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Pesticides Literature Review published by the Ontario College of Family Physicians

The paper below was considered by the Advisory Committee on Pesticides (ACP) at its meeting in May 2004. An ACP statement on the Ontario Review was published in October 2004.

Assessment of the Review by the Chairman of the Advisory Committee on Pesticides

1. This report describes an attempt to review systematically the peer-reviewed epidemiological literature that was published during 1992-2003 on the relation of pesticide exposure to a range of possible chronic health outcomes (12 cancer and four non-cancer). It does not describe any new primary research. For some years, the ACP Medical and Toxicology Panel has had a system for scrutinising annually the abstracts of published papers on pesticides and human health, and the material covered by the report overlaps substantially with that examined by the Panel. Differences include the rather longer time period covered by report, its inclusion of a few papers written in languages other than English, and its restriction to just the 16 specified health outcomes.
2. Some of the conclusions of the report accord with those reached by the Medical and Toxicology Panel. Thus, the Panel has previously noted an apparent consistency of epidemiological reports linking Parkinson's disease with pesticide exposure, and this led to the commissioning of a detailed review of the topic. Similarly, we have more recently asked that the Committee on Mutagenicity (COM) review the literature on biomarkers of genotoxicity in pesticide-exposed workers, in which the frequent report of positive findings seems at odds with the absence of in vivo genotoxicity for almost all pesticides when tested individually for regulatory purposes.
3. Other conclusions differ markedly from those of the Panel. For example, the report concludes (page 16) that "large well-designed cohort studies consistently show statistically significant positive associations" between solid tumours and pesticide exposure, that "these findings strongly support a reduction of pesticide use", and (page 63) "it can be clearly stated that at least some pesticides are carcinogens".
4. The main reason for the difference in conclusions appears to be the failure of the Ontario group to take proper account of all or even most of the available scientific evidence.
5. By design, the review is restricted to papers published during 1992-2003, and important epidemiological evidence that was published before this period is ignored. Thus, for example, the authors conclude (page 165) that "phenoxy herbicide exposure increased lung cancer risk" from an analysis based on one of two sets of controls in a single case-control study with a total of 65 cases, while completely ignoring the results of earlier studies that have also examined this association.
6. Worse still, even within the defined period of interest, only a minority of relevant papers have been properly taken into account. The authors claim (page 14) that they were able to identify only two cohort studies providing information on lung cancer and pesticides

that were published during the period of study, but a quick check on some of the papers considered in relation to other cancer outcomes reveals at least 10 further cohort studies giving data on lung cancer. And remarkably, a major international cohort study of almost 22,000 workers exposed to phenoxy herbicides, chlorophenols and dioxins (Kogevinas et al, 1997) is not mentioned anywhere in the sections on solid tumours or leukaemia. [This analysis included 1,127 cancer deaths in workers exposed to phenoxy herbicides and chlorophenols, among which 380 were from lung cancer. In the subset of subjects with no exposure to TCDD or other higher dioxins, mortality from lung cancer was close to expectation (SMR 1.03 based on 148 deaths).]

7. The explanation for this substantial omission of relevant data is a little uncertain because the exact search strategy and criteria for selection of papers are not clearly articulated. However, it appears that when considering each individual health outcome, the authors limited their review to papers for which that specific outcome was highlighted in their computerised search. Inevitably this will lead to a biased selection of reports since non-positive findings are much less likely to be picked out than those that point to a hazard.
8. On top of this, the authors' discussion of the research findings that they do consider is superficial and naïve. Although in their introduction they identify several potential limitations of epidemiological data, they make almost no attempt to evaluate the strengths and weaknesses of individual studies in this context. The possible influences of bias, chance and confounding are not properly addressed, and there is no attempt to address differences between studies in patterns and levels of exposure, and the implications of this for their interpretation. An important consideration when assessing epidemiological associations is the biological plausibility of a causal link, but in this review the large body of relevant evidence from toxicology is almost completely ignored. A good illustration of the superficiality of the report is its discussion of possible chronic toxicity from organophosphates, which is covered in less than two pages, as compared with the Committee on Toxicity (COT) report on this topic that ran to more than 200 pages (and reached rather different conclusions).
9. Furthermore, where the report does touch on toxicological issues, it tends to be simplistic and misleading. Malathion is said both to stimulate and suppress the immune system (page 63), but no reference is provided to support this statement. The short discussion of genetic polymorphisms (page 65) is an inadequate basis for the strong conclusion drawn. There is reference to erythrocyte cholinesterase as a biomarker of "exposure dose" (page 79), when it would generally be classed as a biomarker of effect. And on page 4 it is suggested that children are more vulnerable to pesticides because they eat and drink more per Kg body weight, whereas vulnerability would normally be judged in terms of the response to a dose adjusted to take account of body weight. [The toxicologists on the ACP may have further comments on paragraph 1 of page 4. I would also value a view on the assertion (page 36) that TCDD used to occur in 2,4-D production. My understanding is that, unlike with 2,4,5-T, the 2,3,7,8- congener would not be produced in this process.]
10. The report is notably unconventional in several of the statements that it makes about epidemiological methods. Case-control studies are said to "provide good exposure histories" (page 3), whereas in cohort studies it is usually impossible to obtain detailed pesticide exposure histories (page 9). However, because they frequently rely on information recalled from memory, the quality of exposure data in case-control studies, particularly in relation to specific chemicals, is generally much poorer than that in cohort studies, which often use documented records of processes and sometimes include occupational hygiene measurements. Cohort studies are said to be good for looking at rare illnesses (page 9), but this is in fact one of their main weak points, particularly if there is also a long latent interval between exposure and the manifestation of

disease. SMRs (standardised mortality rates) are said to underestimate the occurrence of curable and treatable disease (page 10), but the problem in this situation is a loss of statistical precision rather than an under estimation of risk. Cohort studies are said to be confounded by the healthy worker effect (page 10), but this bias is only a problem in cohort studies that use general population rates as a reference, and applies principally to diseases that cause prolonged and serious disability such as chronic obstructive pulmonary disease. It generally has little impact on risk estimates for cancer. A failure of effect estimates at an ecological level to reflect effects at an individual level is said to be the primary limitation of ecological designs (pages 10 and 11), but difficulties in controlling adequately for confounders are at least as important.

11. The section of the report on skin effects ignores findings from reporting schemes, although these are an important source of data on this health outcome. Moreover, the assertion that contact allergic reactions are known for all pesticides tested except paraquat (page 79) seems to be based on findings from a single study. If correct, it would imply that virtually all agricultural pesticides are documented contact allergens, which sounds unlikely.
12. The report advises reducing exposures to all pesticides, but does not indicate how far or on what basis an acceptable level of exposure should be determined. It also recommends that physicians should "correctly diagnose and treat …. chronic pesticide health effects" (page 165), but it gives no indication of how such effects could be diagnosed in the individual patient.
13. In my view, the report overall is scientifically weak, its main flaw being to draw inappropriate conclusions and make impractical recommendations for risk management on the basis of superficial consideration of an incomplete and biased selection of the relevant scientific evidence. However, I think it is important that the ACP should receive views from more than one epidemiologist, and I have therefore asked the secretariat to seek independent opinions from five other epidemiologists.

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