

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

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

Introduction

Background to RCEP report

1. Defra announced a public consultation on the need for buffer zones between agricultural applications of pesticides and residences in July 2003. This followed discussion in the Advisory Committee on Pesticides (ACP), taking account of some stakeholders concerns regarding risks to the health of rural residents as a result of crop spraying. Members of the ACP gave the following advice to Ministers

‘Members had concluded that on the basis of the information currently available the risk assessment for bystanders used at present provided adequate protection, even if spray is applied to the edge of a field. Nonetheless, the Committee recognised that many people may consider it socially unacceptable to spray right to the boundary of a neighbour’s property. If Ministers agree, they may wish to consider options to restrict this practice.’ (<http://www.pesticides.gov.uk/acp.asp?id=586>)

2. The specific conditions of use for individual pesticide products are supplemented by guidance on best practice contained in the statutory Code of Practice for the Safe Use of Pesticides on Farms and Holdings (the "[Green Code](#)"). Although failure to follow the Code’s guidance is not in itself an offence, it may be used in evidence against the user if prosecuted for breach of the law. The consultation document asked for views on the risk assessment process, the Green Code and the need for buffer zones to prevent exposure. The consultation was based on the ACP’s advice that the current regulatory system is adequate to protect human health but that there may be an issue of “social acceptability” in spraying right up to the boundary of someone’s property. A series of options was presented which were i) Do Nothing (i.e. risk assessment process satisfactory), or ii) Introduce buffer zones at varying distances e.g. should these be 6 m, 10 m, 100 m, 300 m. An estimate of the amount of land which would be excluded from agricultural use by each proposed buffer zone was calculated. The outcome of the consultation was one of the highest number of responses to a Defra consultation in recent years (763 replies) but the responses appeared to separate into two distinct types of reply. Farmers/Growers and representative organisations opted for the status quo (i.e. no buffer zone). Pesticide stakeholder groups and the

general public (most of whom were described by Defra as being loosely tied to the campaigns led by Stakeholder groups) opted for a buffer zone. Some of the replies claimed that there were significant public health issues and chronic ill health attributed to pesticides. Defra concluded that it was not possible to make an accurate judgement of public opinion as a whole.

3. The Defra minister (Rt Hon Alun Michael) announced (16 June 2004) that he would not introduce mandatory buffer zones but had asked the RCEP to examine the evidence on which the current system is based and the reasons for people's concerns. Mr Michael in placing this request was mindful of the advice from his chief scientist Professor Howard Dalton who had been asked to review the procedures used by the Pesticides Safety Directorate (PSD) for evaluating bystander risk. Professor Dalton had subsequently confirmed he was satisfied with the procedures used.

4. The RCEP announced its review on 4 August 2004. The remit set by the Commission was; "The Commission will examine the scientific evidence on which Defra has based its decision on bystander exposure and its policy on access to information on crop spraying. The Commission will also consider wider issues related to the handling and communication of risk and uncertainty, as well as public involvement, values and perceptions in this context".

Overview of RCEP report

5. The RCEP published its report on the 22 September 2005.¹ The RCEP introduced their report in chapter 1 by noting that the subject of the review was complex and controversial. Individuals had concerns about potential exposure to pesticides arising because they occupy properties adjacent to farmland or because they have (or have had) access to such land, for example when using footpaths. The RCEP noted the official response that there was no scientific case for taking additional measures, such as the introduction of no-spray buffer zones, to protect members of the public who may be in the vicinity of a sprayed area; however, those who considered themselves to have been adversely affected had not been reassured by this response. The RCEP held an open meeting on the 25 September 2004. A set of questions regarding health aspects, exposure and modelling, legal aspects, policy and other aspects with regard to pesticides (e.g the scale of bystander exposure) arose from this meeting. The health related questions agreed for the RCEP study are reproduced below;

"What are the biological effects of bystander exposure to pesticides (what is the knowledge base)? What are the limits of toxicology and epidemiology in cases of bystander exposure to pesticides? How plausible is it that pesticides cause the health problems reported? What systems are in place to respond to and record bystander exposure and how well do they work (e.g GPs, The Pesticide Incident Appraisal Panel, (PIAP))?"

6. The remaining sections of chapter 1 provide background information on the health effects reported to the RCEP, the definitions of bystander and resident, the potential scale of bystander and resident exposure to agricultural spraying, the level of concern in other countries, the approach taken to gathering evidence and the structure of the RCEP report.

7. Chapter 2 of the RCEP report reviewed pesticide spraying and health and has been the predominant focus of the current COT and COC review. The recommendations given in chapter 6 of the RCEP report relating to health aspects were also considered in detail. Chapters 3 (Exposure), 4 (Legal liability) and 5 (Governance of agricultural pesticides) have not been reviewed in detail by COT and COC.

8. The COT and COC acknowledged that the subject of crop spraying and potential for ill health had generated considerable public concern. The COT and COC are scientific advisory committees which can be requested by Government Departments and Agencies to provide advice on the evidence presented to them. The Committees' remit was restricted to a review of the contents of the RCEP report as written. The Committees were not, on this occasion, asked to undertake an independent review of pesticide safety and use. The Committees agreed that their remit referred to the scientific aspects of the RCEP report in relation to health and did not include wider aspects outlined by the RCEP in their report.

9. The COT and COC appreciated that the subject of crop spraying and potential for ill health is a sensitive and important public issue and gave due regard to this when considering the RCEP report. The COT did express some broad reservations about the way in which the RCEP presented their evidence and the manner in which its findings were expressed.

Background to the COT and COC review.

10. The COT and COC were asked by Defra and the ACP to comment on the RCEP report.. Members of the COM were alerted to the report and asked to provide any comments to the secretariat (none were received) The COT and COC considered the report along with a number of published papers^{2,3}, some information from the DH report published in 1996 on guidance for medical practitioners⁴ and an example copy of a report from the Pesticides Incidents Appraisal Panel (PIAP).⁵ The Committees based their consideration on paragraphs 2.1-2.69 of chapter 2 dealing with pesticides and health and provided only limited general comments on monitoring and reporting of health effects (paragraphs 2.70-2.107) where expertise resided predominantly in the regulatory authorities (PSD and the Health and Safety Executive (HSE)). [Throughout this statement the term "bystander" has been applied as stated in the RCEP report to include other groups such as residents.]

Advice requested from COT and COC.

11. The COT and COC were asked to
 - i) Consider, based on members expertise and the evidence presented in the RCEP report, whether the conclusions and recommendations reached in respect of health related topics are appropriate (see paras 6.20-6.29 of the report)
 - ii) Derive COT/COC conclusions in relation to the health related questions posed by the RCEP on the basis of the evidence reviewed and members' expertise, and to consider whether these concur with those reached with RCEP.
 - iii) Consider whether any further work by COT/COC/COM should be undertaken with respect to bystander pesticide risk assessment and report any suggestions for further work to the ACP.

12. The COT discussed the report on the 14 February 2006 and the COC discussed the report on the 2 March 2006. The COT considered a draft working paper at its meeting of the 28 March 2006. Both committees considered that chapter 2 of the RCEP report (Pesticide spraying and health) was the most relevant section for discussion. The following summary of COT and COC conclusions follows the structure of this chapter. Members agreed that as the COT and COC had no experience of post market monitoring systems for pesticides they only provided general comments on that section of chapter 2.

COT comments on chapter 2 of the RCEP report.

[Readers may wish to access the RCEP report for content on these sections:
<http://www.rcep.org.uk/cropspraying.htm>]

Paragraphs 2.1-2.15: Introduction, health effects attributed to pesticides, acute effects, chronic health effects

13. Members agreed with an RCEP conclusion of this section that no firm conclusion could be drawn that pesticide exposure was causing ill health experienced by bystanders and residents. The COT commented that level of exposure was critical and it was agreed that exposure of bystanders and residents would be significantly lower than for operators, even taking into account use of personal protective equipment by operators. The COT considered identification of adverse effects in operators to be a useful model for bystanders and therefore there was reassurance regarding the potential for adverse effects in bystanders.

14. It was considered that the only possible factor which could explain a difference between exposed bystanders and operators in the incidence of

chronic ill health was a particular susceptibility in some bystanders . It was noted that although operators could be considered not to represent the full heterogeneity of the general population, the systemic acceptable operator exposure level (AOEL), which was used in risk assessment for both operators and bystanders, incorporated an uncertainty factor sufficient to account for inter-individual variation in the general population and was an appropriate approach for risk assessment of bystanders and residents. The COT noted that if a bystander did accidentally get exposed to a high exposure to certain pesticides then some acute adverse effects might occur.

15. Given the heterogeneity of bystanders and their low level of exposure compared to occupationally exposed groups, it was considered that there was little merit in undertaking epidemiological studies in bystanders as a group, and that a more appropriate approach would be to investigate genetic and phenotypic characteristics in individuals with self-reported chronic ill health as compared with equally exposed but symptom free bystanders. Such an approach would be required to identify the causes of ill health, and if there was any increased susceptibility in some individuals. The importance of appropriate controls was emphasised.

Paragraphs 2.16-2.19: Mechanisms of action of pesticides and possible targets in humans

16. The COT considered that the details presented in this section were relatively limited and observed that there were many classes of pesticides other than organophosphates and pyrethroids which had not been considered here. The COT agreed that the classical dose-response relationship was appropriate for the toxicological assessment of all pesticides evaluated to date.

Paragraphs 2.20-2.26: Epidemiology

[See also comments from COC on cancer epidemiology paras 22 and 23 of this statement].

17. The COT agreed that a limitation of epidemiological studies in relation to pesticides was the imprecise exposure assessment, with often a complete lack of quantitation. Thus the Institute for Environment and Health review of studies on Parkinson's disease⁶ had insufficient data available to identify individual pesticides; the best descriptor available was groups such as herbicides. Where associations were found it was not possible to relate them to dose. A key difficulty was the retrospective evaluation of exposure using self-reported questionnaires. Improvements in study design were required in this respect.

18. The COT observed the comparison in the RCEP report of the air quality standard for nitrogen dioxide and the relevant occupational standard. It was noted that the AOEL used in pesticide risk assessment incorporated an uncertainty factor sufficient to account for variation in susceptibility as might be seen in the overall population.

Paragraphs 2.27-2.34: Review of epidemiological studies

19. The COT considered that the review of epidemiological studies had been limited and that a more substantive review of the literature should be undertaken. Members noted that the RCEP did not come to any conclusion as to whether pesticide exposure was causing ill health. It was suggested that one possible way forward would be to consider para-occupational exposure, e.g. spouses and children of farmers who might have exposures above that of bystanders. It was noted that the American Farm Survey of Occupation might be one useful source, but a literature review should identify other relevant research projects (<http://www.aghealth.org/>). It was noted that such data did not necessarily enable cause and effect to be established.

20. The COT was aware of the difficulties in undertaking such work relating to many sources of exposure to pesticides and the many different types of pesticides in addition to potential exposures resulting from spray activities. Thus, for example, preliminary information from an investigation of people attending GP surgeries showed that 45% of them had used some form of pesticide in the domestic environment in the week before consultation.⁷ However, it was noted that the background rate of exposure was not known.

21. It was noted that the RCEP report referred to clusters of ill health, but that clusters were not evidence of causation, and that a hypothesis of a minority of bystanders with heightened susceptibility was unlikely to fit with an area-based cluster pattern of ill health.

COC comments on epidemiology

22. The COC agreed that the RCEP had not had time to undertake a rigorous evaluation of all the available epidemiological literature. COC Members commented that the RCEP report had not clearly distinguished between hypothesis generating studies (such as geographical studies of clusters e.g. as undertaken by the Small Area Health Statistics Unit (SAHSU) <http://www.sahsu.org/>) and analytical studies which could be used to define dose-response relationships for pesticides associated with cancer and were of importance in the assessment of causality. The COC recalled that the main problems identified with regard to the Ontario review⁸ were the selection of data used in it which had not considered available negative data as well as studies reporting positive associations for cancer, the selective interpretation of results and the lack of good exposure data in most studies. This last problem could not be remedied in any future review of such publications.

23. The COC agreed with the RCEP that better exposure definition in cancer epidemiology studies was a high priority for further research. The COC agreed that further evaluation of para-occupational studies would be valuable but that using status such as married to farmer as a proxy for para-occupational exposure limited the value of such studies with regard to identifying association with pesticide exposures. The COC agreed that appropriate biomonitoring studies (e.g. using biomarkers of exposure or of

biological effect) would be helpful with regard to population studies of cancer. The Committee recognised the difficulties in associating current exposures with those that might be causal in cancer.

Paragraphs 2.35-2.39: Multisystem disease (chronic fatigue syndrome, multiple chemical sensitivity)

24. The COT considered that there were two schools of thought with regard to multiple chemical sensitivity (MCS), that it was either psychological in nature or organic. Either cause could indicate a particular susceptibility in some individuals. It was noted that the literature indicated that two important factors in the reporting of ill health by bystanders were odour, which may not reflect exposure to an active ingredient, and the involuntary nature of exposure. These suggested that additional factors may be important in the condition.

25. The differences between multiple chemical sensitivity and chronic fatigue syndrome are unclear. This is, in part, a reflection of uncertainty in the aetiology of these conditions. There were a number of similarities in reported symptoms, however not everyone with chronic fatigue syndrome reported sensitivity to chemicals.

26. The COT noted that a number of papers have been identified in the literature since the COT's last consideration of multiple chemical sensitivity in 2000, and agreed that these could be reviewed. This work might also involve reviewing chronic fatigue syndrome.

27. It was agreed that a fundamental research programme into multi-system disease involving research councils and the Department of Health as recommended by the RCEP was not warranted. With respect to chronic fatigue syndrome it was considered that there could be merit in investigating individuals with chronic fatigue syndrome who believe their condition is due to prior infection in comparison to those who believe it is due to chemical exposure. The COT commented that investigations using brain imaging techniques needed to incorporate appropriate controls. It was noted that even symptoms without an established physical basis could give rise to changes observable on functional brain imaging.

Paragraphs 2.40-2.53: Toxicology

28. The COT reviewed the two references cited in the RCEP on animal models which reflected some aspects of chronic fatigue syndrome.^{2,3} The COT concluded, on the basis of this evidence and members' experience of toxicological test development, that there was no rationale for developing animal models to test for poorly-defined end effects such as multiple chemical sensitivity without a clear mechanistic basis for undertaking such work. One difficulty was the possibility of a psychological component in conditions such as chronic fatigue syndrome and multiple chemical sensitivity. Another was that the majority of the symptoms reported are subjective. Members had

difficulty in identifying the value of *in-vitro* techniques to investigate such complex multi-functional ill-health effects with poorly defined causation.

Paragraphs 2.54-2.64: Monitoring

29.. The COT and COC noted that the majority of currently approved pesticides are eliminated quickly (e.g. within a day or two) once absorbed, and therefore biomarkers reflect exposure over the preceding days.⁹ Levels of any biomarkers may relate more to time of exposure rather than dose, making calibration difficult. The Committee heard information on the studies instigated by PSD relating to permethrin and chlorpyrifos and agreed the proposed research would fulfil the COT suggestions for biomarker-related exposure assessment. Members noted the difficulties in undertaking such research. These include sampling, storage, analysis and obtaining ethical consent for participation. In addition, it was questioned whether the biomarkers which are currently available would be sufficiently sensitive to detect exposure in bystanders. Members noted that if biomonitoring was routinely used in data packages for pesticides there would be scope for comparing data with that derived from toxicological evaluation in animal studies.

30. The RCEP report had advocated large-scale studies along the same lines as the National Health and Nutrition Examination Survey (NHANES <http://www.cdc.gov/exposurereport/>) in the US. The COT considered that such programmes of work provided large numbers of results which were difficult to interpret. The COC noted that large studies such as Biobank (noted in 2.62 of the RCEP report) and EPIC (European Prospective Investigation into Cancer and Nutrition) would only be of value to measure chronic rather than acute exposures. Members agreed that it was important to consider potential biomonitoring studies, but considered that small scale focused prospective studies using pesticides for which there was good knowledge of kinetics in humans would be more informative for non-cancer endpoints. Such studies would form the basis for extrapolating to potential bystander exposure to other pesticide active ingredients.

Paragraphs 2.65-2.69: Recommendations: human health

31 The Committees considered the recommendations for human health presented in the RCEP report (reproduced in italics below).

- i) Regarding 2.65 of the RCEP report; *Based on the conclusions from our visits and our understanding of the biological mechanisms with which pesticides interact, it is plausible that there could be a link between resident and bystander pesticide exposure and chronic ill health. We found that we are not able to rule out this possibility. We recommend that a more precautionary approach is taken with passive exposure to pesticides. The*

existing uncertainties indicate an urgent need for research to investigate the size and nature of the problem and any underlying mechanisms that link pesticide spraying to ill health. The committees did not consider that there was a basis to support the recommendation that there was an urgent need for research. The Committees agreed that recommendations relating to additional precaution in risk assessment above the already precautionary approach used did not have a scientific basis and this was an issue of policy regarding pesticide approvals.

- ii) Regarding paragraph 2.66 of the RCEP report; *We recommend that a comprehensive systematic review of the literature in this field be conducted that takes account of, and avoids, the shortcomings of the Ontario study* The COT agreed that an epidemiological review of para-occupational exposure to pesticides should be undertaken. The COT agreed a review of the literature on chronic fatigue syndrome and multiple chemical sensitivity should be undertaken. COC members doubted that a comprehensive systematic review would be valuable given the deficiencies in exposure measures in published studies. The COC agreed that geographical studies of cancer incidence linked to potential exposure (possibly to include appropriate biomonitoring data) should be considered
- iii) Regarding paragraph 2.67 of the RCEP report; *We recommend that an imaginative systematic approach is taken to apply both well validated as well as novel clinical investigative methods to those with chronic symptoms linked to pesticide spraying such as magnetic resonance spectroscopy (MRS) and gene and protein profiling* The COT agreed that specialist investigations should be aimed at all potential causes of chronic illness such as chronic fatigue syndrome and multiple chemical sensitivity, not just the proposed hypothesis relating to bystander exposure to pesticides.
- iv) Regarding paragraph 2.68 of the RCEP report; *We recommend that the Health Protection Agency and related organizations within the devolved administrations in Scotland and Wales collect population data on pesticides, their metabolites, and biomarkers of effects that would provide a sound basis for exposure assessment and could also be used to establish a national database for monitoring.* The COC considered that appropriate population biomonitoring could be of value in interpreting any studies of cancer and the potential association with exposure to pesticides. The COC noted the role of HPA in co-ordinating such work in the U.K. The COT concluded that targeted biomonitoring work was more preferable to gain an estimate of potential bystander exposure.
- v) Regarding paragraph 2.69 of the RCEP report; *We recommend that the private sector and universities be encouraged to develop new animal models that better reflect the chronic disorders experienced by*

residents and bystanders exposed to pesticide spraying. The COT considered that there was currently no clear rationale for developing animal models to test for poorly-defined end effects such as multiple chemical sensitivity without some mechanistic basis for undertaking such work. The COT considered that there was little value in using *in vitro* techniques to investigate such chronic ill health effects. (The Committees noted that all pesticides are tested for potential carcinogenicity in rodents)

Paragraphs 2.70-2.96: Health effects, monitoring and reporting

32. The Committees had not previously considered health effects monitoring and reporting of pesticides and therefore did not consider the conclusions and recommendations on this section of the RCEP report in any detail. The Committees were aware that expertise and experience of health monitoring scheme for pesticides was available in the relevant regulatory authorities (namely PSD and HSE). The COT made a generic comment that suggestions made in the RCEP report for further involvement of primary care would be difficult to undertake and that the RCEP had not considered the diversity of ways in which primary care is delivered. Members considered that most general practitioners would not have the time to consider the causes of the mainly ill defined symptoms individuals may present with.

33. The COT considered that the advice published by DH in 1996 regarding advice to general practitioners with suspected ill health attributed to pesticides was potentially unhelpful as it did not allow for all causes of illness to be investigated.

COT/COC conclusions

34. The Committees agreed the following overall conclusions with regard to the questions posed:

- i) *Consider, based on members expertise and the evidence presented in the RCEP report whether, the conclusions and recommendations reached in respect of health related topics are appropriate (see paras 2.65-2.69 reproduced in para 31 above (and 6.20-6.29) of the RCEP report)*

The COT and COC did not concur with the recommendation in paragraphs 2.65-2.67 and 2.69 of the RCEP report for the reasons outlined above in para 31 of this statement, but did concur with the suggestion made in para 2.68 of the RCEP report. The COT and COC agreed that it was important that a number of areas of further work were undertaken. These are given in para iii) below.

- ii) *Derive COT/COC conclusions in relation to the health related questions posed by the RCEP (see para 5 above) on the basis*

of the evidence reviewed and member's expertise, and to consider whether these concur with those reached with RCEP.

The COT and COC concluded that the available evidence did not convince members that there was a high degree of urgency for further research. The Committees agreed that there was no scientific basis for an additional precautionary approach to the risk assessment of pesticides.

- iii) *Consider whether any further work by COT/COC/COM should be undertaken with respect to bystander pesticide risk assessment and report any suggestions for further work to the ACP.*

The COT agreed that an epidemiological review of para-occupational exposure to pesticides should be undertaken. The COT agreed a review of the literature on chronic fatigue syndrome and multiple chemical sensitivity should be undertaken. The COC agreed that geographical studies of cancer incidence linked to potential exposure (possibly to include appropriate population biomonitoring data) should be considered. The COT agreed that in the first instance a targeted approach to biomonitoring research would be more informative to gain an estimate of bystander exposure.

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COT/06/05 and COC/06/S1**

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