Gender dependent accumulation of dioxins in smokers
S Fierens, G Eppe, E De Pauw, A Bernard

Aims: To evaluate the contribution of tobacco smoking to dioxin accumulation.
Methods: Dioxin (17 PCDD/F) concentrations in fasting blood from 251 subjects (161 never smokers, 54 past smokers, and 36 current smokers) were quantified.
Results: Whereas serum dioxin concentrations of male smokers were on average 40% higher than those of non-smokers, in women, smoking was associated with significantly lower serum dioxin levels. A synergistic potentiation of dioxin metabolism by tobacco smoke in women is postulated to explain these paradoxical findings.
Conclusions: Current smoking is associated with gender dependent effects on dioxin body burden and is a potential source of confounding in human studies using blood dioxins as indicators of exposure.

Tobacco smoke contains a variety of polycyclic hydrocarbons, including dioxins (polychlorinated dibenzodioxins/dibenzo-furans). It has been estimated that smoking 20 cigarettes per day should lead to a dioxin intake almost equivalent to that from food (1–3 pg TEQ/kg bw/day), the major source of human exposure. However, studies that have measured dioxins in smokers did not find higher levels; some studies on breast milk even reported significantly lower values than in non-smokers. We show here that dioxin concentrations are affected by a gender-smoking interaction that could exert a confounding effect.

METHODS
Volunteers were recruited during a study conducted in order to estimate the environmental exposure to dioxins in different areas of Wallonia, Belgium. A total of 251 non-occupationally exposed participants, aged 21–80 years, were examined, including 36 current smokers, 54 past smokers (13 years on average since smoking cessation), and 161 never smokers. The proportions of subjects living within 2 km of an incinerator, the only environmental source found to affect dioxin body burden in this study, were not significantly different between the three smoking categories (33%, 37%, and 30% respectively; χ² = 0.82; p = 0.66). Information about smoking habits, dietary habits, anthropometric characteristics, residential history, and health status was obtained from a self-administered questionnaire. The volunteers provided approximately 200 ml of blood under fasting conditions in order to evaluate the body burden of dioxins. The seventeen 2,3,7,8-substituted polychlorinated dibenzodioxin/dibenzo-furan (PCDD/Fs) and four “dioxin-like” coplanar polychlorinated biphenyls (cPCBs no. 77, 81, 126, 169) congeners were quantified by gas chromatography-high resolution mass spectrometry (GC-HRMS) on the lipid fraction of serum. The results were reported per gram fat and expressed in toxic equivalents (TEQ).

RESULTS
When data from both sexes were combined, serum dioxin concentrations appeared virtually identical between current smokers, past smokers, and never smokers (geometric mean: 25.6, 25.6, and 25.7 pg TEQ/g fat, respectively; ANOVA: F = 0; p = 1). The analysis by gender, however, revealed that dioxin levels were significantly higher in male current smokers but lower in female current smokers (table 1). The same pattern of effects was observed with coplanar PCBs. Current smokers did not present any difference in age, body mass index (BMI), or animal fat intake, compared with never smokers, that could explain these discrepant variations, the decrease of dioxin levels observed in female smokers being on average associated with a higher animal fat intake. A stepwise multiple linear regression analysis testing possible predictors (smoking status, age, BMI, animal fat intake, residence around incinerator, fish or alcohol consumption, menopause, contraceptive pills, lactation) confirmed the increase of serum dioxin levels in male current smokers (partial r² = 0.038, slope = 0.14, p = 0.013) and the decrease in female current smokers (r² = 0.043, slope = −0.14, p = 0.006). As illustrated in fig 1, serum dioxin levels adjusted for age and other covariates were on average 39.4% higher in male current smokers and 27.5% lower in female current smokers than in the respective control groups of never smokers. A two way ANOVA on adjusted dioxin values showed a highly significant interaction between gender and smoking status (current smokers or not) (model: F = 5.81, p = 0.0008; interaction: F = 17.09, p < 0.0001).

DISCUSSION
The increase in dioxin body burden observed in male current smokers is in accordance with their higher intake of dioxins as predicted from their smoking habits. That past smokers of both sexes present normal levels is not really surprising since they have stopped smoking on average 13 years ago, a time...
Dioxins are known to be indicator of exposure. The potential source of confounding in human studies using tobacco smoke, this gender dependent effect of current smoking is a plausible explanation is a strong stimulation of dioxin metabolism by chemical induction of the Ah receptor, that could then be potent inducers of dioxin metabolism. Indeed, tobacco smoke contains compounds with affinity for the Ah receptor, and smoking is known to increase the expression of the Ah receptor. The most plausible explanation for the increased dioxin levels in male current smokers is that smoking is a risk factor for the development of dioxin metabolism by chemical induction.

**Table 1** Characteristics and dioxin concentrations of men and women according to their smoking status

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>56</td>
<td>105</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>51.9 (9.5)</td>
<td>51.9 (10.3)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>25.4 (24.5 to 26.5)</td>
<td>25.3 (24.4 to 26.2)</td>
</tr>
<tr>
<td><strong>Fat intake (g/wk)</strong></td>
<td>293 (255 to 337)</td>
<td>273 (208 to 360)</td>
</tr>
<tr>
<td><strong>Pack-years</strong></td>
<td>–</td>
<td>9.4 (5.9 to 15.1)</td>
</tr>
<tr>
<td><strong>Cigarettes/day</strong></td>
<td>–</td>
<td>22.6 (19.7 to 25.9)</td>
</tr>
</tbody>
</table>

**Dioxin concentrations in serum according to gender and smoking status**

<table>
<thead>
<tr>
<th><strong>Males</strong></th>
<th><strong>Females</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCDDs</strong></td>
<td>11.9 (10.0 to 14.0)</td>
</tr>
<tr>
<td><strong>PCDFs</strong></td>
<td>12.7 (10.8 to 14.9)</td>
</tr>
<tr>
<td><strong>Total PCDD/DFs</strong></td>
<td>23.5 (20.2 to 27.4)</td>
</tr>
<tr>
<td><strong>Coplanar PCBs</strong></td>
<td>7.2 (6.2 to 8.4)</td>
</tr>
</tbody>
</table>

**Figure 1** Dioxin concentrations in serum according to gender and smoking status. Dioxin values are adjusted for age, BMI, fat intake, and residence around incinerators in men; and in women for age and residence around incinerators. See table 1 for numbers of subjects in each category.

ACKNOWLEDGEMENTS

We thank the volunteers who provided us with blood samples. This work was supported by the Ministry of Environment of the Walloon Region and by the European Union. S Fierens is Research Fellow of the Brussels-Capital Region and A Bernard is Research Director of the National Fund for Scientific Research, Belgium.

**Authors’ affiliations**

S Fierens, A Bernard, Unit of Toxicology and Occupational Medicine, School of Public Health, Université catholique de Louvain, 30.54 Closet-Chapelle-aux-Champs, B-1200 Brussels, Belgium

G Eppe, E De Pauw, Mass Spectrometry Laboratory, University of Liège, Allée de la Chimie 3–Boc, Sart-Tilman B-4000 Liège, Belgium

Correspondence to: Professor A Bernard, Unit of Toxicology and Occupational Medicine, School of Public Health, Université catholique de Louvain, 30.54 Closet-Chapelle-aux-Champs, B-1200 Brussels, Belgium; Bernard@toxi.ucl.ac.be

Accepted 8 July 2004

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