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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Isoxaflutole: Review of Rebuttal to Terrestrial Plant Turnip Study
DP Barcode D246666

FROM: Michael Davy, Agronomist
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Thru: Elizabeth M. Leovey, Chief
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TO: Joanne Miller, PM-23
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EFED has reviewed the registrant's rebuttal of the turnip vegetative vigor data evaluation record for parent isoxaflutole. The rebuttal was submitted under DP Barcode D246666 for section 3 registration of isoxaflutole. This rebuttal was submitted in response to EFED's request to retest the vegetative vigor studies using lettuce and ryegrass (D225503,D232445). The registrant retested the lettuce and ryegrass species (D240106, MRID 44399905). Although the turnip was not requested, they also retested the turnip. All three studies were found not to be core studies.

The registrant has suggested that the original turnip study should not be used because the study provided a shallow concentration-response relationship. **EFED maintains that the original turnip study is a valid study and will continue to be used for the most sensitive phytotoxic indicators.**

EFED concluded the re-analysis in the following manner:

The registrant has stated that the original turnip study (MRID 43573242) should not be used and the cabbage species should be used instead because of the following reasons:

1) There was a shallow concentration-response relationship with the NOEC value higher than the EC_{25} value.

2) The concentration-response study in the repeated study (MRID 44399905) was better defined with a positive slope and all of the NOEC values were below the corresponding EC_{25} values.

3) The EC_{25} values calculated from the repeated study was confirmed by another set of studies done in natural soils. These studies have not been submitted to EPA.

The EFED's responses to the registrant's rebuttal of the original turnip study are as follows:

1) EFED has reexamined the original turnip and cabbage studies using a continuous toxicity data model[1]. The NOEC is determined by using William's test. The results are summarized below:

Turnip EC_{25}= 2.28×10^{-5} lb ai/A (95% C.I. = 0.15 - 33.2×10^{-5} lb ai/A)
Turnip NOEC = 1.1×10^{-5} lb ai/A
Cabbage EC_{25}= 2.97×10^{-5} lb ai/A (95% C.I. = 0.76 - 11.6×10^{-5} lb ai/A)
Cabbage NOEC = 3.4×10^{-5} lb ai/A

The registrant has indicated concerns with the NOEC value being higher than the EC_{25} value. Because of the continuous toxicity data, the NOEC is now less than the EC_{25}.

2) A shallow concentration-response relationship is not a valid reason for rejecting these results. Among weed scientists, several herbicides (sulfonylurea) are noted for having a shallow concentration-response relationship[2]. A plot of the data (attached) reveals that dose-response relationship is reasonable. It also reveals that there was some variability among replicate means, but this is common for terrestrial plant toxicity studies. The data in the controls were pooled legitimately to increase the confidence of the estimated mean response.

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[1] R.D. Bruce and D.J. Versteeg. 1992. A statistical procedure for modeling continous toxicity data. Environ. Tox. and Chem. 11:1485-1494.

[2] D.C. Thill. 1997. *Sulfonylureas and Triazolopyrimidines*, Hericide Action course, Purdue University. P. 350

3) The data provided by MRID 43573242 are completely acceptable data for estimating the EC_{25} for effects on turnip root weight. The Pesticide Reregistration Rejection Rate Analysis: Ecological Effects (EPA 738-R-94-035) states on page 155 that tier-2 plant protection studies (Guideline No. 123-1 and 123-2) "will be rejected if there is not at least one dose greater than the EC_{50} and one dose lower than the EC_{25}." The doses used in this study were well placed for defining the EC_{25} because the highest dose (0.0047 lb ai/A) was greater than the EC_{50} (0.00017 lb ai/A) and the lowest dose (0.000011 lb ai/A) was lower than the EC_{25}. Furthermore, a goodness-of-fit test yielded a P-value of 0.41, suggesting a lack of evidence to reject a null hypothesis that the model does not fit the data. In fact, the fit of the model is better than it usually found with phytotoxicity data. In conclusion, there is no reason not to reject the data from the original turnip study.

EFED believes that the true EC_{25} for the most sensitive non-target plant species is less than the 2.28×10^{-5} lb ai/A value in the above re-analysis for the following reasons:

1. The original turnip study used a high amount of water as a carrier for the isoxaflutole being applied to the vegetative foliage. The label recommends 10 gallons of water to be used on field application. The study provided an equivalent of 200 gallons per acre. Some isoxaflutole residues may have been washed off the foliage. This would underestimate the phytotoxicity. It is believed that the phytotoxicity of isoxaflutole to the turnip species is less than 2.28×10^{-5} lb ai/A.

2. The most sensitive species tested is used as a surrogate for the many thousands of non-target terrestrial plant species known in North America. If each species is tested to represent only that particular species, then several thousands of species would need to be tested. This is an unfeasible method of coming up with data to provide a risk assessment to non-target terrestrial plants. Therefore, because of this uncertainty, the most sensitive species with the most sensitive parameter is used to represent the thousands of untested non-target terrestrial plant species.

3. The cabbage species (same genus as turnip) confirms the phytotoxicity of isoxaflutole with similar EC_{25} results as the turnip.

4. The confidence interval of the re-analysis shows that the 95% lower bound EC_{25} value should be 0.15×10^{-5} lb ai/A and 0.76×10^{-5} lb ai/A for turnip and cabbage, respectively. This approach would be conceptually similar to the way 90% upper bound fate half-lives values are used in modeling. EFED would also argue that these lower values would be protective and would provide more certainty what EC_{25} value should be represented for the vast numbers of untested non-target plant species.

Because of the above cited reasons, EFED will continue to use the most sensitive EC_{25} value as 1×10^{-5} lb ai/A[3] unless field data can prove the EC_{25} value otherwise.

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[3] This is the EC_{25} value of the original turnip study that used a probit model.