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Addendum to MUT/05/11

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT.

CONSIDERATION OF EPIDEMIOLOGY OVERVIEW PAPER FOR COM: BIOLOGICAL MONITORING OF GENOTOXICITY IN PESTICIDE APPLICATORS.

Briefing meeting with Dr L Rushton (IEH) and Professor P Farmer (Chair COM) 16 May 2005. held at IEH Leicester. 11.00 am (J Battershill COM secretariat (Minutes)).

1. The secretariat asked whether it was possible to identify the most adequately conducted studies within that provided. It was noted that all of the studies suffered from small size. The collection of data on confounding was variable and even when these data were available, they had rarely been adjusted for adequately. Overall no specific study was identified in the epidemiological overview report as suitable for identification of exposures (to pesticide active ingredients or occupational categories (such as Floriculturalists), associated with elevated indices of genotoxicity. It was agreed that some of the studies had more design faults than others but one or two were better. It was difficult to compare the studies because so many end points were evaluated.
2. The study by Garry et al 2001 (Environmental Health Perspectives, 109, 495-500, 2001) was considered to have been clearly designed with appropriate use of statistical techniques. This study had reported an effect with urinary 2,4 levels, but was based on a very small number of individuals and had not adequately accounted for potential confounding. The study by Peluso et al (Cancer Epidemiology, Biomarkers prevention, 5, 361-369, 1996) had included adequate modelling (and reported OR ratios for exposure and confounding factors) but was very small and hence only limited conclusions could be reached. It was noted that the Peluso study was based on DNA adduct measurements and not an evaluation of mutagenic events. It was noted all other studies had more limitations than these two studies. It was emphasised that the lack of adequate evaluate of individual exposures severely limited any conclusions which could have been reached with regard to pesticide active ingredients.
3. Other problems highlighted consistently in the data set included selection of individuals (poor reporting, often no *a priori* hypothesis as to why the study was being undertaken), frequent multiple testing with no correction for this, lack of analyses for the influence of confounding.
4. The papers did not discuss the biological significance of the magnitude of response. The secretariat noted that an analysis of magnitude of response and an attempt to evaluate a historical control range (for MN and CA response) had

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been undertaken. There had been some surprise (from the secretariat) that the magnitude of the risk estimates seen with cytotoxic drugs were comparable to that identified in pesticide applicators. It was noted that figure 1 of Annex 1 to MUT/05/12 compared the magnitude of response between nurses/patients exposed to cytotoxic drugs and that in pesticide applicators. It was noted that there were considerable problems in comparing such data (as outlined in the covering paper to MUT/05/12). However it was stated that although there was some evidence for higher responses in pesticide applicators, without a consideration of confounding in these studies and a comparison of the quality of studies in nurses/patients exposed to cytotoxic drugs and pesticide applicators, no study of pesticide applicators could be singled out for further consideration as suitable for identification of exposures (to pesticide active ingredients or occupational categories (such as Floriculturalists), associated with elevated indices of genotoxicity as suitable for identification of exposures (to pesticide active ingredients or occupational categories (such as Floriculturalists), associated with elevated indices of genotoxicity on the basis of this assessment.

5. The evaluation of listed pesticides from negative and positive studies was considered. It was acknowledged that the listings of pesticides used given in the papers did not provide adequate information on actual exposures experienced by the study subjects. It was noted that the higher prevalence of benzimidazoles might simply represent higher frequency of use. However if the COM was to agree that the reason for positive results in these studies might be the occurrence of category 2 and 3 mutagens in exposures, then this would lead to the following argument. There is a biological rationale as to why benzimidazoles might induce positive results in MN/CA monitoring in pesticide applicators, there was evidence that the use of these compounds (noted benomyl no longer approved in UK) had been increasing in the UK, this lead to the argument that these compounds might be a valid starting point for identifying relevant UK exposures for a UK based study. (it was noted that no UK study existed). (It was noted that Bolognesi 2004 (Mutation Research, 557, 109-117, 2004) had reported an effect on centromere positive MN in relation to exposure to benzimidazoles, but it was noted that the statistical approach used by these authors was comparatively poor and the result documented was small in magnitude and might represent multiple testing. It was also noted that Peluso had cited exposure to benzimidazoles, but there was no reason why DNA adducts should be affected by these compounds). The rationale for considering other actives was not considered in detail at this meeting

6. A separate approach would be to focus on occupational categories for further research (e.g UK equivalents to Floriculture in EU studies). It was noted that the review request from ACP did identify occupational categories but regulatory action through ACP was in terms of regulated pesticide products. One possible way forward would be to consider whether the HSE NPTC register was appropriate. (This would be a matter for HSE).

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7. It was noted that the COT WIGRAMP review had considered benzimidazoles and that these compounds had been identified as priorities for further consideration. The FSA review group had recently produced an initial review conducted in accordance with the EPA proposals for reviewing mixtures. It was noted that this aspect had not been considered in the COM papers but members should be made aware of the ongoing work.

8. Other aspects raised included the effect of protective clothing (vis differences in Europe and UK) and the potential effect of cumulative exposure. (These aspects had been considered by COM at the October 2004 and February 2005 meetings).

9. It was agreed that there were a number of studies that could be considered. There were arguments for considering a longitudinal study as more preferential than a cross-sectional study. Chamber studies were discussed but the considerable ethical problems were also raised.

10. It was noted that a preliminary updating information report would go to the July MTP and this might give an opportunity to provide some further suggestions for research.

11. The overall conclusions reached in the IEH report (MUT/05/11) were agreed. The meeting closed at 12.55 pm.

J.Battershill
25 May 2005
COM Secretariat.