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MEMORANDUM

SUBJECT: Isoxaflutole. PC Code 123000. Outcome of the *Ad hoc* Metabolism Assessment Review Committee* Meeting Held on March 23, 1998 Concerning isoxaflutole metabolite RPA 203328. DP Barcode D244555.

FROM: Alberto Protzel
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THROUGH: Richard Loranger, Chair
Metabolism Assessment Review Committee
Health Effects Division (7509C)

TO: Metabolism Assessment Review Committee
Health Effects Division (7509C)

The HED Metabolism Assessment Review Committee (MARC) met on September 4, 1997 to discuss isoxaflutole metabolites of toxicological significance. In this meeting the MARC concluded that metabolite RPA 203328 is among the residues of concern in drinking water. RPA 203328 is a metabolite in rats (0.6-3.6% of the dose). Based on the information available at the time (a 28-day dietary study in rats and a negative Ames assay with RPA 203328), it was concluded in the September 4 meeting that although RPA 203328 is less toxic than the parent it should still be considered to be a metabolite of toxicological concern. In particular, for carcinogenicity potential metabolite RPA 203328 should be considered to be of equal toxicity as the parent.

Recently (March 1998) the Agency received SAR data and additional mutagenicity information (of a preliminary nature) on the RPA 203328 metabolite. An *ad hoc* subgroup of the HED MARC met on March 23 to re-evaluate the status of the RPA 203328 metabolite. The submitted preliminary data consisted of negative genotoxicity results for a micronucleus

assay (report preparation in progress), a CHO/HGPRT Assay (-S9, study in progress), and a chromosomal aberration test (report preparation in progress) .

Pending submission and review with Acceptable Rating of the above mutagenicity studies, it was concluded that the RPA 203328 *at this time does not pose a special toxicological concern as to carcinogenicity* based on the following considerations:

1. On a 28-day feeding rat study with RPA 203328 [MRID 43904813], no significant toxicity was observed at doses up to 1120 or 1270 mg/kg/day (for males and females, respectively). In particular, the liver does not appear to be a target organ for RPA 203328. There were no changes in hematology or clinical chemistry and no hepatic effects or histopathology were seen. In contrast, the parent isoxaflutole, a liver and thyroid carcinogen, produced statistically significant increases in liver weights and microsomal enzymes in two 14-day feeding studies in rats. In one study [MRID 43904819] absolute and relative liver weights were statistically significantly elevated at 100 and 400 mg/kg/day and microsomal enzymes at 10, 100 and 400 mg/kg/day for 14 days in the diet. In the second study [MRID 43904818], T4 was statistically significantly decreased, and absolute and relative liver weights and microsomal enzymes (including UDPGT) were statistically significantly increased. Liver histopathology and increases in absolute and relative liver weights and microsomal enzyme induction have been associated with liver and thyroid tumors.
2. The negative mutagenicity data in 4 assays (Ames, micronucleus, CHO/HGPRT (-S9), chromosomal aberration) indicate a reduced concern for the mutagenicity of this chemical. These results are conditional, pending submission, review and an acceptable rating for the final report of these studies.
3. In contrast to the parent, the RPA 203328 metabolite is rather polar, is likely to undergo a different tissue distribution than the parent and may not undergo extensive metabolism prior to being excreted. If metabolized, it is much less likely to be metabolized to electrophilic structures as the parent isoxaflutole. Furthermore, the structure of RPA 203328 indicates that the compound, if unmetabolized, is less likely than the parent to engage in electrophilic interactions.

Because RPA 203328 is a rat metabolite of isoxaflutole and increased sensitivity to offspring was shown by the parent, it was concluded that RPA 203328 cannot be excluded from risk assessments based on a developmental endpoint. Therefore, until review of an acceptable rat developmental toxicity study on RPA 203328, HED cannot determine if RPA 203328 can be excluded from risk assessments based on a developmental endpoint. Also, the proposed analytical enforcement method for plants involves hydrolysis of isoxaflutole to RPA 202248, conversion of RPA 202248 to RPA 203328, and then derivatization of RPA 203328 to a methyl ester for GC analysis. Therefore, even though there may not be concerns with RPA 203328 for certain tox endpoints, it will need to be included in the dietary risk assessment for food commodities.

Metabolism Assessment Review Committee Members in Attendance

George Kramer
Richard Loranger
Alberto Protzel
Jim Peggins

Metabolism Assessment Review Committee Non-Members in Attendance

Mike Ioannou
Barbara Madden

*formerly the HED Metabolism Committee