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DRAFT

CC/03/35

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

**REVIEW OF PROSTATE CANCER: DH TOXICOLOGY UNIT REVIEW
COVERING DISCUSSION PAPER**

Introduction

1. The Committee reviewed a SAHSU (Small Area Statistics Unit) study on geographical variation in the incidence of prostate cancer at the June 2002 meeting. (Jarup *et al In J of Cancer vol 97*, 695-699, 2002. Members asked whether there was any evidence for a significant variation of chemical exposure throughout the UK. The committee agreed that the study had been adequately performed and that no evidence for significant geographical variation in prostate cancer incidence had been produced. However, members were aware of evidence for an increasing trend. This in part, might be due to improved diagnoses and registration. It was felt that it was appropriate and timely to consider the evidence with regard to potential chemical induction of prostate cancer.
2. The DH Toxicology unit were asked to provide an overview paper for the COC to consider. The appended paper (Annex 1) is intended to provide members with background information on all aspects of prostate cancer epidemiology, investigations regarding aetiology and possible chemical exposures which may be associated with prostate cancer. The conclusions of the review are presented below.

Conclusions of DH Toxicology Unit review

3. A The incidence of Prostate Cancer (PC) varies widely around the world. Gradual increases in incidence have occurred in many countries since the 1960s, with larger increases following the introduction of diagnostic PSA screening. Survival rates have improved in recent decades, possibly as a result of earlier diagnosis. Mortality rates have also shown a slight decrease recently. It is thought that this is unlikely to be due, in greater part, to earlier detection, given the slow rate of development of the disease.

B Well-established indicators of risk for PC are age and family history. Incidence also varies widely depending on ethnicity/country of residence.

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C There is currently no agreement about the involvement of other factors in the aetiology of PC. Credible hypotheses that have been proposed involve hormonal patterns and dietary practices.

D Farming has been the most consistent occupational risk factor for PC, although the majority of studies have not looked at specific risk factors for farmers and farm-related workers. There is no substantive evidence for an association of other occupations with increased risk of PC.

E A recent assessment by IPCS noted that the evidence for a link to herbicide or PAH exposure is weak, the mechanism is unknown and more research is needed. (No conclusions have been drawn with regard to PAHs in this overview.). IPCS also concluded that studies on PCB, TCDD and DDT exposures showed no association with increased PC. Data from epidemiological studies of cadmium and PC are inconsistent.

F Cadmium is one of the few chemicals which has been associated with increased PC risk in animals, but the relevance of tumours in the studies is uncertain. Few other chemicals have been identified that can induce PC in 2-year animal bioassay studies. Most of these chemicals are genotoxic carcinogens, and chronic treatment with T is also required to produce a high carcinoma incidence. Transgenic mouse models for PC are being developed and these will allow for the study of hormone-responsive elements and the effects of chemicals on the multistage progression of PC to be evaluated. Future studies using these models may provide additional information on the aetiology of PC.

Questions for COC

4. A number of areas for further discussion are prompted by the review. A brief overview of the structure/function of the prostate gland has been appended as Annex 2 (abstracted from the Oxford Textbook of pathology volume 2a, 1992 edition). In addition the relevant section from the COMA report on diet and cancer has been appended as Annex 3. A relatively small number of supporting published papers cited in the DH Toxicology Unit review have been appended as Annexes 4-6. It is hoped that the information in the review and appended papers is sufficient for members to consider the suggested conclusions/questions. It is hoped that papers designed to answer specific comments/requests from COC along with a draft statement could be produced for the March 2003 COC meeting.

Prostate Cancer Trends

5. Do Members agree that the introduction of PSA testing and better ascertainment of prostate cancer during surgical intervention for benign

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prostate may account for a large proportion in the increasing trend in prostate cancer incidence? (pages 1-4 of DH Tox Unit review.)

Dietary Factors

6. Members are asked to consider the new results published from approximately 1996 onwards (and summarised on page 8 and in table 1 of the DH Toxicology Unit paper) in the light of the review undertaken by the COMA diet and cancer working group. Overall it is suggested that the new studies are consistent with the conclusions reached by the COMA working group (Annex 3). Do Members agree?

[Suggestions for further work on dietary factors would be outside the terms of reference for COC. The Scientific Advisory Committee on Nutrition (SACN) is responsible for advice on nutrition.]

Exogenous Chemicals: Cadmium

7. Members are asked to consider the DH Toxicology Unit review pages 10-12 and the appended paper from Waalkes MP Journal of Inorganic Biochemistry volume, 241-244, 2000. (Annex 4) Overall it is 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 is of very limited relevance to human exposure. Do Members agree?

Exogenous chemicals: Zinc (Dietary Supplement use)

8. Members are asked to consider the new paper by Leitzman M and colleagues (J National Cancer Institute, volume 95, 1004-1007, 2003, Annex 5) and the review information in the DH Toxicology Unit paper pages 13-14). Do Members consider that further work on zinc is warranted at this point in time?

Exogenous chemicals: potential endocrine disrupting chemicals including pesticides

9. Members are asked to consider the information in the DH Tox Unit on pages 12-13. Does the data support any further work in this area at this point in time? (See also question in paragraph 10 relating to pesticide applicators below)

Exogenous Factors: Occupational studies of Farm works and pesticide applicators.

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10. Members are asked to consider the information in the DH Toxicology Unit review on pages 14-17. In addition two systematic review are appended (Annex 6). These reports are inconclusive. A further recent systematic review which post-dates the DH Toxicology Unit review is appended to CC/03/36 (Van Maele-Farby G and Willems PL Occupational and Environmental Medicine volume 60, 634-642, 2003). This latter study examined pesticide applicators and reviewed studies published between 1995-2001. There was evidence of a small association between occupational application of pesticides and prostate cancer but the authors did not consider exposure to pesticides to be an independent risk factor for prostate cancer. The authors noted the that the study was limited by the paucity of exposure data to pesticides and called for better data on exposure. Overall it is suggested that there is no conclusive evidence to suggest that pesticide exposure is associated with prostate cancer. Do members agree?

Secretariat September 2003