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CC/06/22

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

Report on prostate cancer and pesticide exposure

1. The COC published a statement on prostate cancer in December, 2004 (COC/04/S6). 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.

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2. In 2006, a Department of the Environment, Food and Rural Affairs (Defra) commissioned report entitled “Desk Study on Prostate Cancer and Pesticide Exposure”, project number PS2609, was produced by the Institute of Occupational Medicine (IOM) in Edinburgh. The Advisory Committee on Pesticides (ACP) has requested the COC’s views on this report from the IOM. The view of the COC is sought on whether the report impacts on conclusion ii of the COC statement. The view of the COC is also sought on the recently published paper in Cancer Causes Control (CCC) by Van Maele-Fabry *et al* (2006). The outcome of this paper and the report from the IOM are not entirely consistent re phenoxy herbicides.

Paper by Van Maele-Fabry *et al* (2006) entitled “Review and meta-analysis of risk estimates for prostate cancer in pesticide manufacturing workers”

3. The paper by Van Maele-Fabry *et al*, (2006) (attached at Annex 1) provides a review of cohort studies that examine the occurrence of prostate cancer in pesticide manufacturing workers in order to undertake a qualitative and quantitative evaluation of the risk as well as to assess the level of epidemiology evidence for each class of chemical compound.

4. The study examines workers employed in manufacturing of pesticides rather than end product users such as farmers and pesticide applicators. The authors chose manufacturing workers as they have a less diverse occupational environment and are likely to have been more frequently and potentially exposed, especially during the early years of production when industrial hygiene controls were not very sophisticated. According to the authors, manufacturing workers may have had relatively high cumulative exposure, although no data were available for the authors to confirm these assumptions. The manufacturing environment also offers a different set of potential confounding exposures than those existing on the farm. As well as pesticides, employees engaged in production-related activities are potentially exposed to raw materials, intermediate products and end products.

5. A search of Medline was conducted for the period 1966 – 7th August 2004. Cohort studies were chosen as they have the best observational design to assess causality of a disease.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none">• Surveys published in English, in peer reviewed journals between 1966 and 2004• With a Cohort design• Provided sufficient data to determine an estimator of relative risk (RR) for prostate	<ul style="list-style-type: none">• Included subjects already included in another more complete or more recent study examining a greater no. of subjects or with a longer follow-up duration• Were case-control (due to

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<p>cancer and its confidence intervals (CI)</p> <ul style="list-style-type: none">• Referring to the occupational group of interest (Workers engaged in manufacturing of pesticides)	<p>concern about quality of exposure information and biases in case or control selection and as case-control studies are less useful to explore causation) or proportional mortality ratio (PMR) studies</p> <ul style="list-style-type: none">• Did not report original results• Investigated women cohorts• Clearly examined a specific cancer type other than prostate cancer
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6. Given the various pesticide classes for which the cohorts were followed and the known contamination of some of them (e.g. phenoxy herbicides) with polychlorinated dibenzo-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs), several groupings of the data were performed. Estimators of relative risk were extracted for phenoxy herbicides, organochlorines, chloroacetanilides, triazines and halogenated hydrocarbon nematocides. An overall meta-analysis including all classes of pesticides was conducted, with separate meta-analyses conducted for phenoxy herbicides and for the classes of pesticides other than phenoxy herbicides. Meta-analysis could also be conducted for the triazines and the halogenated hydrocarbon nematocides.

7. More than 100 scientific references were found in the literature that dealt with manufacturing workers exposed to pesticides. After application of the exclusion criteria, 63 studies were selected. A further 45 studies were excluded from the analysis. This left 18 studies that could be used in the meta-analysis. These 18 studies contributed a total of 20 RR estimators and contained ten cohorts that followed workers in the USA and ten cohorts that followed European workers.

8. The estimators of RR for the manufacturing workers to develop or die from prostate cancer varied between 0.17 and 5.2 and included from 1 up to 28 cases. 16 RR estimators indicated a positive association between prostate cancer and occupation (Acquavella et al., 2004; MacLennan et al., 2002; MaLennan et al., 2003; Olsen et al., 1995; Wong et al., 1984; Coggon et al., 1986; Bueno de Mesquita et al., 1993; Burns et al., 2001; Bodner et al., 2003; Flesch-Janys et al., 1998; Becher et al., 1996; Collins et al., 1993; Ott and Zober, 1996; Hooiveld et al., 1998; Steenland et al., 1999 and Hooiveld et al., 1998), 3 estimators of RR indicated a negative association (Swaen et al., 2002; Becher et al., 1996 and Ramlow et al., 1996) and one study indicated no association (RR = 1) (Lynge, 1998).

9. Four of the results were incidence rate ratios (Acquavella et al., 2004; MacLennan et al., 2002; Lynge, 1998 and Ott and Zober, 1996) and 16 were mortality rate ratios (Swaen et al., 2002; Becher et al., 1996 and Ramlow et

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al., 1996; MacLennan et al., 2003; Olsen et al., 1995; Wong et al., 1984; Coggon et al., 1986; Bueno de Mesquita et al., 1993; Burns et al., 2001; Bodner et al., 2003; Flesch-Janys et al., 1998; Becher et al., 1996; Collins et al., 1993; Hooiveld et al., 1998; Steenland et al., 1999 and Hooiveld et al., 1998).

10. In the overall meta-analysis, all selected studies were included except those by Collins et al, 1993, Ramlow *et al*, 1996 and Bodner *et al*, 2003. As a consequence, the meta-rate ratio estimate for the overall meta-analysis was based on 16 studies from the 18 initially selected. Ramlow *et al*, (1996) and Collins et al, (1993) were excluded as these papers represent subset data of a larger study of US production workers exposed to PCDDs and the last comprehensive review was already included in the overall meta-analysis, in the paper of Steenland *et al*, (1999). Bodner *et al*, (2003) was not included in the overall meta-analysis but was included in the analysis concerning phenoxy herbicides contaminated "without accident". In the overall meta-analysis, application of the fixed effects procedure on the 16 studies of workers ever employed in pesticide manufacturing and potential exposure to pesticides yielded a meta-rate ratio of 1.28 (95% CI 1.05-1.58). The paper combined RR estimates from both SIR and SMR studies to derive the overall RR value of 1.28. The study of Steenland *et al*, (1999) contributed 47 % of the total weight applied. Removal of this study from the overall meta-analysis resulted in a meta-ratio of 1.33 (95% CI 1.05-1.69). No other study contributed more than 30% of the total weight. The suggestion that prostate screening programs may have confounded the results of the cancer incidence studies prompted the authors to rerun the overall meta-analysis excluding the incidence studies. The meta-RR after pooling the 12 remaining mortality studies was 1.32 (95% CI 1.03-1.69).

11. Examination of the 16 RR estimators included in the overall meta-analysis versus publication date did not reveal any clear positive or negative trend with time. The funnel plot of $\ln(\text{RR})$ versus $1/\text{SE}$ did not reveal a systematic association between study size and the magnitude of risk. After grouping the data into specific chemical class of pesticide, increased pooled rate ratios were observed for all groups but statistical significance was found only for accidental and non accidental exposure to phenoxy herbicides contaminated with dioxins and furans. Statistically significant increases were observed for the workers contaminated with PCDDs/PCDFs as a result of an accident (RR 1.80, 95% CI 1.03 - 3.13) as well as for workers who did not experience an accident (RR = 1.50, 95% CI 1.06-2.11).

12. Most of the sensitivity analyses did not substantially alter the results of the meta-analysis. In the overall meta-analysis, exclusion of the studies with the highest and lowest estimator of RR, exclusion of studies with highest and lowest precision, deletion of studies concerning workers exposed as a result of an accident as well as deletion of incidence studies did not markedly change the pooled RR.

IOM report on Prostate Cancer and Pesticide Exposure

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13. The IOM report on Prostate Cancer and Pesticide Exposure (attached at Annex 2) had two aims i) to review the epidemiology on pesticide exposure and the risk of prostate cancer and ii) to review the potential mechanisms that might underlie any link between pesticide exposure and prostate cancer. Early literature searches showed that there was relatively little information available on workers in the manufacturing industry and the scope of the study was extended to include workers exposed to pesticides in other occupations. Over 140 relevant publications were identified and reviewed in detail.

14. The report cites a number of previous papers that review the role of pesticide exposure in the development of prostate cancer. The studies of Van Maele-Fabry and Willems (2003, 2004) analysed data from peer-reviewed, case referent and cohort studies of prostate cancer in pesticide applicators (2004) and more generally in occupational groups potentially exposed to pesticides (2003). The results of the meta-analysis published by Van Maele-Fabry and Willems (2003, 2004) indicate that pesticide applicators have an increased risk of prostate cancer, although it was not possible to establish that this was associated solely with pesticide exposure. Two reviews and meta-analyses report excess risk of prostate cancer in farmers (Blair *et al*, 1992 and Keller-Byrne, 1997) while Sathiakumar and Delzell (1997) have reported that there were insufficient data to assess cancer risk. A number of studies reported no excess risk of prostate cancer (Maroni and Fait, 1993; Morrison *et al*, 1992; Johnson, 1990; Johnson *et al*, 1990 and Bond *et al*, 1990).

15. The IOM report found that a number of studies of pesticide manufacturing workers did not demonstrate any consistent association between pesticide exposure and prostate cancer. The results of large studies of manufacturing workers exposed to phenoxy herbicides do not suggest a link with prostate cancer (IARC study as described by Kogevinas *et al*, 1997; Coggon *et al*, 1991, 1986; Lygne, 1993 and 1998; Bueno de Mesquita, 1993 and Saracci *et al*, 1991). Although the authors of the report found that the power of these studies to detect an excess risk of prostate cancer from phenoxy herbicides would have been lower than in more recent studies the size of the studies and the length of the follow-up suggest it is unlikely that an important excess risk of prostate cancer remained undetected. There is some evidence of an excess risk associated with the manufacture of atrazine.

16. The report reviews a large number of studies of agricultural workers exposed to pesticides but found that the results of these studies of pesticide users have been inconsistent. Of the 18 studies involved in the meta-analysis study of Van Maele-Fabry *et al* (2006), only 9 were included in the IOM study. Also the Van Maele-Fabry *et al* paper includes data only from manufacturing workers, while the report includes manufacturer workers and end product users. The report states that exposures to pesticides during use are much less controlled than during manufacturing and some users may experience relatively high levels of exposure. Many of the studies of prostate cancer in agricultural workers handling pesticides which were reviewed in the report were negative or inconclusive, with a few showing positive results. The report

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found that most of the positive findings have been in more recent studies, indicating that prostate cancer is associated with more modern pesticide formulations and/or much longer periods of exposure than was typical in previously studied workers. It may also reflect a greater sensitivity in the detection of prostate cancer. Excess risk of prostate cancer has been most commonly reported in US farmers, particularly in recent studies including the Agricultural Health Study (AHS); Fincham *et al*, (1992); Delzell and Gruffermann, (1985); Saftlas *et al*, (1987); Parker *et al*, (1999) and Burmeister *et al*, (1983). A number of risk factors for prostate cancer were suggested in these studies as causes including high fat diet, farm animals, zoonotic viruses, genetic susceptibility, farm chemicals but not specifically pesticides. Both Parker *et al*, (1999) and Burmeister *et al*, (1983) highlighted a greater excess prostate cancer risk in older farmers but there has been little investigation of prostate cancer risks in younger men. The report highlights a marked discrepancy between the findings in studies of farmers undertaken in North America and those undertaken in Europe. Most European studies have not found an excess of prostate cancer.

17. The report found that different studies have reported different pesticides to be most strongly associated with increased risk of prostate cancer. Pesticides that appear to be associated with prostate cancer in more than one study are methyl bromide (AHS, Mills and Yang, 2003), DDT (AHS, Settimi *et al*. 2003) and heptachlor (AHS, Mills and Yang, 2003). Two studies also reported an association for atrazine that failed to reach statistical significance (AHS, Mills, 1998). Several studies have suggested an excess risk of prostate cancer among US veterans exposed to Agent Orange (Akhtar *et al*. 2004 and Giri *et al*. 2004) but other studies have not (Zafar and Terris, 2001).

18. The report also highlights studies that investigated the employment history of prostate cancer cases where some studies have found that farmers are among the occupational groups with elevated risks (Buxton *et al*, 1999; Band *et al*, 1999; Brownson *et al*, 1988; Krstev *et al*, 1998a; Mallin *et al*, 1989; Sharma-Wagner *et al*, 2000; van der Gulden *et al*, 1995). Potti *et al*. (2003) specifically reported a link with pesticides. Other similar studies did not find a link with farming or pesticides (Krstev *et al*, 1998b; Elghany *et al*, 1990; Fincham *et al*, 1990; Aronson *et al*, 1996; Boers *et al*, 2005; Zeegers *et al*, 2004; Heiskel *et al*, 1998; Ilic *et al*, 1996; Pearce *et al*, 1987; Frith *et al*, 1996). No marked differences between findings of European and North American studies were noted in the report.

19. The IOM report also reviewed the potential mechanisms that might underlie any link between pesticides and prostate cancer. The report found that there is considerable information in the literature that demonstrates that pesticides possess a wide range of activities which permit them to copy/counteract the actions of hormones in target tissues. The prostate depends on a continuous supply of steroid hormones to maintain normal growth and function. Pesticides as endocrine disruptors could interfere with these processes and lead to abnormal growth of the prostate. The report found a number of recent mechanistic studies have demonstrated that

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pesticides might induce androgen imbalance by interfering with the action of natural hormones (Giusi *et al*, 2006; Hayes, 2004; Timms *et al*, 2005; Wozniak *et al*, 2005; Meeker *et al*, 2006), but the report found that studies have yet to be undertaken on the possible effects on the prostate. The report also suggested that the pesticides might target the prostate directly, influence steroid metabolism, receptor binding activity or degradation and trigger the sequence of events leading to the onset of neoplasia.

20. According to the authors of the report, limited conclusions can be drawn from the available evidence. They found insufficient evidence to conclude that pesticide exposure is associated with an increased prostate cancer risk. However, they also report that there is insufficient evidence to be certain that such a risk does not exist, although the failure to consistently detect a risk suggests that typical levels of pesticide exposure among pesticide workers do not have an important influence on prostate cancer risk. The report highlights that there has been little investigation of the mechanisms by which exposure to pesticides may lead to increased prostate cancer risk and the authors of the report suggest the need for further such studies.

Questions for the committee

The committee is asked to address the following questions:

- i) What are Members' views on the IOM report? Does the committee agree with the report's conclusions about there being insufficient evidence to conclude that pesticide exposure is associated with an increased prostate cancer risk?
- ii) What are Members' views on the paper and method used by Van Maele-Fabry *et al*, (2006) to examine the occurrence of prostate cancer in pesticide manufacturing workers?
- iii) Can members comment on the difference found in results for the phenoxy herbicides between the IOM study and the Van Maele-Fabry paper?
- iv) The views of the COC are sought on whether the IOM report impacts on conclusion ii of the COC Prostate cancer statement

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