

# This is a draft paper for discussion. It should not be quoted, cited or reproduced.

Draft

CC/04/2

## COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT

### Prostate Cancer: Additional data and 1<sup>st</sup> draft statement.

#### Introduction

1. The Committee considered an overview paper from the DH Toxicology unit at the November 2003 meeting.  
(<http://www.doh.gov.uk/pdfs/annex1cc0335.pdf>)
2. Members asked for additional information from one paper on the effects of cadmium on the regulation of AR gene expression and activity and for information from the HSE review of occupation and prostate cancer particularly with respect to farm workers and pesticide applicators.  
([http://www.hse.gov.uk/research/crr\\_pdf/1998/CRR98191.pdf](http://www.hse.gov.uk/research/crr_pdf/1998/CRR98191.pdf)).
3. In addition one further cancer mortality study has also been retrieved.
4. A 1<sup>st</sup> draft statement is also appended for members consideration.

#### *Further information on cadmium (Annex 1)*

5. The available epidemiology suggested that there is no convincing evidence that occupational exposure to cadmium is associated with cancer of the prostate. The finding of adenocarcinoma of the prostate following direct injection into the prostate of rats was considered to be of very limited relevance to human exposure.
6. Martin MB and colleagues (Endocrinology, 143, 263-275, 2002) undertook a set of in-vitro experiments in human prostate cancer cells where a number of changes were reported to be mediated by cadmium binding to the AR receptor and were consistent with an androgenic action (e.g. cell proliferation accompanied by reduction in AR protein and mRNA levels, increased expression of prostate specific antigen and homeobox gene NKX 3.1. Some of the effects noted in these studies were identified using concentrations  $10^{-10}$ M cadmium chloride. effects were blocked by co-administration of an antiandrogen (cyproterone acetate or hydroxflutamide). Further evidence of AR binding and effects were documented in studies using mouse L cells containing a MMTV luciferase reported gene ( $10^{-6}$ M cadmium chloride) and in COS-1 cells transfected with wild type AR and an MMTV-CAT reporter gene ( $10^{-12}$ M cadmium chloride). In further studied cadmium chloride ( $10^{-6}$ M) activated a chimeric receptor containings DNA binding region for yeast transcription faqctor GAL4. No evidence of binding

## This is a draft paper for discussion. It should not be quoted, cited or reproduced.

was found using a mutant AR receptor. The  $K_d$  for cadmium binding to AR from human LNCaP cells was  $1.19 \pm 0.55 \times 10^{-10} M$ .

7. The authors also undertook in-vivo experiments in castrated male wistar rats of C57BL/6 TgN mice (groups of 6-8 animals) given intraperitoneal doses of cadmium chloride (10 ug/kg or 2x10ug/kg over 2 days). Prostate weight were determined on day 10. A number of groups were also given anti-androgen (50 mg/ kg i.p. CPA) for 10 days before determining prostate weight. A single dose of cadmium chloride induced a 1.61 fold and 1.43 fold increase in prostate and seminal vesicle wet weight respectively (statistically significant). Administration of two doses of cadmium chloride resulted in a 1.97 and 1.65 fold increase in prostate and seminal vesicle wet weight respectively. Administration of anti-androgen abolished these effects.
8. Overall the authors provided evidence that absorbed systemically available cadmium may interact with the AR receptor.

### *Additional data epidemiology*

#### Farmers/Farm workers and pesticides

9. Extracts from the HSE review of occupations are enclosed as Annex 2 to this paper. In respect of framers/farm workers the HSE review recommends continued monitoring. The review notes that relative risk for increased mortality from prostate cancer is elevated among farmers/farm workers but overall cancer mortality is not increased in this group. The HSE review cites the retrospective mrtality study of canadian farmers as providing a study of sufficient size to assess specific practices. The hypothesis relating to herbicides was noted in this study.
10. Members will be aware that three meta- analysis studies were cited in the information provided to the November 2003 meeting.
  - a. Acquavella J et al Ann Epidemiol vol 8, 64-74, 1998. Meta-analysis of 37 studies published through to 31 December 1994 (16 Follow-up, 11 PMR, 9 case-control, 1 other). (54% USE, 43% Europe, 2.7% New Zealand). An overall RR based on 30 studies of 1.07 (95% CI 1.02-1.13). The authors reported an interaction for study design and geographical location. Overall the authors didn't conclude a significant association existed. (Data from follow-up studies RR 0.95 95% CI 0.93-0.98), from PMR (RR 1.12, 1.08-1.18), case-control 1.21 95% CI 1.15-1.28). (Authors based much of their work on an earlier meta-analysis, Blair et al Scan J Work Env health, 18, 209-215, 1992, which based on 18 studies had reported an overall estimate of 1.09 (95% CI 1..04-1.15) which had been considered significant).

**This is a draft paper for discussion. It should not be quoted, cited or reproduced.**

- b. Keller-Bryne JE et al Am J Ind Med vol 31, 580-586, 1997). The estimated relative risk based on 24 studies was 1.12 (95% CI 1.01-1.24). From retrospective studies (1.29 95% CI 1.10-1.51 and from PMR studies 0.93 (0.77-1.11).
  - c. Maele-Fabry G Van Occ Environ Med vol 60, 634-642, 2003. Authors noted three previous studies had covered literature up to 1995 and considered the data suggested a slightly increased relative risk. Current study covered studies published from 1995-2001. Overall RR was 1.13 (95%CI 1.04-1.22). based on 25 estimates from 22 studies. However this estimate is for ALL occupations not just farmer where pesticides were used. Subdivision by occupation revealed a RR for farmers of 0.97 (95%CI 0.92-1.03) and 1.64 (95% CI 1.13-2.38) for pesticide applicators. Major sources of heterogeneity were geographical location, study design and healthy worker effect.
11. Overall the data support the conclusion reached in 1998 in the paper prepared for HSE that continued monitoring is appropriate but do not clearly identify farmers/farm workers as occupational group with elevated risk of prostate cancer. The paper prepared for HSE makes a specific citation of the Morrison H et al study in support of this conclusion. This paper is appended as part of Annex 2.
12. The review prepared for HSE also suggests that exposure to pesticides may be a potential risk factor but are not definitive enough to identify a category of pesticide or particular applications which might pose a risk. The relevant section from the HSE review is also appended as part of Annex 2. This supports the view that no definitive conclusions can be reached.
13. Members are asked to consider these suggested conclusions

*Additional information on evaluation of pesticide exposure by use of biomonitoring approaches. (Ritchie Annals of Epidemiology, 13 (8), 571-2, 2003.)*

14. Members were informed at the November 2003 meeting that there was some published information which attempted to correlate estimated exposure of farmers/farm workers to pesticides derived from questionnaires, and biomonitoring data was available; this had not been cited in the DH Toxicology unit report. A copy of this information (available as an abstract only) has been appended at the end of Annex 2 largely for members information.

Vitamin supplement use

15. At the November 2003 meeting, it was thought unlikely that there were many individuals in the U.K. regularly consuming 100 mg zinc/day

**This is a draft paper for discussion. It should not be quoted, cited or reproduced.**

(as supplements). Members asked whether there would be sufficient numbers of individuals consuming such high levels of dietary supplements containing zinc in the EPIC cohort (European Prospective Investigation of Cancer) and asked the secretariat to respond to this query. Information from the EPIC-Norfolk cohort (for first 1860 individuals entering the cohort in 1993/4) reported that 5% of subjects were consuming zinc supplements (the intake of zinc from supplements was 4.9(4.1) mean(SD) (mg/d)). Thus the number of individuals consuming above 50 mg/day as supplements is likely to be very small suggesting that it would not be possible to identify sufficient individuals for study using the EPIC cohort.

16. This information is reflected in the wording of the draft statement.

**Draft statement**

17. This is appended as Annex 3. The format follows the layout of the DH Toxicology review. Members are asked for comments.

**Secretariat February 2004**