Temporal trends in human exposure to PCDD/Fs: A link with testicular cancer incidence rates?

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Introduction

Examination of medical surveillance data from many countries, including the UK, confirms that male reproductive health is deteriorating. Reproductive abnormalities such as cryptorchidism and hypospadias and cancers of the testis, prostate and breast are increasing and evidence from many developed countries suggests that semen quality is also deteriorating. Even accounting for improvements in medical detection and diagnostic techniques, the reason for such detrimental changes is unclear and it has been suggested that exposure to chemicals capable of disrupting the human endocrine system may be important risk factors (*inter alia* Toppari[1]). This paper examines the link between temporal trends of exposure to PCDD/Fs and temporal trends in testicular cancer.

We have focused on PCDD/Fs as they are strongly suspected to interfere with human endocrine systems. Animal studies have demonstrated that PCDD/Fs can have profound effects on mammalian reproductive systems, including effects on the testis[2-5]. The incidence of testicular cancer has steadily risen over the last 20-30 years and we have examined the link with human exposure. For the purpose of this study, the major route of human exposure was considered to be consumption of food derived from the agricultural food chain.

Materials and Methods

In order to estimate temporal trends in exposure to PCDD/Fs from the agricultural food-chain the following methodology was employed. Retrospective measurements of PCDD/Fs in archived soil and herbage from the Rothamsted Field Experiment[6,7] were used as source data in a mathematical model describing grass/soil to animal transfer; measurements of PCDD/Fs concentrations in air not being available prior to 1980. The model used is partly based on the air-to-beef food chain model developed by Lorber et al[8] but has been extended to predict transfer to milk, eggs, poultry and below-ground food crops; exposure via the consumption of fish was not considered.. A detailed description of the design and structure of the model is given elsewhere[9]. In order to validate the model, contemporary measurements of PCDD/F in food by MAFF were used as comparison data[10-11]. Current and temporal trends in dietary intakes of PCDD/Fs in a range of food-stuffs were then estimated for an average UK consumer using food consumption data from a number of dietary and nutritional surveys of British adults[12]. The average intake of PCDD/Fs from each of the food groups was calculated by multiplying the predicted concentration in that food group by the daily amount of that food group eaten by an average adult consumer in the U.K. for that particular time period. Our predicted trend in PCDD/F exposure took into account temporal changes in dietary consumption patterns that could influence dietary exposure.

Results and Discussion

Temporal trends in PCDD/Fs concentrations in foodstuffs and human exposure

The model proved reasonably successful in predicting the concentration of PCDD/Fs in a variety of foodstuffs (Table 1) and we derived temporal trends in daily dietary intake for a 70 kg adult over the period 1941-1990. The predicted temporal trend for daily dietary exposure indicates that exposure peaked at 4.6 pg I-TEQ/kg bodyweight in the early to mid 1960s followed by a second peak around the mid 1970s, since when exposure has steadily declined (Figure 1). Our predictions of contemporary dietary intakes correlate closely with estimated dietary intakes based on actual measurements; *e.g.* for the period 1986-90, the model predicts a dietary intake of 73 pg I-TEQ/person/day, compared with an estimated dietary intake for 1992 of 88 pg I-TEQ/person/day (which includes fish intake)[10,11].

This trend reflects known changes in dietary habits over this period, most notably the substantial drop in the amount of fat consumed in the UK[12] and known changes in PCDD/F concentrations in the environment. Data from sediment cores and archived soil and herbage samples indicate that PCDD/F concentrations in the environment peaked in the 1960s/70s and have steadily declined since (*inter alia* Jones et al[13]). This exposure trend is also consistent with those reported elsewhere. Pinsky and Lorber modelled past human exposure in the USA to 2,3,7,8-TCDD using a pharmacokinetic model fitted to age related body-burden data, and reported that human exposure peaked in the late 1960s and early 1970s[14].

Table 1. Comparison of observed and predicted PCDD/F concentrations in a range of foodstuffs (ng TEQ/kg freshweight). Observed values taken from MAFF[10,11].

Year	Foodstuff	Observed (O)	Predicted (P)	P/O Ratio
1981-85	Carcase meat	0.49	0.303	0.62
	Poultry	0.50	0.596	1.19
	Oils and fats	1.26	1.72	1.36
	Eggs	0.92	0.367	0.40
	Milk	0.16	0.109	0.68
	Milk products	1.2	1.11	0.93
1988-91	Carcase meat	0.26	0.15	0.58
	Poultry	0.29	0.257	0.89
	Oils and fats	0.41	0.653	1.59
	Eggs	0.16	0.141	0.88
	Milk (rural)	0.05	0.040	0.80

Comparison with temporal trends in testicular cancer incidence in the UK

While the rate of testicular cancer in the UK has increased significantly over the last 20 years, dietary exposure to PCDD/Fs has declined from the mid to late 1970s onwards (Figure 1); a relationship suggesting that adult exposure to PCDD/Fs is not related to testicular cancer, and confirmed by the fact that linear regression of temporal trends in our estimates of adult exposure with those in testicular cancer incidence did not reveal any significant positive correlation. This finding is unsurprising as the available evidence suggests that most testicular cancers are initiated in early life; a period when the foetus and young infant are thought particularly sensitive to endocrine disruption. Early life exposure was defined as *in utero* exposure and exposure until the age of 1 year and was considered to be equivalent to that of an adult during the same period. While this is probably an underestimate - especially for breast fed infants - the trend and not the exact

exposure level is sufficient for the purposes of this preliminary investigation. Given that the incidence of testicular cancer peaks at around 25 to 35 years, we assumed a mean age at diagnosis of 30 years. Based on this assumption and our predicted temporal trend in adult dietary exposure, it was possible to examine the relationship between temporal trends in early life exposure and testicular cancer incidence. For example, early life exposure for a 30 year old adult in 1996, was taken to equal our predicted exposure estimate for 1966. Our analysis focused on testicular cancer incidence in the West Midlands Region over the period 1982 to 1996[15]. Figure 2 reveals a positive correlation between testicular cancer incidence and predicted early life exposure 30 years previous. This relationship is statistically significant and suggests that early life exposure to PCDD/Fs may be linked with an increased risk of testicular cancer in later life (Pearson's correlation coefficient = 0.961 (P=0.000)).

It must be emphasized that this apparent relationship is highly tentative and could simply be an artifact of the time periods examined. However, the wide range of male reproductive problems (including testicular cancers) reported in the offspring of women given the synthetic oestrogen diethylstilbestrol (DES) is evidence both of the profound effects of endocrine disruption and the sensitivity of exposure in early life. Furthermore, a known risk factor for testicular cancer, cryptorchidism (failure of the testis to descend), is reported to be associated with low maternal testosterone levels during pregnancy[16]. Finally recent evidence suggests that the risk of testicular cancer in humans may be associated with low fertility and developmental urogenital abnormalities; suggesting a common mechanistic factor may be involved[3,17,18].

Conclusion

This paper predicts temporal trends in human dietary exposure to PCDD/Fs through the terrestrial food-chain from 1941 to 1990. This trend indicates that dietary exposure peaked around the 1960s/70s and has declined since. Using this trend, we have examined whether a link exists between human exposure to PCDD/Fs and incidence of testicular cancer. Our initial work indicates that early-life but not adult exposure may result in an increased risk of testicular cancer in later life. More work is clearly warranted to examine this link and to improve predictions of past human exposure to PCDD/Fs.

References

[1]Toppari J et al; *Environ. Health. Perspect.* **1996**, 104 (Suppl 4), 741
[2]Faqi AS, Dalsenter PR, Merker H-J, Chahoud I; *Toxicol. Appl. Pharmacol.* **1998**, 150, 383
[3]Sommer RJ, Ippolito DL, Peterson RE; *Toxicol. Appl. Pharmacol.* **1996**, 140, 146
[4]Malby TA, Moore RW, Peterson RE; *Toxicol. Appl. Pharmacol.* **1992**, 114, 97
[5]Malby TA et al; *Toxicol. Appl. Pharmacol.* **1992**, 114, 118
[6]Kjeller LO, Jones KC, Johnston AE, Rappe C; *Environ. Sci. Technol.* **1996**, 30, 1398
[7]Kjeller LO, Jones KC, Johnston AE, Rappe C; *Environ. Sci. Technol.* **1991**, 25, 1619
[8]Lorber M et al; *Sci. Total. Environ.* **1994**, 156, 39
[9]Harrad SJ, Smith DJT; *Chemosphere.* **1997**, 34, 1723
[10]MAFF. Food Surveillance Paper No.31. HMSO, **1992**, ISBN 01-1242-926-2.
[11]MAFF. Food Surveillance Information Sheet No. 71, **1995**.
[12]MAFF. Household Food Consumption and Expenditure 1990. HMSO, **1991**.
[13]Alcock RE, Jones KC; *Environ. Sci. Technol.* **1996**, 30, 3133
[14]Pinsky PF, Lorber MN; *J Exp. Anal. Environ. Epid*. **1998**, 8, 187

[15]West Midlands Cancer Intelligence Unit, Public Health, University of Birmingham, **1999**.
[16]Key TJA et al. *Brit. J. Cancer.* **1996**, 73, 698
[17]Møller H, Skakkebæk NE; *Brit. Med. J.* **1999**, 318, 559
[18]United Kingdom Testicular Cancer Study Group; *Brit. Med. J.* **1994**, 308, 1393

Figure 1: Predicted temporal trend in daily dietary exposure (pg I-TEQ/kg bodyweight) from the terrestrial food-chain for a 70 kg adult

Figure 2. Relationship between testicular cancer incidence rate and predicted early life exposure (assuming mean age at diagnosis of 30 years). Pearson correlation = 0.961.