9-30-97

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

September 30, 1997

**MEMORANDUM**

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Meeting to Discuss Issues Regarding Cancer Peer Review Document for the New Chemical Isoxaflutole (123000). DP Number: None.

FROM: Barbara Mádden, Branch Senior Scientist
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

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

TO: Daniel Kenny
Herbicide Branch
Registration Division (7505C)

Members of the Health Effects Division, William Burnam, Sanjivani Diwan, Barbara Madden, Hugh Pettigrew and Esther Rinde met on August 26, 1997 to discuss issues regarding the August 6, 1997 Carcinogenicity Peer Review of Isoxaflutole document. In the August 6, 1997 document the Cancer Peer Review Committee (CPRC) recommended that for the purpose of risk characterization, a non-linear approach - Margin of Exposure (MOE) be applied to the most sensitive precursor lesion in the male rat thyroid, and that a linear low-dose extrapolation be applied for the tumors of the rat liver.

In the August 26, 1997 meeting, upon review of the data and CPRC document it was recommended that for the male rat thyroid, the No Observable Effect Level (NOEL) of 2 mg/kg/day** observed in a 104 week combined chronic toxicity/carcinogenicity study in rats (MRID 43904806) be used for the non-linear (MOE) cancer risk assessment. The Lowest Observable Effect Level (LOEL) for this study was 20 mg/kg/day** based on thyroid hyperplasia. Tumors were statistically significantly increased in this study only at the 500 mg/kg/day dose.

It was also decided that the results from the 78-week feeding/carcinogenicity study in mice (MRID 3904807) should also be included when determining the Q* to be used for risk assessment for the linear low-dose extrapolation. It was recommended that a Q* be developed for the female mouse liver, female rat liver, male mouse liver and male rat liver and the Q* with the highest unit of potency be used for risk assessment.

1

**Please note that the LOEL for hyperplasia (20 m/k/d) is 10-fold greater than the dose at which an increase in thyroid tumors (numerical only) first occurs in male rats (2 m/k/d) - see TABLE 5 from the Peer Review Document (attached).

Table 5. Isoxaflutole - CD(SD)BR VAF Plus Rat Study

**Male Thyroid Follicular Cell Tumor Rates**[+]
and Peto's Prevalence Test Results (p values)

| | Dose (mg/kg/day) | | | | |
|---|---|---|---|---|---|
| | 0 | 0.5 | **2.0** | 20.0 | 500.0 |
| Adenomas (%) | 3/66 (5) | 1/60 (2) | **5[a]/69 (7)** | 7/68 (10) | 15/69 (22) |
| p = | 0.000** | - | 0.271 | 0.127 | 0.005** |
| Carcinomas (%) | 0/53 (0) | 1/46 (2) | **2/59 (3)** | 1/58 (2) | 3[b]/62 (5) |
| p = | 0.113 | 0.117 | 0.159 | 0.169 | 0.042* |
| Combined (%) | 3/66 (5) | 2/60 (3) | **7/69 (10)** | 8/68 (12) | 17[c]/69 (25) |
| p = | 0.000** | - | 0.120 | 0.081 | 0.002** |

+Number of tumor bearing animals/Number of animals examined, excluding those that died before the observation of the first tumor; also excludes week 53 interim sacrifice animals.

[a]First thyroid follicular cell adenoma observed at week 70, dose 2.0 mg/kg/day.

[b]First thyroid follicular cell carcinoma observed at week 91, dose 500.0 mg/kg/day.

[c]One animal in the 500.0 mg/kg/day dose group had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis. There were no thyroid follicular cell tumors in any interim sacrifice animals.

Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.