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DATA EVALUATION RECORD UNDATED

STUDY 1

CHEM 068102 Vedexil §161-1

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 150229
Macdonald, I.A. and D.A. Howes. 1985. The determination of the hydrolysis of methylene bis thiocyanate as a function of pH. HRC Project No. A & W 460/85626. Unpublished study performed by Huntington Research Centre Ltd., Cambridgeshire, England, and submitted by Buckman Laboratories, Memphis, TN.

DIRECT REVIEW TIME = 6

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CONCLUSIONS:

Degradation - Hydrolysis

1. This study is unacceptable and cannot be used to fulfill data requirements.

2. The rate of vedexil hydrolysis in sterile aqueous buffered solutions increased with increasing alkalinity. Vedexil did not hydrolyze in pH 5 solution, and hydrolyzed with half-lives of 21.2 hours and 133.5 minutes in pH 7 and 9 solutions, respectively. The degradates formaldehyde and the thiocyanate ion were identified in the pH 7 and 9 solutions.

3. This study has been reviewed earlier and was found acceptable. However, the study is rereviewed and is found unacceptable for the following reasons:

   the material balances for PH 7 and 9 test solutions were incomplete;

   the PH 7 and 9 test solutions were analyzed for the aldehyde and thiocyanate ions for only one and two sampling intervals respectively (23 hours posttreatment for PH 7; 265 mins and 445 mins posttreatment for PH 9). At all the remaining intervals the test solutions were analyzed for parent Vedexil only;

   the test substance used for the entire study was of commercial grade.

4. Since the test substance was not technical grade or purer for the pH 5, 7, and 9 solutions, the material balances for the pH 7 and 9 solutions were incomplete, and the test solutions were analyzed for the degradates at only one or two sampling intervals, the problems with this study cannot be resolved with the submission of additional data. A new study must be submitted.

METHODOLOGY:

Vedexil ("commercial grade", test substance not further characterized, Tenneco Organics Limited) was finely ground and added at a nominal concentration of 250 ug/mL to duplicate Erlenmeyer flasks containing sterile (autoclaved) aqueous buffered solutions adjusted to pH 5 (0.1 M sodium hydroxide plus 0.1 M potassium hydrogen phthalate), pH 7 (0.1 M nitric acid plus 0.1 M tris buffer), and pH 9 (0.1 M sodium bicarbonate plus 0.1 M sodium carbonate). The test substance was dissolved in the buffer solutions using sonication, the flasks were sealed with sterilized glass stoppers, and the solutions were incubated at 25 $\pm$ 0.1 C in the dark. Duplicate aliquots were removed for analysis at intervals up to 30 days for the pH 5 solution, up to 144 hours for the pH 7 solution, and up to 2460 minutes for the pH 9 solution.

Prior to analysis, aliquots of the pH 5 and 7 test solutions were diluted with glass-distilled water. The diluted aliquots of the pH 7 test solution and undiluted aliquots of the pH 9 test solution were acidified with 6 M nitric acid; the acidified aliquots of the pH 9 test solution were then diluted with glass-distilled water. Aliquots of the diluted solutions were analyzed for vedexil by HPLC using an Apex ODS column with a mobile phase of methanol:water (20:80) and UV detection (250 nm). Additional aliquots of the pH 7 (23 hours only) and pH 9 (265 and 445 minutes only) solutions were also analyzed for the degradates formaldehyde and thiocyanate ion. To analyze for formaldehyde, an aliquot of the test solution was added to a solution of phenylhydrazine hydrochloride. The resulting phenylhydrazine was

oxidized with aqueous potassium ferricyanide. The reaction solution was analyzed for formaldehyde using spectrophotometry (517 nm). To analyze for thiocyanate, aliquots of the test solutions were treated with 6 M nitric acid, 40% w/v aqueous ammonium ferric sulphate, and aqueous silver nitrate. The resulting mixture was titrated against 0.01 M ammonium thiocyanate to a "brownish/red" end point.

DATA SUMMARY:

Vedexil (purity unspecified), at a nominal concentration of 250 ug/mL, did not hydrolyze in a sterile buffered aqueous solution adjusted to pH 5 that was incubated in the dark at 25 C for 30 days (Table 7). Under similar incubation conditions, vedexil hydrolyzed at pH 7 and 9, with registrant-calculated half-lives of 21.2 hours and 133.5 minutes, respectively (Table 7). Two degradates,

formaldehyde and

thiocyanate ion,

were identified in both the pH 7 and 9 solutions.

In the pH 5 solution, the vedexil concentration was 252-258 ug/mL immediately posttreatment, and 246 ug/mL at 30 days posttreatment (Table 7).

In the pH 7 solution, the vedexil concentration was 257-262 ug/mL at 15 minutes posttreatment, 118 ug/mL at 23 hours, 65 ug/mL at 72 hours, and 45-46 ug/mL at 144 hours (Table 7). Formaldehyde was 1.31-1.38 ug/mL and thiocyanate ion was 81-82 ug/mL at 23 hours posttreatment (Tables 10 and 11).

In the pH 9 solution, the vedexil concentration was 263 ug/mL at 10 minutes posttreatment, 152 ug/mL at 78 minutes, 105-106 ug/mL at 145 minutes, 25 ug/mL at 445 minutes, and <1 ug/mL at 1020 minutes (Table 7). Formaldehyde was 0.97-0.99 ug/mL at 265 minutes and 2.37-3.06 ug/mL at 445 minutes (Table 10). Thiocyanate ion was 96-97 ug/mL at 265 minutes and 144 ug/mL at 445 minutes posttreatment (Table 11).

The material balance for the pH 5 solution was 98.4-103% of the initial concentration (reviewer calculated from Table 7). The material balances were incomplete for the pH 7 and 9 solutions.

COMMENTS:

1. The material balances for the pH 7 and 9 test solutions were incomplete. In the pH 7 test solution, only 17.5% of the starting material was accounted for (as vedexil) at 144 hours posttreatment.

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In the pH 9 test solution, only 12% of the starting material was accounted for at 6.4 hours; all of the starting material was lost at 17 hours.

2. The test substance was not technical grade or purer. The test substance was specified as "commercial grade"; the purity was not reported. Subdivision N guidelines require that the test substance be technical grade or purer.

3. The test solutions were analyzed for only two degradates, formaldehyde and the thiocyanate ion, at only one or two sampling intervals. The pH 7 test solution was only analyzed at 23 hours posttreatment and pH 9 test solution was only analyzed at 265 minutes and 445 minutes posttreatment. At all remaining sampling intervals, the test solutions were only analyzed for parent vedexil.

3. For the pH 7 and 9 solutions, samples were not analyzed immediately following treatment; rather the first sampling interval was 15 minutes for the pH 7 solution and 10 minutes for the pH 9 solution.

4. The starting concentrations of vedexil (252-263 ug/mL) were slightly in excess of the 250 ppm maximum stated by the Subdivision N guidelines.

5. Recovery efficiencies for fortified samples and method detection limits were not provided.

6. The study authors stated that during the study, the pH of the pH 7 buffer solution was 6.2 at 72 hours and 5.9 at 144 hours. Apparently, the sterility of the solution was not verified at the end of the experiment.