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

MEMORANDUM AUG - 2 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: R. Mountfort (23)
Registration Division (TS-767)

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Review of Thidiazuron Mutagenicity Studies;
Reg.#2139-122 CASWELL#659A

Registrant: Nor-Am Agricultural Products
350 West Shuman Blvd.
Naperville, Illinois 60566

Recommendation:

It is recommended that the dominant lethal study be classified as Supplementary Data and that individual animal data be requested from the sponsor. Although the results are not conclusive, a weak dominant lethal effect is suggested.

The micronucleus assay was reviewed in my memo of April 30, 1982.

Review of Data:

1. Dominant Lethal Assay, Mouse. Conducted by Schering AG, Berlin, West Germany, April 15, 1981 (Report PF 29/81) and submitted by Nor-Am Co., on May 25, 1982.

Male NMRI/SPF mice, 11 to 12 weeks old, were administered by gavage either 0.05 mg/kg of tetramine aqueous solution, 100, 200 or 400 mg/kg of thidiazuron technical (97.3% purity) in a Myrj 53 solution or 10 ml/kg of vehicle. Fifty males per group were treated in each dose group for seven weeks and, after the final week of treatment, each was housed with an untreated virgin female for 7 days. After 7 days the female was replaced and each male was mated with a total of 3 females over a 3 week period. Males were sacrificed after the 3rd mating and females were sacrificed after 13-18 days of gestation. The uterus of all females were examined for number of live fetuses and early and late fetal deaths.

Results:

Mid and high dose treated animals showed a weight loss after 7 weeks of treatment; vehicle and positive control groups and the low dose group showed weight gains.

The number of dead implants/total number of implants were as follows for weeks 1-3:

	Week 1	Week 2	Week 3
Vehicle Control	23/587	24/622	23/612
100 mg/kg	22/550	18/567	23/625
200 mg/kg	27/558	33/597	22/612
400 mg/kg	56/573	30/590	31/607
Tetramine	130/586	77/586	34/637

Statistically significant differences ($p < .01$) are found in the positive control group for weeks 1 and 2 and the high dose group for week 1. The increase in the high dose group at week 1 was discussed in the Final Report as follows:

"However, this result is not considered as an effect of dominant lethality, since the other parameters were normal and there was no increase in subsequent weeks of breeding. The observed effect at week 1 was mainly due to 4 females, showing totally 21 dead implants (nearly as much as the complete vehicle control), whereas at weeks 2 and 3 the corresponding males sired totally 49 and 51 live implants with only 0 and 2 dead implants, respectively."

Based on the increased number of implantation deaths at week 1 in the high dose group, it is the opinion of this reviewer that a weak dominant lethal effect is suggested, but not demonstrated.

The arguments advanced in the Final Report (noted above) to dismiss the apparent effect are not conclusive. Although it is true that other parameters were normal, the ratio of dead implants/total implants is the most relevant indicator of dominant lethality (Bateman, 1977). The lack of an apparent effect during weeks 2 and 3, cannot be denied; however, it is noted that the positive control results were also decreased at week 2 and were indistinguishable from the vehicle control during week 3. Finally, regarding the contribution of 4 females

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to the apparent effect, it seems unlikely, to this reviewer, that the 4 females with the highest rates of resorption all occurred in the high dose group due to chance alone. Because individual values were not reported for males or females on test, further analysis of the data is difficult.

Classification:

Supplementary Data, inconclusive. A weak dominant lethal effect is suggested at 400 mg/kg. It is recommended that individual findings be requested from the sponsor.

Bateman, A.J. "The Dominant Lethal Assay in the Male Mouse" in Handbook of Mutagenicity Test Procedures, Kilbey, Legator, Nichols and Ramel, eds., Elsevier/North Holland Biomedical Press, 1977.

2. Modified Micronucleus Test. Conducted by Huntingdon Research Center, Huntingdon, England and submitted by Nor-Am Agricultural Products, Inc., Naperville, Illinois on May 29, 1981.

This study was reviewed in my memo of April 30, 1982.

Gary J Burin 7/28/82

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