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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

**MEMORANDUM:**

Subject: I.D. No. 080801-000100: Ametryn. Phase 4 Response Submission

From: Myron S. Ottley, Ph. D
Section IV
Toxicology Branch I
Health Effects Division (H7509C)
Myron S. Ottley 11/12/91

Tox. Chem. No. 431
HED Proj. No. 2-0182
Submission No. S405107

To: Christine Rice PM52
Special Review and Reregistration Division (H7508W)

Thru: Marion P. Copley, D.V.M., D.A.B.T.
Section Head
Section IV, Toxicology Branch I
Health Effects Division (H7509C)
Marion Copley 11/13/91
KE 11/24/91

**CONCLUSIONS**

1. The Neurotoxicity Screen requirement [81-8-SS and 82-7-SS] should be postponed pending HED review of the chronic and oncogenicity data on Ametryn Technical.

2. The Combined Chronic Feeding/Onco Rat [83-1(a), 83-2(a)] study should be accepted for review, since EPA concerns have been answered and the deficiencies noted are not sufficiently grave to disqualify the study outright.

3. The Chronic Toxicity Nonrodent (Dog) study [83-1(b)] should be accepted for review, since EPA concerns have been answered.

4. A decision on the Mouse Oncogenicity study [83-2(b)] is reserved at this time, pending in-depth review of 1) the study (MRID #40349904), 2) its summary (MRID # 92002022) and 3) the companion 28-day pilot feeding mouse study (MRID #92002041). Concern is due primarily to an apparently inadequate degree of toxicity at the high dose level. If a new mouse oncogenicity study is required based on the outcome of the in-depth review, the other deficiencies cited (no homogeneity determinations of test material in vehicle; no individual observation; no blood smears; no histopathological evaluation of rectum) should be rectified.

## RESULTS

The accompanying table (pages 3, 4) lists HED's comments and requirements concerning data submitted for review on Ametryn, Ciba Geigy's response to HED's comments, and HED's current disposition on the data based on Ciba Geigy's comments and availability of new information.

After cross-checking HED's files for previously evaluated studies, and taking into account the data screened in this submission, it appears that, with the exception of the mouse onco study, sufficient data have been submitted to satisfactorily meet the Acceptance Criteria for the Subdivision F pre-review screen.

## DISCUSSION

### Data Set

The studies discussed in the attached table are just part of the data submitted in previous actions in the 1980s on Ametryn Technical by Ciba Geigy. Other required data, such as acute toxicity (with the exception of acute inhalation), developmental toxicity, reproductive toxicity, and mutagenicity, have been submitted and judged acceptable by HED in previous submissions.

### Significant Toxicity

Concern was raised by HED during the pre-review toxicity screen about the potential of Ametryn to cause neurotoxicity because of the toxic signs seen in the acute rat study (cf. accompanying table). However, these observations appear not to be corroborated in the chronic data that have been submitted, with the possible exception of the chronic dog study, where ataxia, cachexia, coma, convulsions, hypersensitivity, hypoactivity, hypothermia and tremors were observed at lethal dose levels (10,000 ppm or approx. 250 mg/kg/d).

Ciba Geigy remarked that none of the other triazines they have tested (thio-, methoxy-, chloro-triazines) showed any manifestations of neurotoxicity, neither clinically, behaviorally, nor histopathologically. Therefore the recommendation to postpone neurotoxicity screening requirements pending HED review of chronic/onco data seems prudent.

### Data Review and Acceptance

Acceptance of the data discussed in this action, at this stage, does not constitute a Core Classification. This is part of an Acceptance Criteria Screen only. In-depth review of each study and the supporting documents is required before final conclusions can be drawn on the acceptability of the data.

✳ Toxicology Branch I (TBI) requests a **Bean** for immediate in-depth review of the data cited in Conclusion #4. TBI already has hard copy of these studies.

| Study / Guideline # | Previous EPA Comment/Requirements | Ciba Geigy Response | Current Recommended Disposition |
|---|---|---|---|
| Acute/90-day Neurotox. Screening/Rats 81-8 & 82-7 90-day Feeding in rodent & nonrodent 82-1(a) & (b) | EPA requires Neurotoxicity screening based on these clinical signs observed in the acute test: piloerection, decreased activity, lacrimation, nasal discharge, ptosis, salivation, polyuria, dyspnea, tremors, dilated pupils, constricted pupils | These signs are commonly seen in acute toxicity studies, especially in moribund animals. Most animals exhibiting these signs were moribund and died. Survivors showed only transient signs and no neurotoxicity was observed. Therefore neurotoxicity screening unnecessary. | Chronic &/or subchronic data would verify presence or absence of effects. None has been received at this point, since this is a pre-review screen process. Data from the 4-week oral range-finding study (MRID #92002001) reported hyper-sensitivity, hypo-activity and/or hypothermia at 6000 & 10000 ppm. Nothing was seen in Summaries of Chronic/Rat (#92002020), mouse 4-week pilot feeding study (#92002041), 102-week mouse onco study (#92002022). In the 52-week dog chronic summary (#92002021), ataxia, cachexia, coma, convulsions, hypersensitivity, hypoactivity, hypothermia, tremors were observed at lethal dose levels. Recommend postponing neurotoxicity screen requirement pending HED review of chronic/onco data. |
| Combined Chronic Feeding/Onco Rat 83-1(a),83-2(a) | Test article purity not noted. | Test Article purity provided on page 8 of Phase 3 Summary (EPA SUMMARY MRID NO. 92002020) | Verified |
| | High dose level reductions (5000 -> 4000 -> 2000 ppm) required further study. | Disagrees ("does not seem to be an objection"). Refers EPA to 4-week Oral range-finding study (MRID # 40382001). | Dose levels in 4-week rangefinding study were 0, 2,000, 4,000, 6,000, 10,000. Submitter claims MTD (submitter's language) < 4000 ppm, NOEL < 2,000 ppm. in 4 wks. Therefore, the rationale for the initial high dose selection of 5,000 ppm is not clear. This concern does not disqualify this study. |
| | Survival low in controls. | Guidelines require min. 25% survival. Study achieved 43% survival. | Verified. However 43% survival is low, and may suggest substandard testing procedures or housing conditions. |
| | Creatinine not measured. | Addressed on page 8 of Phase 3 Summary (EPA SUMMARY MRID NO. 92002020). Also, Acceptance Criteria Checklist has this only as Supplemental | Verified as optional. |

| Study / Guideline # | Previous EPA Comment/Requirements | Ciba Geigy Response | Current Recommended Disposition |
|---|---|---|---|
| Chronic Toxicity Non-rodent 83-1(b) | Test article purity and stability not noted. | Test Article information provided on page 8 of Phase 3 Summary (EPA SUMMARY MRID NO. 92002021) | Verified. |
| | Lung and spleen weights not measured. | Phase 3 Acceptance Criteria Checklist indicate that lung and spleen weights not required. | Acceptance Criteria used by submitter (12/24/89) do not require lung and spleen weights. However, later versions do. This deficiency, however, does not result in failure to pass the acceptance criteria. |
| Mouse Oncogenicity 83-2(b) | Test article purity, stability, homogeneity and concentration not noted. | Addressed by Phase 3 Summary of study (EPA SUMMARY MRID NO. 92002022). | Purity, stability and concentration were verified. Homogeneity was not determined. An HED decision on acceptability of this deficiency is reserved pending in-depth review of the data. |
| | Unusual dose selection, and no defined NOEL or adequate toxicity at high dose. | Addressed by reformatted 28-day feeding study (EPA SUMMARY MRID NO. 92002041). | In a 28-day pilot study (#92002041) LOEL (and "MTD" according to Submitter) = 3000 ppm (decreased body wt., hunching). NOEL = 1000 ppm. Adequate toxicity at high dose level apparently was not achieved. An HED decision on acceptability is reserved pending in-depth review of the data. |
| | No individual observations; no blood smears or histo-pathological evaluation of rectum. | Addressed by Phase 3 Summary of study (EPA SUMMARY MRID NO. 92002022). | Submitter claims there is nothing to indicate that measurement of these endpoints would alter the oncogenic conclusions of this study. Since these parameters were measured in the Combined Chronic/Onco Rat study, it's absence here should not result in a retesting requirement. |
| | No Quality Assurance review of study. | Signed statement by Manager of the Office of Quality Assurance for lab is included with Phase 3 Summary (EPA SUMMARY MRID NO. 92002022), that the study was reviewed by QA office. | Verified. |