Contribution of tobacco smoking to dioxin accumulation: opposite effects according to gender

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Introduction

Tobacco smoke contains a variety of polycyclic hydrocarbons including dioxins (polychlorinated dibenzodioxins/dibenzofurans). It has been estimated that smoking 20 cigarettes per day should lead to a dioxin intake almost equivalent to that from food (1 to 3 pg TEQ/kg bw/day), the major source of human exposure[1,2]. However, studies that have measured dioxins in smokers have found no increased levels, some of them even reporting significantly lower values than in non-smokers[3]. We show here that dioxins concentrations are affected by a gender-smoking interaction that could exert a confounding effect.

Methods

Volunteers were recruited during a population-based study conducted in different areas of Wallonia, Belgium. A total of 251 participants, aged 21-80 years, were examined, including 36 current smokers, 54 past smokers and 161 never smokers. Subjects in these three categories were comparable with respect to their place of residence (rural/urban/industrial). The proportions of subjects living in the vicinity of an incinerator, the only environmental source found to affect dioxin body burden in this study[4,5], were not significantly different between the three smoking categories (33%, 37% and 30% respectively; χ^2=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/dibenzofuran (PCDD/Fs) and four "dioxin-like", coplanar polychlorinated biphenyls (cPCBs n° 77; 81; 126; 169) congeners were quantified by gas chromatography – high resolution mass spectrometry (GC-HRMS) on the lipid fraction of serum[6]. The results were reported per gram fat and expressed in toxic equivalents (WHO-TEQ)[7].

Results

When data from both sexes are combined, concentrations of dioxins in serum appear 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 reveals that dioxin levels are significantly increased in male current smokers but decreased in female current smokers (table). The same pattern of effects is observed with coplanar PCBs but the increase in men is not significant. Current smokers did not present any difference in age, body mass index (BMI) or fat intake that could explain these discrepant variations, the lower dioxin levels in smoking female being even associated with a higher fat intake. A stepwise multiple linear regression analysis testing possible predictors (smoking status, age, BMI, fat intake, residence around incinerator, fish or alcohol consumption, menopause, contraceptive pills, length of breastfeeding period) confirms the increase of serum dioxin levels in male current smokers (partial r^2=0.038, slope=0.14, p=0.013) and the decrease in female current smokers (r^2=0.043, slope= -0.14, p=0.006). As illustrated in figure 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 shows also 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).

Table 1. Characteristics and dioxin concentrations according to smoking status

Men (n=112)			
Smoking status	**Never**	**Past**	**Current**
Number	56	37	19
Age (years)	51.9 (9.5)	52.9 (9.9)	53.3 (7.5)
BMI (kg/m²)	25.4 [24.5-26.5]	27.3 [26.4-28.4]*	26.3 [24.9-27.9]
Fat intake (g/week)	293 [255-337]	272 [230-322]	273 [208-360]
Pack-years	—	20.4 [15.3-27.1]	18.8 [11.6-30.5]
Cigarettes / day	—	22.6 [19.7-25.9]	11.3 [7.2-17.7]*
Dioxin and cPCBs concentrations (pg TEQ / g fat)			
PCDDs	11.9 [10.0-14.0]	12.7 [10.1-16.0]	17.7 [14.1-22.2]*
PCDFs	11.4 [9.9-13.3]	12.7 [10.8-14.9]	15.4 [12.4-19.2]
Total PCDD/Fs	23.5 [20.2-27.4]	25.9 [21.8-30.9]	33.4 [26.9-41.4]*
Coplanar PCBs	7.2 [6.2-8.4]	7.6 [6.2-9.2]	8.7 [6.4-12.0]
Women (n=139)			
Smoking status	**Never**	**Past**	**Current**
Number	105	17	17
Age (years)	51.9 (10.3)	47.7 (8.09)	50.1 (10.7)
BMI (kg/m²)	25.3 [24.4-26.2]	26.2 [24.2-28.7]	24.3 [22.5-26.4]
Fat intake (g/week)	241 [221-263]	282 [232-344]	324 [266-394]*
Pack-years	—	9.4 [5.9-15.1]	13.1 [7.5-22.8]
Cigarettes / day	—	13.8 [10.3-18.5]	10.5 [7.5-14.8]
Dioxin and cPCBs concentrations (pg TEQ / g fat)			
PCDDs	13.9 [12.6-15.5]	13.3 [10.8-16.3]	9.3 [6.2-14.1]*
PCDFs	12.8 [11.6-14.1]	11.4 [8.9-14.6]	9.4 [7.2-12.3]*
Total PCDD/Fs	27.0 [24.5-29.7]	24.8 [19.9-31.0]	19.1 [13.8-26.3]*
Coplanar PCBs	7.8 [7.0-8.8]	6.5 [4.7-9.0]	5.1 [3.5-7.4]*

Data are geometric mean [95% CI] except age (arithmetic mean [SD]) and BMI (harmonic mean [95% CI]). *$p<0.05$ for differences with never smokers (past smokers in case of tobacco consumption) by gender.

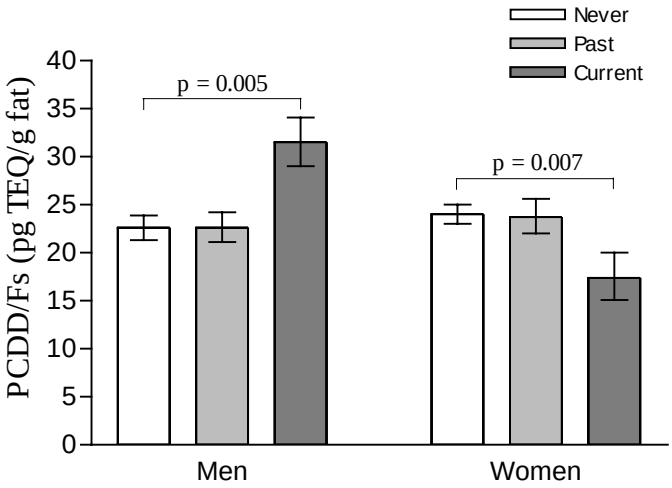

Figure 1. Dioxin concentrations in serum according to gender and smoking status. Data are geometric means (± SE). Values are adjusted for age, BMI, fat intake and residence around incinerators in men and for age and residence around incinerators in women. See Table for numbers of subjects in each category.

An analysis of the congeners profiles shows also sex-dependent alterations in the patterns between current smokers and never smokers (figure 2). In men, the most pronounced increases are found with the PeCDD and the 2,3,4,7,8-PeCDF, which are precisely the major contributors to the total TEQ activity. The PCB-126 and especially the PCB-169 are also increased. In women, the different congeners are also unequally affected by current smoking. The higher chlorinated PCDDs and the PCB-126 show the greatest decreases followed by the PCDFs (figure 2.B).

Discussion

The increased dioxin body burden observed in male current smokers is in accordance with their higher intake of dioxins as predicted from their smoking habits.[1] 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 sufficient for their dioxin body burden to re-equilibrate with that of never smokers. By contrast, the significant decrease of dioxin levels in female current smokers as opposed to the increase in male smokers is a quite unexpected finding. The most plausible explanation is a strong stimulation of dioxin biotransformation by polycyclic aromatic hydrocarbons (PAHs) or other chemicals contained in tobacco smoke. Indeed, tobacco smoke contains compounds with affinity for the Ah-receptor, that could then be potent inducers of cytochrome P450 enzymes[8,9]. The reason why this induction which proceeds through the Ah-receptor would manifest mainly in women is still unclear. A possible mechanism could involve the recently demonstrated cross-talk between the Ah-receptor and estrogen-mediated signalling pathways, a co-operation between receptors that could lead in women to a synergistic potentiation

of dioxin metabolism by chemical compounds of tobacco smoke[10]. Independently of its mechanism, this gender-dependent effect of current smoking is a potential source of confounding in human studies using blood dioxins as indicator of exposure.

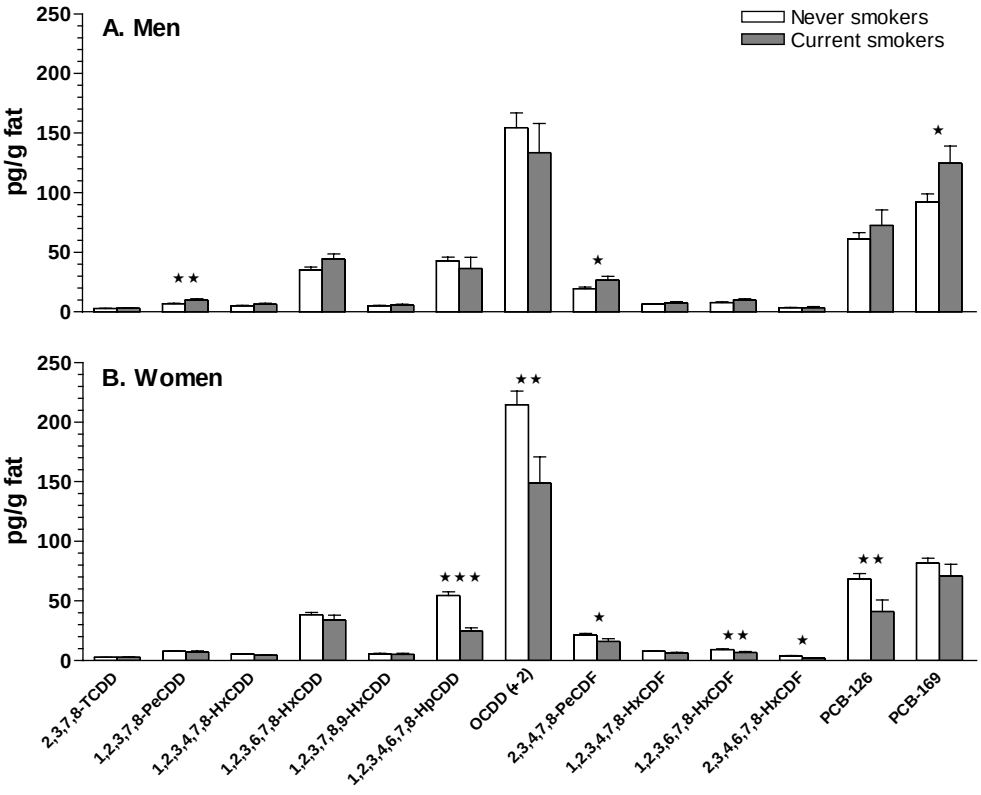

Figure 2. Congener profiles according to gender and smoking status.
Data are geometric means (+SE). Only congeners with more than 50% of values above limit of quantification were represented. Values for OCDD have been divided by 2. Differences between current smokers and never smokers were tested by t-tests for each congener. *p<0.05; **p<0.01 and ***p<0.0001.

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References

1. Muto H. and Takizawa Y. (1989) *Archives of Environmental Health* 44, 171-174.
2. Aoyama T., Ikeda K., Takatori A., and Obal T. (2003) *Organohalogen Compd.* 65, 321-324.
3. Furst P., Furst C., and Wilmers K. (1992) *Chemosphere* 25, 1029-1038.
4. Fierens S., Mairesse H., Focant J.-F., Eppe G., De Pauw E., and Bernard A. (2002) *Organohalogen Compd.* 55, 243-245.
5. Fierens S., Mairesse H., Hermans C., Bernard A., Eppe G., Focant J. F., and De Pauw E. (2003) *Journal of Toxicology and Environmental Health-Part A* 66, 1287-1293.
6. Focant J. F. and De Pauw E. (2002) *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences* 776, 199-212.
7. Van den Berg M., Birnbaum L., Bosveld A. T., Brunstrom B., Cook P., Feeley M., Giesy J. P., Hanberg A., Hasegawa R., Kennedy S. W., Kubiak T., Larsen J. C., van Leeuwen F. X., Liem A. K., Nolt C., Peterson R. E., Poellinger L., Safe S., Schrenk D., Tillitt D., Tysklind M., Younes M., Waern F., and Zacharewski T. (1998) *Environ.Health Perspect.* 106, 775-792.
8. Bao H. F., Vepakomma M., and Sarkar M. A. (2002) *Journal of Steroid Biochemistry and Molecular Biology* 81, 37-45.
9. Lofroth G. and Rannug A. (1988) *Toxicol.Lett.* 42, 131-136.
10. Ohtake F., Takeyama K., Matsumoto T., Kitagawa H., Yamamoto Y., Nohara K., Tohyama C., Krust A., Mimura J., Chambon P., Yanagisawa J., Fujii-Kuriyama Y., and Kato S. (2003) *Nature* 423, 545-550.