term pattern of the studied metabolic effect. In conclusion, this study suggests that even though current levels of HCB in Flix may not be high enough to trigger PCT, the persistent organochlorine exposure at current levels in children from the general population may induce subtle toxic effects on the hepatic heme-synthesis pathway and the excretion of coproporphyrins different from the major effects seen in PCT. These findings indicate that detection of urinary porphyrin alteration may be a method for identifying functional early effects of environmental chemicals (Ng et al. 2005).

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