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315AD

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

AUG 25 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **TRIETHYLAMINE Salt of 2,4-D:** Review of Mutagenicity Studies.

FROM: Jess Rowland, M.S., Branch Senior Scientist 6/27/97
Science Analysis Branch, Health Effects Division (7509C)

TO: Walter Waldrop / Judy Coombs
Product Manager 71
Reregistration Division (7508W)

THRU: Alberto Protzel, Ph.D., Branch Senior Scientist 8/12/97
Toxicology Branch I, Health Effects Division (7509C)

DATA PACKAGE IDENTIFICATION: Submission: S476055 DP Bardcode: D208825
PC Code: **030034** Tox.Chem.No. **315AD**

ACTION REQUESTED: Review the *Salmonella*/microsomal and the *in vivo* micronucleus assays with the triethylamine salt of 2,4-dichlorphenoxy acetic acid submitted by the Chas. H. Lilly Co., to fulfill Subdivision F guideline requirement §84-2.

RESPONSE: Data Evaluation Records (DERs) for the two studies referenced above are attached. The Executive Summaries are presented below. The triethylamine salt of 2,4-dichlorophenoxyacetic acid was shown to be non mutagenic both *in vitro* and *in vivo*.

These studies are classified as **Acceptable/Guideline** and satisfy the Subdivision F guideline requirement §84-2 for *in vivo/in vitro* mutagenicity assays.

I. *Salmonella tryphimurium*/mammalian activation gene mutation assay. §84-2

CITATION: Stankowski, L. (1994) Ames/*Salmonella* plate incorporation assay on Lilly/Miller Envy 2,4-D (EPA Reg. #802-241). Pharmakon Research International, Inc., Waverly, PA. Laboratory study number PH 301-CHL-001-94. March 22, 1994. **MRID 43418101.** Unpublished.

EXECUTIVE SUMMARY: In a reverse gene mutation assay in bacteria (MRID 43418101), strains TA98, TA100, TA1535, TA1537, and TA1538 of *Salmonella typhimurium* were exposed to Envy 2,4-D (42.86% a.i.), in deionized water in the presence and absence of S9 mammalian metabolic activation at concentrations of 50.0, 167, 500, 1670, 5000, and 10,000 µg/plate. Envy 2,4-D (42.86% a.i.) was tested up to cytotoxic concentrations. The positive controls induced the appropriate responses in the corresponding strains. **The test material was non-mutagenic; there was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable/Guideline** and satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity bacterial reverse gene mutation data.

II. *In vivo* mammalian cytogenetics - micronucleus assay in mice.

CITATION: San Sebastian, J. (1994) *In vivo* micronucleus test with Lilly/Miller Envy 2,4-D (EPA Reg. No. 802-241) in mouse bone marrow erythropoietic cells. Pharmakon Research International, Inc., Waverly, PA. Laboratory Study No. PH 309-CHL-001-94. July 26, 1994. **MRID 43374801.** Unpublished.

EXECUTIVE SUMMARY: In an *in vivo* mouse bone marrow micronucleus assay (MRID 43374801), groups of five CD-1 albino mice/sex received a single IP injection of 20, 100, or 200 mg/kg of the triethylamine salt formulation of 2,4-D (42.86% a.i.). Bone marrow cells were harvested at 24, 48, or 72 hours posttreatment and scored for micronucleated polychromatic erythrocytes (MPCEs). No unscheduled deaths occurred. Clinical signs of toxicity noted in the high-dose animals included abnormal gait, body drop, decreased activity and body tone, and piloerection. Dosing with the 2,4-D triethylamine salt formulation resulted in depressions in the PCE/NCE ratios ($p \leq 0.05$ or 0.01) in the 20 and 200 mg/kg groups at the 48-hour sacrifice. The positive control induced significant increases in MPCEs in both sexes. There was no clastogenic or aneugenic effect at any 2,4-D acid dose at any harvest time. **The test material was non-mutagenic; there was not a significant increase in the frequency of MPCEs in bone marrow after any treatment time.**

This study is classified as **Acceptable/Guideline** and satisfies the requirements for FIFRA Test Guideline 84-2 for *in vivo* cytogenetic mutagenicity data.

DATA EVALUATION RECORD

TRIETHYLAMINE SALT OF 2,4-D

Study Type: 84-2; Micronucleus Assay in Mice

Work Assignment No. 1-12B (MRID 43374801)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Ann Foster, Ph.D.

Signature: Ann Foster
Date: 4/12/96

Secondary Reviewer:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 4/15/96

Project Manager:
William Spangler, Ph.D.

Signature: William J. Spangler
Date: 4/8/96

Quality Assurance:
Reto Engler, Ph.D.

Signature: Reto Engler
Date: 4/18/96

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

TRIETHYLAMINE SALT OF 2,4-D **Micronucleus Assay (84-2)**

EPA Reviewer: Jess Rowland, M.S. 6/21/97
Branch Senior Scientist, Science Analysis Branch

EPA Secondary Reviewer: Alberto Protzel, Ph.D., 8/12/97
Branch Senior Scientist, Toxicology Branch I

DATA EVALUATION RECORD

STUDY TYPE: *In vivo* mammalian cytogenetics - micronucleus assay in mice

OPP Guideline Number: §84-2

DP BARCODE: D208825 SUBMISSION CODE: S476055

P.C. CODE: 030034 TOX. CHEM. NO.: 315 AD

TEST MATERIAL (PURITY): Lilly/Miller Envy 2,4-D (42.86% a.i.)

SYNONYMS: 2,4-D Triethylamine salt

CITATION: San Sebastian, J. (1994) *In vivo* micronucleus test with Lilly/Miller Envy 2,4-D (EPA Reg. No. 802-241) in mouse bone marrow erythropoietic cells. Pharmakon Research International, Inc., Waverly, PA. Laboratory Study No. PH 309-CHL-001-94. July 26, 1994. MRID 43374801. Unpublished.

SPONSOR: The Charles H. Lilly Company, Portland, OR.

EXECUTIVE SUMMARY: In an *in vivo* mouse bone marrow micronucleus assay (MRID 43374801), groups of five CD-1 albino mice/sex received a single IP injection of 20, 100, or 200 mg/kg of the triethylamine salt formulation of 2,4-D (42.86% a.i.). Bone marrow cells were harvested at 24, 48, or 72 hours posttreatment and scored for micronucleated polychromatic erythrocytes (MPCEs).

No unscheduled deaths occurred. Clinical signs of toxicity noted in the high-dose animals included abnormal gait, body drop, decreased activity and body tone, and piloerection. Dosing with the 2,4-D triethylamine salt formulation resulted in depressions in the PCE/NCE ratios ($p \leq 0.05$ or 0.01) in the 20 and 200 mg/kg groups at the 48-hour sacrifice. The positive control induced significant increases in MPCEs in both sexes. There was no clastogenic or aneugenic effect at any 2,4-D acid dose at any harvest time. **The test material was non-mutagenic; there was not a significant increase in the frequency of MPCEs in bone marrow after any treatment time.**

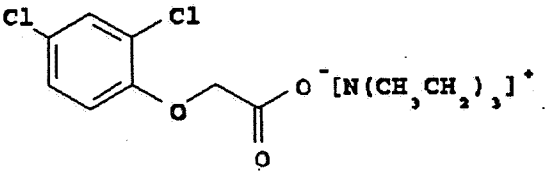
This study is classified as **Acceptable/Guideline** and satisfies the requirements for FIFRA Test Guideline 84-2 for *in vivo* cytogenetic mutagenicity data.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: 2,4-D Triethylamine salt

Description: Clear liquid
Lot/Batch #: 37693341R
Purity: 42.86% a.i.
Stability of compound: Not reported
CAS #: 2646-78-8



Solvent used: Deionized water
Other comments: The test material was stored at room temperature and protected from light.

2. Control Materials:

Vehicle/Final volume/Route of administration: Deionized water, 10 mL/kg, IP injection

Positive/Final dose/Route of administration: Cyclophosphamide in deionized water; 60 mg/kg

3. Test compound administration

Volume of test substance administered: 10 mL/kg
Route of administration: IP injection
Dose levels used:
Preliminary Toxicity Study: 100, 175, 250, 500, 1000 mg/kg
Micronucleus Assay: 20, 100, 200 mg/kg

Rationale for dose selection: Based on mortality at 500 and 1000 mg/kg and the clinical signs of toxicity observed in the 250 mg/kg group during the preliminary toxicity study, a high dose of 200 mg/kg was chosen for the micronucleus assay.

4. Test animals

a. Species: Mouse (Strain: CD-1)
Age: approximately 8 weeks
Weight: Pilot Study, male 32-49 g, female 22-32 g; Micronucleus Assay, male 28-41 g, female 21-34 g
Source: Charles River Laboratories, Wilmington, MA

b. Number of animals used per dose:
Pilot Study: 2/sex/dose
Micronucleus Assay: 15/sex/dose

c. Properly maintained? Yes

B. TEST PERFORMANCE

1. Treatment and Sampling Times

a. Test compound and vehicle control:
Dosing: Once
Sampling: 24, 48, and 72 hours after dosing

b. Positive control:
Dosing: Once
Sampling: 24 hours after dosing

2. Tissues and Cells Examined

Bone marrow was the only tissue examined.
No. of polychromatic erythrocytes (PCEs) examined per animal: 1000 erythrocytes were scored and PCE/NCE ratio was determined.
No. of normochromatic erythrocytes (NCE; more mature RBCs) examined per animal: 1,000

3. Details of slide preparation

At 24, 48, and 72 hours after dosing, animals from each dose group were sacrificed by cervical dislocation. Marrow was aspirated from the femur and mixed in fetal bovine serum. After centrifugation and resuspension, the cells were spread on slides, fixed in methanol, air-dried, stained with a Modified Wrights Stain Pak containing polychrome methylene blue-eosin, and permanently mounted. Slides were coded prior to scoring.

4. Statistical methods

Statistical significance ($p \leq 0.05$ or ≤ 0.01) was evaluated using one-tailed t-tests and two-tailed t-tests following an arcsin transformation.

5. Evaluation Criteria

The test was considered valid if the following conditions were met: the number of MPCEs per 1000 PCE/mouse was ≤ 6, the frequency of MPCEs for the negative control was $< 0.25\%$, the incidence of MPCEs in the positive control significantly increased with respect to the negative control ($p \leq 0.05$), and ≥ 7 mice per dose group survived.

A positive response was a statistically significant (t-test) increase in the MPCEs relative to the vehicle control. Each sacrifice time was treated separately.

C. COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

II. REPORTED RESULTS

A. Solubility/Analytical Determinations

Data on stability and achieved concentrations of dosing solutions were not submitted.

B. Pilot Toxicity study

Groups of two mice/sex were administered the 2,4-D triethylamine salt by IP injection at 100, 175, 250, 500, or 1000 mg/kg. Pharmacotoxic signs observed in the treated mice are presented in Appendix 1 (Table 1; study page 15) included in this DER. Pharmacotoxic signs and mortality were monitored immediately, at 10 minutes, and at 2, 24, 48, and 72 hours after dosing. In the 1000 mg/kg group, mortality occurred in all animals within 10 minutes of dosing. In the 500 mg/kg group, mortality occurred in 1/2 males and in 1/2 females within 24 and 72 hours of dosing, respectively. In the 250 mg/kg group, all animals experienced abnormal gait and decreased activity immediately after dosing; partial paralysis was observed in all animals within 10 minutes of dosing, and piloerection was detected in 1/2 males at 24, 48, and 72 hours postdosing. Based on the mortalities at 500 and 1000 mg/kg and the clinical signs of toxicity observed in the 250 mg/kg group, a high dose of 200 mg/kg was chosen for the micronucleus assay.

C. Micronucleus Assay

1. Animal observations

No unscheduled deaths occurred. Clinical signs of toxicity noted in the high-dose animals included abnormal gait, body drop, decreased activity and body tone, and piloerection.

2. Micronucleus assay

The results of the micronucleus assay are presented in Appendices 2 and 3 (Tables 3 and 4; study pages 18 and 19) included in this DER. The 2,4-D triethylamine salt caused statistically significant ($p \leq 0.05$ or 0.01) depressions in the PCE/NCE ratios for the 20 and 200 mg/kg groups at the 48-hour sacrifice. The chemical, however, did not cause a significant increase in micronucleated PCEs, compared with vehicle controls, in bone marrow cells collected from male or female mice 24, 48, or 72 hours after dosing with 20, 100, or 200 mg/kg. The positive control (60 mg/kg cyclophosphamide) induced significant ($p < 0.01$) increases in micronucleated PCEs in both sexes and induced depressions in the PCE/NCE ratios ($p \leq 0.01$).

The study author concluded that the 2,4-D acid was negative in this *in vivo* mouse micronucleus assay.

III. DISCUSSION/CONCLUSIONS

A. Investigator's Conclusions

The study author concluded that, under the conditions of this study, there was no statistically significant increase in the frequency of micronucleated PCEs over the spontaneous background in mouse bone marrow erythropoietic cells of treated mice 24, 48, or 72 hours after a single IP injection of the 2,4-D triethylamine formulation.

B. Reviewer's Discussion

The reviewer agrees with the study author that the 2,4-D triethylamine salt formulation was not clastogenic or aneugenic in this *in vivo* assay when tested to a dose level of 200 mg/kg. The sensitivity of this test to detect genotoxic response was demonstrated by the significant ($p \leq 0.01$) increase in MPCEs induced by the positive control (60 mg/kg CP). We conclude that the 2,4-D triethylamine salt was adequately tested and found non-genotoxic in this *in vivo* micronucleus assay.

IV. STUDY DEFICIENCIES

Stability and concentration data were not submitted, and the tests were performed using a 42.86% formulation of the a.i. rather than TGAI. However, the pharmacotoxic signs in the pilot study and this mutagenicity study, as well as the change in the PCE/NCE ratio indicate that an adequate concentration of the test substance reached the target cells, and that the test was unaffected by inert ingredients in the test formulation.

APPENDIX 1

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_____ Identity of the source of product ingredients.

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_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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APPENDIX 2

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APPENDIX 3

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DATA EVALUATION RECORD

TRIETHYLAMINE SALT OF 2,4-D

Study Type: 84-2; *Salmonella typhimurium*/Mammalian Activation Gene Mutation Assay

Work Assignment No. 1-12A (MRID 43418101)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Sandra Daussin, B.S.

Signature: _____
Date: 4/16/96

Secondary Reviewer:
Steven Brecher, Ph.D.

Signature: _____
Date: 4/15/96

Project Manager:
William Spangler, Ph.D.

Signature: _____
Date: 4/18/96

Quality Assurance:
Reto Engler, Ph.D.

Signature: _____
Date: 4/18/96

Disclaimer

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EPA Reviewer: Jess Rowland, M.S. 9/21/97
Branch Senior Scientist, Science Analysis Branch

EPA Secondary Reviewer: Alberto Protzel Ph.D., 8/12/97
Branch Senior Scientist, Toxicology Branch I

DATA EVALUATION RECORD

STUDY TYPE: *Salmonella typhimurium*/mammalian activation gene mutation assay

OPP Guideline Number: §84-2

DP BARCODE: D208825 SUBMISSION CODE: S476055

P.C. CODE: 030034 TOX. CHEM. NO.: 315 AD

TEST MATERIAL (PURITY): Lilly/Miller Envy 2,4-D (42.86% a.i.)

SYNONYMS: 2,4-D triethylamine salt

CITATION: Stankowski, L. (1994) Ames/*Salmonella* plate incorporation assay on Lilly/Miller Envy 2,4-D (EPA Reg. #802-241). Pharmakon Research International, Inc., Waverly, PA. Laboratory study number PH 301-CHL-001-94. March 22, 1994. MRID 43418101. Unpublished.

SPONSOR: The Charles H. Lilly Company, Portland, OR.

EXECUTIVE SUMMARY: In a reverse gene mutation assay in bacteria (MRID 43418101), strains TA98, TA100, TA1535, TA1537, and TA1538 of *Salmonella typhimurium* were exposed to Envy 2,4-D (42.86% a.i.), in deionized water in the presence and absence of S9 mammalian metabolic activation at concentrations of 50.0, 167, 500, 1670, 5000, and 10,000 µg/plate.

Envy 2,4-D (42.86% a.i.) was tested up to cytotoxic concentrations. The positive controls induced the appropriate responses in the corresponding strains. **The test material was non-mutagenic; there was no evidence of induced mutant colonies over background.**

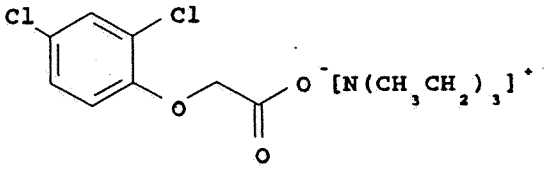
This study is classified as **Acceptable/Guideline** and satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity bacterial reverse gene mutation data.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Triethylamine salt of 2,4-D

Description: Clear colorless liquid
Lot/Batch #: 37693341R
Purity: 42.86% a.i.
Stability of compound: Not reported
CAS #: 2646-78-8
Structure:



Solvent used: Deionized water
Other comments: The test substance was stored at room temperature. Dosing solutions were prepared within 2 hours of use. Dosing solutions were not analyzed to verify homogeneity or stability. The report did not indicate whether analytical determinations for nominal concentrations were performed.

2. Control Materials

Negative: Deionized water or DMSO (for all positive controls except sodium azide)
Solvent/final concentration: Deionized water/0.1 mL per plate

Positive: Nonactivation:

Sodium azide	10 μg/plate	TA1535, TA100
2-Nitrofluorene	5 μg/plate	TA98, TA1538
9-Aminoacridine	150 μg/plate	TA1537

Activation:

2-Aminoanthracene	2.50 μg/plate	*S. typhimurium*, all strains

3. Activation

S9 derived from:

X	Aroclor 1254	X	Induced	X	Rat	X	Liver
	Phenobarbital		Non-induced		Mouse		Lung
	None				Hamster		Other
	Other				Other		

The S9 homogenate was prepared by the testing laboratory and contained 8 mM $MgCl_2$, 33 mM KCl, 4 mM NADP, 5 mM glucose-6-phosphate, 100 mM Na_2HPO4 (pH 7.4), and 6% (v/v) Aroclor 1254-induced male Sprague-Dawley rat liver homogenate.

4. Test organisms

S. typhimurium strains

	TA97	X	TA98	X	TA100		TA102
	TA104	X	TA1535	X	TA1537	X	TA1538

Properly maintained? Yes
Checked for appropriate genetic markers (rfa mutation, R factor)? Yes

5. Test compound concentrations used

Preliminary cytotoxicity test: Five dose levels of Envy 2,4-D (50.0, 167, 500, 1670, and 5000 μg/plate) were evaluated with the *S. typhimurium* strains TA100 and TA1538 in the absence of S9 activation. Duplicate plates were used per dose. Solvent controls were included.

Mutagenicity assay: *S. typhimurium* strains TA98, TA100, TA1535, TA1537,

and TA1538 were evaluated with Envy 2,4-D concentrations of 50.0, 167, 500, 1670, 5000, and 10,000 μg/plate. All evaluated dose levels were assayed with and without S9 activation. Triplicate plates were used for each dose, strain, and condition. Solvent and positive control groups were included.

B. TEST PERFORMANCE

1. Type of Salmonella assay

X	standard plate test
	pre-incubation (minutes)
	"Prival" modification *(i.e. azo-reduction method)*
	spot test
	other

2. Protocol Tester strains were inoculated into nutrient broth culture, incubated for approximately 6 hours and diluted 1:4 with deionized water to obtain cultures that were at the appropriate cell densities (1×10^9 to 2×10^9 cells/mL). Envy 2,4-D and the sodium azide positive control were diluted in deionized water to specified concentrations. The other positive control materials were diluted in dimethyl sulfoxide (DMSO). Molten top agar (2.0 mL) supplemented with 0.5 mM histidine/0.05 mM biotin was mixed with 0.1 mL of the appropriate tester strain culture, 0.1 mL of Envy 2,4-D test solution, solvent, or positive control, and 0.5 mL of the S9 mix. The mixture was poured over a minimal glucose plate. After incubation (37 C for 48 hours), the number of revertant colonies were determined using an automated colony counter. The background lawn and/or the frequency of spontaneous revertants were examined to determine the toxicity of the test compound. Means and standard deviations for the mutation tests were determined from the counts of triplicate plates per strain, per dose, per condition. The sterility of the solvent, top agar, S9 mix, and the most concentrated test material dosing solution used in the mutation assay was determined by plating on minimal glucose plates.

3. Evaluation Criteria

(a) Assay validity: An assay was considered acceptable if the numbers of spontaneous revertants (negative values) were within the historical ranges.

(b) Positive response: The test material was considered mutagenic if it caused a statistically significant dose-related increase in the mean number of revertants with at least one positive dose level. A positive dose level was one where the increase in the mean number of revertants is at least 2-fold the negative control value.

C. COMPLIANCE: Signed and dated GLP, Quality Assurance and DataConfidentiality were provided. The study was conducted in accordance with GLP with the exception that the dosing solutions were not analyzed for homogeneity or stability. As the test material demonstrated dose-related cytotoxicity, this is considered a minor deficiency and has no impact on the acceptability of the results.

II. REPORTED RESULTS

A. Preliminary cytotoxicity assay

The test results for the preliminary cytotoxicity assay are presented in Appendix 1 (Table 1; study report page 15) included in this DER. Five dose levels of Envy 2,4-D (50.0, 167, 500, 1670, and 5000 μg/plate) were evaluated with the *S. typhimurium* strains TA100 and TA1538 in the absence of S9 activation. Duplicate plates were used per dose. Solvent controls were included. The test material was completely soluble at all dose levels. Toxicity was observed as inhibited growth ("reduced background lawns and/or the presence of pinpoint colonies") in both strains at 5000 μg/plate. No toxicity was observed at dose levels $\leq$1670 μg/plate in either strain.

Based on these results, the mutation assay was performed with a dose range of 50.0-10,000 μg/plate +/-S9 activation.

B. Mutagenicity assay

The test results for the mutagenicity assays with Envy 2,4-D are presented in Appendix 2 (Table 2; study report page 16) included in this DER. *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were evaluated with Envy 2,4-D at concentrations of 50.0, 167, 500, 1670, 5000, and 10,000 μg/plate. All evaluated dose levels were assayed with and without S9 activation. Triplicate plates were used for each dose, strain, and condition. Solvent and positive control groups were included. The test material was completely soluble at all dose levels.

Toxicity was observed as inhibited growth ("reduced background lawns and/or the presence of pinpoint colonies") in both strains at concentrations ≥ 1670 μg/plate with and without S9 activation. The mean number of revertant colonies in all of the tester strains at any dose level/condition were less than or equal to those of the concurrent negative controls. The numbers of spontaneous revertants (negative values) and positive control values were within acceptable limits.

Based on the findings, the study author concluded that Envy 2,4-D was not mutagenic under the conditions of this microbial gene mutation assay.

III. DISCUSSION/CONCLUSIONS

A. Investigator's Conclusions

The study author concluded that Envy 2,4-D was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 in the presence and absence of S9 mammalian metabolic activation in this reverse gene mutation assay.

B. Reviewer's Discussion

The reviewer agrees with the study author's conclusion that Envy 2,4-D was not mutagenic under the conditions of the submitted microbial gene mutation assay. Envy 2,4-D was assayed over an appropriate dose range as it was tested to cytotoxic concentrations. Envy 2,4-D failed to induce a genotoxic response in any of the tester strains. The sensitivity of the test system to detect mutagenesis was adequately demonstrated by the response obtained with the nonactivated and S9-activated positive controls. The study is classified as acceptable.

IV. STUDY DEFICIENCIES

The study was conducted in accordance with GLP with the exception that the dosing solutions were not analyzed for homogeneity or stability. In addition, the report did not indicate whether analytical determinations for nominal concentrations were performed. As the test material demonstrated dose-related cytotoxicity, this is considered a minor deficiency and has no impact on the acceptability of the study.

APPENDIX 1

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_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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APPENDIX 2

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