UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MAR 15 1989

MAR 15 1989

007074

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Identification No. 476-EEEE;
SC-0224 4-LC (Containing 39.9% Sulfosate);
Registration for Noncrop Uses Around the Farm

Tox Chem No. 893C
Project No. 9-0414
Record No. 235,371

FROM: Edwin R. Budd, Section Head
Review Section I, Toxicology Branch-I (IRS)
Health Effects Division (H7509C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (E7505C)

THRU: Judith W. Hamswirth, Chief
Toxicology Branch-I (IRS)
Health Effects Division (H7509C)

Requested Action:

ICI Americas, Inc. has requested registration of SC-0224 4-LC (also known as Touchdown® 4-LC), containing 39.9% sulfosate as the active ingredient, for weed control in noncrop areas around the farm. Sulfosate is a new (i.e. not previously registered) nonselective foliar systemic herbicide.

This is an amended request for registration in that registration was previously sought for a similar end-use product now identified as SC-1224 (or Touchdown® 4-LCE. The end-use product for which registration is presently sought contains a different surfactant than the 4-LCE formulation and is identified more precisely as SC-0224 (or Touchdown® 4-LCE. Based on a set of acute toxicity studies conducted on the 4-LCE formulation and submitted in this package in support of the present request, the 4-LCE formulation is less toxic, on an acute basis, than the 4-LCE formulation. Hereafter, in this review, the 4-LCE formulation (for which registration is being sought) will be referred to as the 4-LC formulation, unless specifically noted otherwise.

Recommendation:

Sufficient toxicological information and studies have been submitted to support conditional registration of this end-use product and Toxicology Branch-I (TB-I) has no objection to conditional registration of this product at this time, provided that the applicant agrees to submit in the near future suitable responses to the deficiencies and concerns described below.

Based on an overall evaluation of the totality of toxicological information presently available on wildgate, including several acute studies on the 4-LC end-use product, the proposed use of SC-0224 4-LC for weed control in noncrop areas around the farm is not considered by TB-1 to present a significant toxicological hazard to persons exposed to the product. These studies include acute toxicity studies on several similar products, a subchronic dermal study on rabbits, teratology studies on rats and rabbits, reproduction and fertility studies on rats, chronic feeding studies on dogs and rats, oncogenic studies on mice and rats, metabolism data and numerous mutagenicity studies. Although not all these studies are fully acceptable at this time, there is nevertheless ample toxicological information to fully support this conditional registration for noncrop use.

On the other hand, certain toxicity studies required to support full registration of this end-use product are not satisfactorily completed or are not available at this time, hence the recommendation for a conditional registration. The specific study deficiencies (data gaps) are:

- an acute inhalation LC_{50} study on the SC-0224 4-LC formulation (see item 1 below), and

- a 21-day dermal study on the SC-0224 4-LC formulation (see item 2 below).

It is not anticipated that submission of these studies at a later time will affect the regulatory status of this end-use product in any significant way. Nevertheless, these two studies should be performed and submitted to the Agency in the near future to complete the toxicity data base required for full registration of this product and to fully confirm that use of this product will not present an unreasonable hazard to persons exposed to it.

Comments:

1. An unsuccessful attempt to perform an acute inhalation LC_{50} study on the 4-LC end-use product was reported in this package (Stauffer Chemical Co., No. T-12983, 6/22/87). The authors stated that "it was not possible to generate a respirable aerosol. Repeated attempts at generating an aerosol were unsuccessful due to the high viscosity and foaming properties of SC-0224 4LC-E.---(and therefore) the formulation evaluated does not pose an inhalation hazard because a respirable aerosol could not be generated." TB-1 does not concur with this viewpoint at this time and believes "that certain additional effort should be directed toward the evaluation of the test material for inhalation toxicity. The Registrant should be advised to pursue additional testing taking into advisement the following suggestions:

   1) Dilute the SC-0224 4LC-E (40% a.i.) with [redacted] until foaming stops.

   2) Reduce surfactants until foaming stops.

   3) If necessary, form a dense fog and run through a cyclone separator to remove large particles.

   4) Consult with Toxicology Branch if testing problems continue." (from review of this study by Dr. Brian Dementi, attached).

2. The applicant has requested a waiver of the previously required 21-day dermal study to be performed on the 4-LC end-use product. The applicant believes that this study is not necessary for the following reasons:

   "The formulation is of low acute dermal toxicity.

   We have replaced the formulation previously proposed for use, the 4LCB formulation, (Toxicity Category I) with the 4LCE formulation, (Toxicity Category III).

   The active ingredient is of low subchronic dermal toxicity.

   We have completed a 21-day dermal study with SC-0224 Concentrate (57.3% active) (EPA File Symbol 476-EEEL). In all respects, including food consumption, hematology, blood chemistry and organ weights, rabbits treated with sulfosate showed no biologically

significant treatment-related effects. It was concluded that sulfosate is of low systemic toxicity on repeated dermal applications to the abraded and nonabraded skin of the male and female rabbit. The no-effect level was considered to be 1000 mg/kg/day.

Thus further testing of the 4LCE formulation which contains 39.9% active is unlikely to provide additional information and would be a wasteful use of experimental animals and contrary to the Agency's policy of reducing the use of experimental animals."

TB-I does not agree that this study is not necessary and recommends that the study be required to be submitted to the Agency. TB-I would have no objection, however, to the study being submitted following conditional registration of the 4-LC product.

The rationale for this determination is based on the differences in product composition between the aqueous SC-0224 concentrate, for which a 21-day dermal study has already been conducted (see above), and the SC-0224 4-LC which contains about [redacted] surfactant. The presence of surfactant in the latter product is likely to substantially increase dermal absorption of the formulation and/or active ingredient and possibly produce greater dermal irritation and/or greater systemic toxicity than for the concentrate, particularly following repeated dermal applications. Inasmuch as mild dermal irritation (erythema) was observed in all treated groups in the 21-day dermal study on the concentrate (at doses as low as 10 mg/kg/day, LDT), it is possible that increased irritation and/or systemic toxicity might occur in a 21-day dermal study on the 4-LC product or at dose levels below which similar effects were observed in the first study. For reasons described above under Recommendations, however, this study may be submitted at a later time--in order to complete the toxicity data base for full registration and to fully confirm the lack of unreasonable hazard to persons exposed to the product.

3. The applicant has submitted in this package six acute toxicity studies on SC-0224 4-LCE, which are to be differentiated from acute toxicity studies previously submitted on SC-0224 4-LCE. With the exception of the acute inhalation toxicity study (which was discussed above in 1. and which is classified as Core-Supplementary), all of the remaining five studies are classified as Core-Guideline. The results of these studies are summarized below:

1) Acute oral toxicity study, rats
   LD_{50} (males) = 1760 mg/kg
   LD_{50} (females) = 1298 mg/kg
   Toxicity Category III

INERT INGREDIENT INFORMATION IS NOT INCLUDED

2) Acute dermal toxicity study, rabbits
   LD_{50} (males/females) >2000 mg/kg
   Toxicity Category III

3) Dermal irritation study, rabbits
   non-irritating (4 hour exposure)
   Toxicity Category IV

4) Eye irritation study, rabbits
   moderate irritation, clearing by day 7
   Toxicity Category III

5) Skin sensitization study, guinea pigs
   negative in modified Buehler test

The TB-I reviews of these acute toxicity studies, by Dr. Brian Dementi, are attached.

4. The proposed label (attached) for this Toxicity Category III product is acceptable provided that the following changes are made:

1) On page 1, add the following to the statement of practical treatment (as on the TB-I approved label for SC-0224 Concentrate, EPA Identification No. 476-EEEL):

   "If on Skin, Flush with plenty of water for at least 15 minutes. Remove contaminated clothing and shoes. Get medical attention if skin irritation occurs. Wash clothing before re-use."

   "If Inhaled, Remove to fresh air. Seek medical attention if respiratory irritation occurs or if breathing becomes difficult."

2) On page 2, the precautionary statements paragraph should be modified so as to be exactly the same as for the TB-I approved label for SC-0224 Concentrate, EPA Identification No. 476-EEEL).

   "HARMFUL IF SWALLOWED, ABSORBED THROUGH THE SKIN OR INHALED. PROLONGED CONTACT MAY CAUSE SKIN IRRITATION. MAY CAUSE ALLERGIC SKIN REACTIONS. Avoid contact with skin, eyes or clothing. Wear rubber gloves when handling. Avoid breathing spray mist.

   Wash thoroughly with soap and water after handling and before eating or smoking. Remove contaminated clothing and wash before re-use."

5

3) On page 5, all references to the mixing of this product with a surfactant should be deleted.

Attachments

Tof Review 007074

Page____ is not included in this copy.

Pages 7 through 13 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ 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.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Prepared by: Brian Dementi, Ph.D., D.A.B.T.
Section 1, Toxicology Branch I - IRS (TS-769)
Secondary Reviewer: Edwin F. Budd, Section Head
Section 1, Toxicology Branch I - IRS (TS-769)

DATA EVALUATION REPORT

Study Type: Acute studies — TOX Chem No.: 8030

Accession No.: [illegible] — EPA ID No.: 474-EEPA

Test Material: Sulfosate (Touchdown 4LC-T Formulation)

Synonyms (Technical Active Ingredient): N-Phosphonomethyl glycine trimethyl sulfonium salt; SC-0224

Study Number: T-10589

Sponsor: ICI Americas, Inc.

Testing Facility: Stauffer Chemical Company
Richmond Toxicology Laboratory
Richmond, CA

Title of Report: "Acute Toxicity Tests For SC-0224 4LC-T"

Author(s): P.L. Morgan

Report Issued: February 10, 1987

Classification: Core-Guideline

Conclusions:

I. Acute Oral Toxicity (Rat)

Male LD_{50} = 1761 mg/kg; Female LD_{50} = 1029 mg/kg;
Toxicity Category III

II. Acute Dermal Toxicity

Mixed gender rabbit LD_{50} > 2000 mg/kg;
Toxicity Category III

III. Dermal Irritation Study

Nonirritating to intact skin of the rabbit;
Toxicity Category IV

007074

IV. Ocular Irritation

In the washed eyes of rabbits the test material elicited mild to moderate conjunctival irritation, which cleared by day 4. In unwashed eyes the test material produced moderate iritis in one rabbit and mild to moderate conjunctival irritation in all six rabbits under study. All such effects cleared by day 7.

Toxicity Category = III

15

1. Acute Oral Toxicity Tests - Rat

Animals (Sprague-Dawley albino rats) were obtained from Charles River Laboratories. Sixty male and 60 female rats were employed where 35 rats of each sex received test material and 25 of each sex served as controls. The body weight for males used in the study was 160 to 200 g and for females, 140 to 210 g. Each dose of the test material was prepared by dissolving/suspending the appropriately weighed amount in water, which neither served as the vehicle. Tests were performed by oral gavage by a single administration. A minimum of five males and five females were used at each dose tested. The animals were fasted for 16 to 18 hours prior to treatment. The rats were observed for at least 14 days posttreatment for mortality and signs of toxicity. Necropsies were performed on all rats.

The following tabulates the level of mortality which occurred at each dose.

Dose (mg/kg)*	Mortality Males (%)	Females (%)
5[illegible]	5/5 (100)	5/5 (100)
2[illegible]	4/5 (80)	5/5 (100)
1[illegible]	6/10 (60)	4/5 (80)
1[illegible]	2/5 (40)	3/5 (60)
1[illegible]	2/5 (40)	3/5 (60)
1[illegible]	0/5 (0)	1/5 (2[illegible]

*Test solutions administered at a dosage volume to body weight ratio (ml/kg) of 10.

Not shown in the tabulation were 10 male and 10 female rats administered water as vehicle control which were without mortality.

By inspection of a plot of the above data it was determined that for male rats, LD_{50} = [illegible] mg/kg and for females, LD_{50} = [illegible] mg/kg.

A review of the description of clinical signs and necropsy results at each dose (pages 15 to 17 for males and 20 to 22 for females) confirms the statements of the study author (page 11) to the effect that for males, the only commonly observed adverse clinical sign was depression. At necropsy, observations included darkened livers, darkened spleens, testicular material in the stomach or GI tract, and pale testes. For females there were no commonly observed clinical signs. There was some evidence of rough coats.

16

hypersensitivity to touch and sound, and depression. At necropsy, observations included reddened and/or darkened lungs, darkened livers, darkened spleens, and reddish material in the stomach and GI tract.

Conclusion: Male Rat LD_{50} = [illegible] mg/kg;
Female Rat LD_{50} = [illegible] mg/kg.

II. Acute Dermal Toxicity Test

Stauffer albino rabbits were employed in the study. The supplier of rabbits for this test was Mirabell Rabbitry, Broward, FL. The weight range for the mixed population of male and female rabbits used in the study was [illegible] to [illegible] kg. Five male and five female rabbits had the test material applied to the closely clipped abdominal skin beneath a protective binder. One day later the binder was removed. The test animals were observed for at least 14 days following the initial treatment. Necropsies were performed on all rabbits. The results of this study were that at a single dermal dose of 2000 mg/kg, 1 of the 10 rabbits died within 24 hours. Adverse clinical signs included mild depression and diarrhea. Survivors appeared normal after 2 days. The only local dermal effect was mild-to-moderate erythema following 24 hours of exposure. Necropsy observations for the survivors were normal.

The conclusion for this study is that the acute dermal LD_{50} > 2000 mg/kg for SC-[illegible] when tested on a mixed gender population of albino rabbits.

III. Dermal Irritation Study

Stauffer albino rabbits were also employed in this study. The primary irritation of the skin was measured by a patch-test technique on the intact skin, where 0.5 ml of the test material was introduced under a 1-inch square gauze patch. The patch was held in place by adhesive tape and wrapped with rubberized fabric for a 4-hour period. After the 4 hours of exposure, the patches and test material were removed. Readings were made after 30 minutes, and [illegible], and [illegible] hours. The final score represents an average of all readings. Scoring and evaluating criteria are those described by Draize.

As tested in three male and two female rabbits the test material did not produce any erythema-eschar or edema at any time after [illegible].

It is concluded that Stauffer [illegible] was a [illegible] on intact skin of six rabbits.

IV. Ocular Irritation

Albino rabbits were employed in the study. Eyes of rabbits were examined before application of test material for ocular and periocular abnormalities. Additional examination with fluorescein dye was performed to detect corneal epithelial abnormalities. Rabbits with preexisting ocular lesions or abnormalities were excluded from further ocular testing. In this study, 0.1 ml of test material was placed in the conjunctival sac of the left eye of each of nine (3 M, 6 F) rabbits. The treated eye was washed for about 20 to 30 seconds after the exposure in three rabbits with the eyes of the remaining six animals left unwashed. The untreated eyes of each rabbit served as control. The cornea, iris, and the bulbar and palpebral conjunctivae were observed at 1, 24, 48, and 72 hours and at 4 and 7 days posttreatment. Observations with fluorescein staining were made at 24 hours after application of the test material and until there was no staining for three consecutive observations. Draize (1965) guidelines were used to assign scores to the observed effects.

In the three rabbits where eyes were washed 20 to 30 seconds after treatment, there was dose-related mild to moderate conjunctival irritation. All such irritation cleared by day 4. With respect to eyes of those rabbits treated, but left unwashed, SC-0024 ALC-F (pH 5.85) produced moderate iritis in one rabbit and mild to moderate conjunctival irritation in six rabbits. All irritation cleared by day 7, as confirmed in Tables 2 to 4, pages 15 to 17 (Attachments).

Conclusion: Toxicity Category III.

TH Review 007074

Page____ is not included in this copy.

Pages 19 through 21 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ 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.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

007074

Reviewed By: Brian Ferenti, Ph.D., D.A.B.T.
Section I, Toxicology Branch I - IRS (TS-769C)
Secondary Reviewer: Edwin P. Budd, Section Head
Section I, Toxicology Branch I - IRS (TS-769C)

DATA EVALUATION REPORT

Study Type: Acute Inhalation Study — TOX Chem No.: 8660

Accession No.: 408938-03 — EPA ID No.: 476-EFFA

Test Material: SC-0224 4LC-F

Synonyms (Technical Active Ingredient): N-Phosphoromethyl glycine trimethylsulfonium salt: SC-0224

Study Number: T-10983

Sponsor: ICI Americas, Inc.

Testing Facility: Stauffer Chemical Company
Farmington, CT

Title of Report: EPA Acute Inhalation Study with SC-0224 4LC-F.

Author(s): S.M. MacAskill and P.A. Grisel

Report Issued: June 22, 1987

Classification: Core - Supplementary

Conclusions:

The study authors report no success in generating a respirable aerosol for acute inhalation testing and, hence, conclude that SC-0224 4LC-F does not pose a threat by inhalation.

According to the study authors, the SC-0224 4LC-F used in the study lacked the physical properties necessary to generate a respirable aerosol for 4 hours. A very small amount of aerosol was visible in the chamber for only a few minutes after starting the generator. The test material property of high viscosity in concert with excessive foaming rendered the generator incapable of producing a satisfactory aerosol with SC-0224 4LC-F. The generator used in this study was a Solosphere® (McCay Respiratory

22

Therapy, Irvine, CA) nebulizer. The study authors explain that this is the only design that their laboratory has found capable of generating the high concentrations required in acute inhalation studies. The authors also advise that other types of generators ([illegible], Chio Ball Jet, etc.) would have been of no advantage in dealing with the excessive foaming action of the test material (page 5).

The test protocol which would have been followed in testing this material for inhalation toxicity is attached. Successful pursuit of the protocol would have satisfied EPA Guideline 81-3. In the absence of successful testing, consultation with Toxicology Branch resident expert in inhalational toxicity testing (Dr. Stan Gross) discloses that certain additional effort should be directed toward the evaluation of the test material for inhalational toxicity. <u>The Registrant should be advised to pursue additional testing taking into advisement the following suggestions:</u>

1) Dilute the SC-0224 ALC-E (40% a.i.) with [redacted] until foaming stops.
2) Reduce surfactants until foaming stops.
3) If necessary, form a dense fog and run through a cyclone separator to remove large particles.
4) Consult with Toxicology Branch if testing problems continue.

Attachment

INERT INGREDIENT INFORMATION IS NOT INCLUDED

23

Tech. Review 007074

Page ____ is not included in this copy.

Pages 24 through 29 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ 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.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

007074

Reviewed By: Brian Perenti, Ph.D., D.A.B.T.
Section I, Toxicology Branch - IPS/HFD (TS-769C)
Secondary Reviewer: Kevin Rudd, Section Head
Section I, Toxicology Branch - IPS/HFD (TS-769C)

DATA EVALUATION REPORT

Study Type: Dermal Sensitization Test TOX Oher No.: 5030

Record No.: 235171 MRID No.: 40868-04

Test Substance: SC-0224 4LC-F

Synonyms (technical active ineredient): N-phosphonomethyl glycine trimethylsulfonium salt; SC-0224

Study Number: T-10588

Sponsor: ICI Americas, Inc.

Testing Facility: Stauffer Chemical Co.
Richmond Toxicology Laboratory
Richmond, CA

Title of Report: "Dermal Sensitization Test with SC-0224 4 LC-F"

Author: L.C. Vetter

Report issued: 6/2/87

Classification: Core - Guideline

Conclusions: As evaluated by the modified Buehler test procedure, SC-0224 4 LC-F did not cause dermal sensitization in the guinea pig. Furthermore, there was no evidence of an adverse effect of the test mixture on guinea pigs as measured by weight gain, general appearance or behavior.

30

A. Materials

1. Test Compound

Identification: SC-0024 41C-F (40.0 wt% of active ingredient)

Description: Brown liquid

Lot No.: JWP 10190-50-1

Purity, Contaminants: Unable to locate any additional information on test material purity (this is a formulation for which a Confidential Statement of Formulation exists).

2. Test Animals

Species: Guinea pig

Strain: Hartley

Age: 3[illegible]-4[illegible] days

Weight: 275-4[illegible] grams

Source: Charles River Laboratories
Newfield, NJ

B. Study Design - (The following is quoted from pages 9-10 of the study).

"The dermal sensitization potential of SC-0024 41C-F was tested using a modified Buehler test according to the Richmond Toxicology Laboratory protocol RTL-DS-7 (Appendix I). Briefly, the modified Buehler included a primary irritation study, an induction phase (day 1-22), a challenge phase (day 35-39) and a rechallenge phase (day 42-45).

"Eight animals were used in the primary irritation phase. A 3[illegible] solution of SC-0024 41C-F in distilled water was applied to the shaved right flank of all the animals. Observations of skin responses were made at 24, 48 and 72 hours following the initial application. One week later, SC-0024 41C-F was applied neat to the animals shaved left flank. Skin responses were again evaluated at 24, 48 and 72 hours following the initial application.

"There were three groups of guinea pigs (n=10) in the induction and challenge phases. One group served as the Test Group and was induced, challenged and rechallenged with SC-0024 4 1C-F. Another group, the Negative Control Group, was induced with saline and challenged/rechallenged with SC-0024 4 1C-F.

31

The Positive Control Group was induced, challenged and rechallenged with 0.1% DNCB. Each animal was concurrently challenged with the appropriate challenge vehicle and, in effect, served as its own control.

"All materials were applied topically (in a volume of 0.5 ml.), occluded and left on the skin for six hours. Liquids were applied to a 1.5 cm diameter chamber without adhesive, placed on the skin and secured by wrapping the abdomen with gauze. Induction applications were made to the shaved right flank on alternate days (Monday, Wednesday, and Friday, starting on Wednesday), for a total of ten applications. Induction applications were made to the shaved right flank. Two weeks after the last induction application, each animal was challenged on the test material and the vehicle. All animals were rechallenged one week later on the shaved and depilated upper left flank with concurrent applications of the test material and the vehicle. To minimize variations in response to flank location, the application site sequence of test material and vehicle were reversed for half of the animals of each group. The skin reactions were evaluated for erythema (redness) and edema (swelling) according to a 4-point scoring system (Table I). Other responses, e.g. skin flaking, eschar, induration, etc. were also noted if present but were not included in the score. Eschar is defined in this test as clear or colored exudate or injuries in depth. These evaluations were made on Tuesdays and Thursdays during induction and daily for the 3 days following challenge/rechallenge and primary irritation applications.

"A known sensitizer, dinitro-chlorobenzene (DNCB), was used as the positive control material. DNCB was dissolved in 70% ethanolic water for induction and acetone for the challenge and rechallenge. The change in DNCB vehicles was made to optimize the induction of sensitized animals and prevent the possibility of ethanol sensitization. SC-0224 w/c-F was applied neat for the induction challenge and rechallenge phases, and for purposes of this test, saline will be considered as the vehicle for SC-0224 w/c-F.

"Positive control material dose solutions were analyzed by UV spectrophotometry according to the Richmond Toxicology Laboratory protocol RTL-AM-4 (Appendix VI).

"A group was considered to have a positive response if one or more animals in the group exhibited an erythema or edema score of 2 or greater. The material was considered to be a sensitizer if the challenge reaction was positive, persistant and greater than the irritation reaction. Irritation was determined from the primary irritation results and the challenge response of the Negative Control Group."

c. Results

With the exception of skin flaking noted for three animals at certain time points during the induction phase among the SC-0224 4LC-E group and also for several animals of both SC-[illegible] 4LC-E and saline controls during the challenge phase, no adverse effects were produced by SC-0224 4LC-E in this study. There were no deaths. The test material did not produce any effects on weight gain of animals during the study. However, the positive control (DNCB) group gained more weight than the control group, an effect which appeared to be manifested only during week 7, the final week of observation. This seems to be a questionable change since it was so marked during week 7 without any evidence of a positive control effect up to week 7. (Table 2, p. 16)

SC-0224 4LC-E test results do not reveal any evidence that the material elicited erythema or edema during the induction phase (Table 4, p. 18).

As to the principal objective of this study, which was to determine whether SC-0224 4LC-E causes dermal sensitization, there was no evidence of a positive response either during the first challenge (Table 5, p. 19) or during the rechallenge phase of the study (Table 6, p. 20). By contrast, the positive control substance, DNCB, elicited positive responses during both the first challenge and rechallenge phases. Inspection of individual animal test data as displayed in Appendices II-IV, pp. 39--7 of the study, confirm the tabulated findings.

(Attachments: Tables 4, 5 and 6, pp. 18-20 of the study)

DERMAL SENSITIZATION TEST
SC-0224 4LC-E

TABLE 4

SUMMARY OF INDUCTION PHASE RESULTS

EXPERIMENTAL GROUP	SKIN RESPONSE		DAY NUMBER 2	7	9	14	16	21	23
TEST MATERIAL (SC-0224 4LC-E)	ERYTHEMA	SCORE[a]	0	0	0	0	0	0	0
		FREQUENCY[b]	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	EDEMA	SCORE	0	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10	0/10
NEGATIVE CONTROL (Saline)	ERYTHEMA	SCORE	0	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	EDEMA	SCORE	0	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10	0/10
POSITIVE CONTROL (0.1% DNCB)	ERYTHEMA	SCORE	0	1.3	1.6	1.8	1.9	1.9	2.0
		FREQUENCY	0/10	9/10	8/10	9/10	10/10	10/10	9/10
	EDEMA	SCORE	0	0	0	0	0	0	1.7
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10	3/10

[a] AVERAGE SCORE OF RESPONSES ≥ 1
[b] FREQUENCY OF RESPONSE SCORES ≥ 1

TABLE 5

SUMMARY OF FIRST CHALLENGE RESULTS

EXPERIMENTAL GROUP	SKIN RESPONSE		HOURS AFTER FIRST CHALLENGE APPLICATION					
			24		48		72	
			TM[c]	V[d]	TM	V	TM	V
TEST MATERIAL (SC-0224 4LC-E)	ERYTHEMA	SCORE[a]	0	0	0	0	0	0
		FREQUENCY[b]	0/10	0/10	0/10	0/10	0/10	0/10
	EDEMA	SCORE	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10
NEGATIVE CONTROL (0.85% Saline)	ERYTHEMA	SCORE	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10
	EDEMA	SCORE	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10
POSITIVE CONTROL (0.1% DNCB)	ERYTHEMA	SCORE	1.9	0	2.0	0	2.0	0
		FREQUENCY	10/10	0/10	10/10	0/10	8/10	0/10
	EDEMA	SCORE	1.8	0	2.0	0	0	0
		FREQUENCY	9/10	0/10	8/10	0/10	0/10	0/10

a AVERAGE SCORE FOR RESPONSES ≥ 1
b FREQUENCY OF RESPONSE SCORES > 1
c TM - TEST MATERIAL OR DNCB SITE
d V - VEHICLE SITE

TABLE 6

SUMMARY OF RECHALLENGE RESULTS

EXPERIMENTAL GROUP	SKIN RESPONSE		HOURS AFTER FIRST CHALLENGE APPLICATION					
			24		48		72	
			TM[c]	V[d]	TM	V	TM	V
TEST MATERIAL (SC-0224 4LC-E)	ERYTHEMA	SCORE[a]	0	0	0	0	0	0
		FREQUENCY[b]	0/10	0/10	0/10	0/10	0/10	0/10
	EDEMA	SCORE	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10
NEGATIVE CONTROL (0.85% Saline)	ERYTHEMA	SCORE	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10
	EDEMA	SCORE	0	0	0	0	0	0
		FREQUENCY	0/10	0/10	0/10	0/10	0/10	0/10
POSITIVE CONTROL (0.1% DNCB)	ERYTHEMA	SCORE	2.1	0	1.9	0	1.7	0
		FREQUENCY	10/10	0/10	10/10	0/10	10/10	0/10
	EDEMA	SCORE	2.3	0	2.7	1.0	1.0	0
		FREQUENCY	3/10	0/10	7/10	1/10	8/10	0/10

a AVERAGE SCORE FOR RESPONSES ≥ 1
b FREQUENCY OF RESPONSE SCORES ≥ 1
c TM = TEST MATERIAL OR DNCB SITE
d V = VEHICLE SITE