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MEMORANDUM

SUBJECT: Ad Hoc Meeting of HED Cancer Assessment Review Committee on EBDC's: Maneb and Metiram

FROM: Linda Taylor, Ph.D.
Reregistration Branch I
Health Effects Division (7509C)

and

Esther Rinde, Ph.D.
Science Analysis Branch
Health Effects Division (7509C)

THROUGH: William Burnam, Chief
Science Analysis Branch
Health Effects Division (7509C)

TO: Anne Overstreet
Reregistration Branch III
Special Review and Reregistration Division (7508W)

The *ad hoc* HED Cancer Assessment Review Committee (CARC) met on June 9, 1999 to determine (1) whether the chronic toxicity/carcinogenicity studies in rats on Maneb and those in rats and mice on Metiram were adequate; (2) whether Maneb and/or Metiram should be presented to the full CARC or whether the data on ETU would continue to drive the risk assessment with respect to carcinogenic potential; and (3) whether these studies, if inadequate, along with the mouse study on Mancozeb, should be repeated. The CARC members present were William Burnam, Mike Ioannou, Karl Baetcke, Linda Taylor and Esther Rinde.

BACKGROUND:

ETU is a contaminant/metabolite/degradation product of the ethylene bisdithiocarbamates (EBDC's). Maneb, Mancozeb and Metiram are fungicides/pesticides

(and REDs for the year 2000) which degrade and/or are metabolized to ETU. Only ETU and Mancozeb were reviewed/classified by the HED Carcinogenicity Peer Review Committee (CPRC).

ETU was associated with statistically significant increases in thyroid follicular cell adenomas and carcinomas with significant positive trends in both sexes of the F344 rat at doses up to 250 ppm; and in the B6C3F1 mouse there were statistically significant increases and significant positive trends in hepatocellular adenomas, carcinomas and combined adenoma/carcinoma in both sexes at doses up to 1000 ppm and statistically significant increases in pituitary adenomas with significant positive trends in both sexes. ETU was classified by the CPRC as a Group B2 carcinogen with a Q* based on combined liver tumors in female mice.

Mancozeb was associated with statistically significant increases and significant positive trends in thyroid follicular cell adenomas, carcinomas and combined adenoma/carcinoma in both sexes of Sprague Dawley rats at doses up to 750 ppm. The study in CD-1 mice was considered inadequate because the dosing was not high enough to assess the carcinogenic potential of Mancozeb in mice. The CPRC classified Mancozeb as a Group B2 carcinogen and concluded that since Mancozeb is known to be converted to ETU, which is classified as a B2, and the types of tumors are the same as with ETU, the Q* for Mancozeb should be the same as for ETU.

1) Whether the chronic toxicity/carcinogenicity studies in rats on Maneb and those in rats and mice on Metiram were adequate:

The *ad hoc* Committee reviewed the long-term rodent studies for Maneb and Metiram and concluded that for Maneb there was one acceptable study (in the mouse) in which hepatocellular adenomas were observed in both sexes, but the rat study was not acceptable; for Metiram, neither the rat nor mouse long-term studies were adequate for assessing the carcinogenicity potential for Metiram. Information from the available adequate studies for Maneb (and for Mancozeb) were not inconsistent with that for ETU in terms of the tumor types. The unacceptable studies, while considered inadequate for assessment of carcinogenic potential, still provided information on precursor lesions which were consistent with the effects observed with ETU; i.e., there were liver/thyroid effects. There is also a commonality of metabolism for all the EBDC chemicals. It was agreed that Maneb and Metiram, like Mancozeb, are converted to ETU and should be considered similarly for risk assessment purposes.

2) Whether Maneb and/or Metiram should be presented to the full CARC or whether the data on ETU would continue to drive the risk assessment with respect to carcinogenic potential:

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The *ad hoc* Committee concluded that because the EBDCs are known to be converted to ETU, each EBDC (including Maneb and Metiram) should be classified as Group B2, and after applying the metabolic conversion factor for EBDC to ETU of 0.075, the Q_1* of ETU will be used. It was also agreed that there was no need for an assessment of Maneb or Metiram by the full CARC at this time. Based on the weight of evidence, the Committee is confident that the risk would not be underestimated with respect to cancer potential for all of the EBDCs using the ETU data.

3) Whether these studies, if inadequate, along with the mouse study on Mancozeb, should be repeated:

The *ad hoc* Committee did not at this time recommend that any of the inadequate long-term studies be repeated; however, the requirement to repeat them would be RESERVED. Future requests for a re-evaluation of the classification of any individual EBDC, based on a mechanistic approach to risk assessment, would warrant/necessitate submissions of adequate long term studies to assess the full carcinogenic potential for that chemical.