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**TOX/2006/1
CC/06/1**

**COMMITTEES ON TOXICITY AND CARCINOGENICITY OF CHEMICALS
IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT.**

**ROYAL COMMISSION ON ENVIRONMENTAL POLLUTION: CROP
SPRAYING AND THE HEALTH OF RESIDENTS AND BYSTANDERS**

Additional note for COC members.

1. The COC has been asked to comment on the RCEP report on crop spraying and the health of residents and bystanders. A cover summary has been produced to assist in focusing the discussion on those areas relevant to COT/COC consideration.

2. COC members may wish to note that the key references to cancer are contained in paras 2.20-2.34 of chapter 2 of the RCEP report (Annex 1 to CC/06/1). Members will recall that COT and COC epidemiologists were involved in the evaluation of the Ontario college report as requested by the ACP (See June 2004 COC minutes under AOB), A copy of the letter forwarded to the ACP dated 12 July 2004 summarising COC epidemiologists views is appended for members information.

<http://www.advisorybodies.doh.gov.uk/coc/meetings/coc042.htm>.

3. The letter to the ACP on the Ontario college review refers to the COC consideration of prostate cancer. The key conclusions on prostate cancer from the published COC statement (<http://www.advisorybodies.doh.gov.uk/coc/prostate.htm>) are given below for ease of reference. The ACP proposed a review of published cohort studies of pesticide manufacturers, which might provide more information on whether the risk of prostate cancer was increased in relation to exposure to specific pesticides. PSD are to fund this work.

Secretariat February 2006

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COC conclusions on prostate cancer. (from published statement)

The Committee agreed the following overall conclusions:

- i. The increase in incidence of Prostate Cancer reported over the past 2-3 decades is largely accounted for by improved identification of cases due to increased numbers of individuals undergoing surgery for benign prostatic conditions and the use of Prostate Specific Antigen Screening.
- ii. The Committee concluded that there was some limited evidence to suggest an association between farmers/farm workers, exposure to pesticides and increased risk of Prostate Cancer. The possibility of such an association being causal could not be discounted and the published literature should continue to be monitored for further studies. Members commented on the need for improved measures of exposure to pesticides and in particular herbicides. It was considered that the potential association between herbicide use by farmers and farm workers should be kept under review.
- iii. The information from the available epidemiological studies are consistent with the view that overall, there is no convincing evidence of an increased risk of Prostate Cancer in rubber workers as a whole.
- iv. There is no convincing evidence to associate other occupations with Prostate Cancer.
- v. There is no convincing evidence to associate occupational exposure to cadmium with cancer of the prostate. The possibility that cadmium might induce androgen imbalance and thus might potentially be associated with Prostate Cancer should be monitored and relevant new information considered in the future.
- vi. The one available epidemiological study on dietary zinc supplementation and risk of Prostate Cancer dose found increased risk of Prostate Cancer at high levels of supplementation (>100 mg/day). Further epidemiology studies are unlikely to provide sufficient numbers of individuals regularly consuming high doses of supplements for a study to be undertaken in the UK. The Committee agreed that it could not identify a biologically plausible rationale as to why zinc should be associated with Prostate Cancer.

ACP conclusions on COC advice on prostate cancer. January 2005.

11.1 Advice from the Committee on Carcinogenicity (CoC) on prostate cancer [ACP (311/2005)]

11.1.1 The Chairman explained that the CoC had recently been investigating possible explanations for an apparent increase in rates of prostate cancer in the UK. The CoC had concluded that most of the apparent increase in incidence could be accounted for by changes in diagnostic practices and the increased longevity of men. However in considering a large number of

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possible risk factors, they had noted that quite a number of studies had indicated small excesses of prostate cancer in farmers using pesticides. The Medical and Toxicology Panel had also noted this in their monitoring of the published epidemiological literature on pesticides, and had been awaiting the views of the CoC.

11.1.2 Overall the CoC had concluded that there was limited evidence of a small increase in the risk of prostate cancer among farmers and farmworkers using pesticides, although the evidence did not point clearly to any single pesticide or group of pesticides that might be responsible.

11.1.3 Members agreed with this assessment, and endorsed a recommendation of the CoC that the relevant scientific literature should continue to be monitored. They noted that they already had in place a system for routine monitoring of the literature that would address this proposal. They also supported the CoC's recommendation that future epidemiological studies should aim to include better information on exposure to pesticides - possibly using biomonitoring data, although they noted that there were practical limitations to what could be achieved in this respect. In addition, the ACP proposed a review of published cohort studies of pesticide manufacturers, which might provide more information on whether the risk of prostate cancer was increased in relation to exposure to specific pesticides.

11.1.4 Members noted that a recently published study had found no evidence of an increased risk of prostate cancer among men living in rural areas of Britain, and no significant clustering of cases in rural areas. The Committee concluded that if there were an increased risk from pesticide exposure, then the principal concern would relate to men exposed occupationally.

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COC advice to ACP on Ontario College review.

DRAFT

12 July 2004

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Dear Jayne

Subject: ONTARIO COLLEGE OF PHYSICIANS REPORT ON PESTICIDES

A copy of the Ontario College report was forwarded to COC epidemiologists. In addition, a number of references were obtained and the results of these studies cross checked with the data cited in the Ontario review. Some literature searching was undertaken to evaluate the adequacy of the literature search strategy used by the Ontario project team. The COC epidemiologists briefly discussed the Ontario review at the 24 June 2004 COC meeting. It was agreed that the secretariat would prepare a letter summarising the views of COC epidemiologists. These comments could be forwarded to the Ontario project team for their response.

Search Strategy/Identification of primary literature

The report suggests that for selected cancer searches began using the term “pesticides”. In addition reference lists from each paper were examined for the identification of papers missed by the literature search. COC members noted that a number of relevant references appeared to be missed by the Ontario project team (Examples are given below in list 1).

A data extraction and quality scoring form was used to aid in the evaluation process. The form (given on pages 173-177) was relatively complete but didn't include any assessment of the information on exposure as part of the quality scoring process.

Presentation of results

The results of the epidemiology studies consulted were reported in tables and an evaluation presented in the text. COC epidemiologists noted that there were a considerable number of predominantly negative findings from studies consulted by the project team which could have been included in the tables but were apparently not included. The reason for this is unclear. (List 2 given below gives an overview of publications cited in the solid tumour chapter).

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Evaluation of results.

COC members considered that the text for chapters 3,4, and 5 was difficult to follow. For example information pertaining to adults and children could be separated and exposures to groups of pesticides (e.g herbicides and insecticides) considered in separate section.

COC epidemiologists found that in the results of some studies could be interpreted differently and in some instances greater consideration of potential confounding, exposure assessment, and multiple significance testing was needed (cf when risk estimates were less than 1.5).

Thus for example, the risk estimate for Hooviold et al 1998 of 1.7 (page 39, reference 13) had a wide confidence interval of 0.2-16.5 and probably reflects a null result rather than a positive association.

Overall COC epidemiologists agreed that that there were aspects of the search strategy, study selection and data reporting which needed to be addressed by the Ontario project team. COC epidemiologists considered the conclusions reached were not supported by the weight of evidence presented. In general the data presented might be informative in developing hypotheses for further consideration but not for reaching definite risk management strategies. It was felt important that the study should be subject to independent peer review as part of a submission to a scientific journal before the report could be reviewed any further.

COC epidemiologists considered that it was not possible to draw conclusions based on the information presented in the Ontario review but that didn't exclude that the published literature might suggest associations or hypotheses for further study. In this respect the COC was considering a draft statement on prostate cancer where evidence for an association in farmers/farm workers with exposure to herbicides has been cited. The statement will be forwarded to the ACP secretariat upon completion.

I hope these comments will be of value to the ACP Chair in his consideration of the Ontario College Report.

Yours sincerely

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Cc COC Epidemiologists, Professor PG Blain, Khandu Mistry

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EPIDEMIOLOGY STUDIES OF PESTICIDE APPLICATORS AND CANCER

LIST 1: SOME EXAMPLE REFERENCES

Wiklund K and Dich J. Low cancer risk among female agricultural workers. *Lakartidningen*, vol 128, 2661-3, 1995 (In Swedish).

Fritschi L and Siemiatycki J. Lymphoma, myeloma and occupation: results of a case-control study. *Int J cancer*, vol 67, 498-503, 1996

Zahm SH. Mortality study of pesticide applicators and other employees of a lawn care service company. *J Occupational and Environmental Medicine*, vol 39, 1055-67, 1997.

Settimi L et al. Cancer risk among male farmers: a multi-site case-control study. *Int J of Occupational Medicine and Environmental Health*. Vol 14, 339-47, 2001.

LIST 2: CITATION OF RESULTS FROM REFERENCES QUOTED IN THE SOLID TUMOUR CHAPTER.

Fear NT et al *Br J Cancer*, vol 77, 825-829, 1998. Significantly raised PMR for kidney reported in Ontario review. PMRs below 1 reported for brain (0.83 (CI 0.69-1.00)), NHL, (0.87 (CI 0.61-1.23)) Leukaemia (0.87 (CI 0.76-1.01)) not reported in Ontario review.

Fleming LE et al *JOEM*, vol 41, 279-88, 1999. Reports significant excess of prostate and testicular cancer, and cervical cancer. No significant association for cancer of stomach, lung, brain (males RR 1.09 (0.70-1.62), female, 0.92 (0.10-3.31)), leukaemia (males 0.93 (0.60-1.37), females 1.17 (0.01-4.30)). Breast cancer reduced in females (0.61 (0.40-0.90)). I don't think any of the negative findings are reported. The only citation is to prostate and testicular cancer.

Kristensen et al *Int J of Cancer*, 65, 39-50, 1996,. Evidence for association with CNS tumours documented (included in Ontario review), although I couldn't trace all the RR values reported in the Ontario report, particularly brain tumours and pesticide purchase. No trend for increasing RR estimate was found for acute leukaemias and pesticide expenditure (surrogate for exposure). Increased rate ratio for pig farming. These data are reported in the Ontario College report in the relevant section on leukaemia.

Littorin M *Int Arch Occ Env health*, 65, 163-169, 1993.

Slight but not statistically significant increase in SMR for brain tumours (1.5 (CI 0.8-2.7)), not reported in Ontario review. Statistically significant increases in young/middle aged horticulturists with brain tumours (SMR 3.2 (CI 1.6-5.7)) reported in Ontario review. Other SMR values not reported

Stomach 1.2 (0.8-1.8)

NHL 0.8 (CI 0.3-1.7)

Lymphatic leukaemia 1.0 (0.3-2.7)

Myeloic leukaemia 1.1 (0.2-3.3)

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Kross BC Am J Ind Med, vol 29, 501-506, 1996. Elevated lung, brain, NHL, prostate reported in Ontario review. Leukaemia result (PMR 162 (CI 83-316) also reported in Ontario review. Results for pancreas (128 (CI 70-236)) and kidney (80 (27-244) not reported.

Ramlow JM Am J of Ind Med, vol 30, 180-194, 1996. The authors reported increased SMR for kidney cancer as reported in Ontario review. SMR data for other cancers were grouped (ie. Respiratory, all lymphopietic, and all digestive). Authors did report risk ratios stratified into two exposure categories. Kidney cancer showed a statistically significant trend. There was no evidence for a trend for cancer of stomach, pancreas, lung, leukaemia or brain (and other CNS). These latter data are not reported in Ontario review.

Cantor K Am J Ind Med vol 36, 239-247, 1999. Elevated Rate ratio for pancreatic cancer reported in Ontario review. However other RRs not reported in Ontario review (even though elevated leukaemia RR was significant).

Stomach 2.81 (0.9-6.2)

Pancreas 2.71 (1.4-5.3)

Lung 1.0 (0.8-1.3)

Prostate 1.32 (0.8-2.3)

Kidney 1.82 (0.7-4.6)

Leukaemia 3.35 (1.9-8.5)

MacLennan PA JOEM, vol 44, 1048-1058, 2002. SIR for prostate cancer for all employees and those actively in work reported in Ontario review. Paper focuses on prostate but does report SIR for other cancer for all employees.

Lung 71 (15-206)

Breast 104 (38-225)

NHL 136 (28-398)