UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DATE **December 10, 1997**

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **ISOXAFLUTOLE** - Report of the Risk Assessment Review Committee

FROM: Jess Rowland, Executive Secretary 12/10/97
Risk Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Karen Whitby, Chair 12/10/97
Risk Assessment Review Committee
Health Effects Division (7509C)

TO: Barbara Madden, Branch Senior Scientist
Risk Characterization and Analsysis Branch
Health Effects Division (7509C)

and

Daniel Kenny/Joanne Miller
PM Team 23
Herbicide Branch
Registration Division (7505C)

PC Code: 123000

The Health Effects Division (HED) Risk Assessment Review Committee (RARC) conducted an in-depth review of the risk assessment document that evaluated the Registrant's request for the establishment of permanent tolerances for residues of Isoxaflutole in/on corn (PP # 6F4664) as well as the registration of an end-use product formulation (*Balance WDG Herbicide 264-LAT*). The Committee's conclusions are attached.

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Page #	Recommendations
3	*Paragraph 7:* Revise the last statement "A risk.....considered appropriate for adult workers".
9	*Section B.1.d:* The summaries of the rat and rabbit developmental studies do not indicate if the developmental effects (skeletal malformations/variations) were based on the fetal or litter incidences and whether or not the current incidences were compared with historical control incidences of the testing laboratory to ascertain if the developmental effects are truly treatment related.
13	*Section B.1.i*: Please consult with the reviewer and provide more details for the dermal absorption study. Also, the dermal absorption factor (0.2% at 24 hours) is incorrect. A dermal absorption factor of 3.46% at 10 hours should be used for risk assessments. Because of this change, the dermal risk assessments should be re-evaluated.
13/14	*Section B.1.j*: Please consult with the toxicologist to provide how the special studies discussed on Page 13 and 14 are "used" in the "overall" evaluation of the toxicity of Isoxaflutole. Were the studies that evaluated the mode of action used in assessing the carcinogenic potential of the compound ? Also, are thyroid stimulating hormone (TSH) data available for MRID No. 43904806 ?
15	*Paragraph 4:* The decision logic used in the application of the 3 x factor for risk assessments is unclear. Revise this section after the revist by Hazard Identification Assessment Review Committee.
15/16	The chronic dietary risk assessment (RfD) is based on a NOEL established in a chronic study and a UF of 300 (10 x , 10 x and 3 x). The additional 3 x factor was used for special sensitivity of infants and children.
18	The acute dietary risk assessment is based on a developmental LOEL and with a MOE of 300. The additional 3 x factor is applied because of the use of a LOEL (i.e., lack of a NOEL in the critical study).

18 The 3 x factor is applied for different reasons for these dietary risk assessments. (i.e., for acute it because of the use of the LOEL and for the chronic its because of increased sensitivity) Also, there is no discussion regarding the need for a developmental neurotoxicity study. **It is recommended that this issue be re-evaluated by the Hazard Identification Assessment Review Committee.**

19 *Paragraph 3:* Revise the statement "This endpoint.....the RfD"-mention the endpoint observed in the study which was used for the RfD.

21 *Paragraph 3:* Clarify the statement "that metabolite 202248 is any less toxic than the parent and there was not sufficient enough evidence to rule out that metabolite 203328 is any less toxic than the parent". This statement is ambiguous.

27 *Paragraph 5:* in the text, a tolerance level of 0.2 ppm is indicated for poultry, liver, whereas, for the same commodity, a tolerance level of 0.3 ppm is indicated in the list at the top of the page. Also, include"Fat" in the list on the top of the page.

29 *Table 5:* For the 3rd column, a "heading" of Total Toxic Residues would be more appropriate than the current "Anticipated Residues for DRES Run ". Also, the Poultry AR's are "higher" than the required tolerances. Include Liver, ruminant.

32 *Table 8:* Include only the "days" used (i.e., delete Days 4, 21, 60 and 90).

33 *Paragraph 2:* The last line indicates a water solubility of 3.5 mg/L, where as on Page 5, the water solubility is indicated as 5.5 mg/L - check values (Is this due to a difference in pH?)..

35 *Paragraph 5:* Delete the statement " It is important.....in male rats". Delete this statement which is also made on Page 17. For carcinogenicity risk assessments, the "point of departure" dose for non-neoplastic lesions (i.e., thyroid hyperplasia) can not be higher than the dose in which tumors were seen. Consult with Bill Burnam for assistance with revision..

36 *Paragraph* 8: Change the term "PCO" to Private Commercial Applicantors.