UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

02/25/00

MEMORANDUM

Subject: D261351
BAQUACIL® Ultra Swimming Pool and Spa Sanitizer and Fungicide
EPA File Symbol 072674-EE

From: Wallace Powell, Biologist
Product Science Branch (PSB)
Antimicrobials Division (7510C)

Thru: Karen P. Hicks, Team Leader
Chemistry/Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

Michele E. Wingfield, Chief
Product Science Branch
Antimicrobials Division (7510C)

To: Adam Heyward, Product Manager, Team 34
Nader Elkassabany, Team Reviewer, Team 34
Regulatory Management Branch II
Antimicrobials Division (7510C)

BACKGROUND

The applicant, Avecia Inc., has submitted acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary dermal irritation, dermal sensitization, and primary eye irritation studies – MRID Nos. 449407-01 through -05 and 449639-02, respectively. The studies were submitted in support of product registration for BAQUACIL® Ultra Swimming Pool and Spa Sanitizer and Fungicide, EPA File Symbol 72674-EE. The studies were initially reviewed for Product Science Branch (PSB) by Oak Ridge National Laboratory. The reviews are attached to this memorandum.

The active ingredient in the product is poly(iminoimidocarbonlyiminoimidocarbonyliminohexamethylene) hydrochloride – i.e., poly(hexamethylenebiguanide) hydrochloride, EPA code 111801 – at 20 percent of the product by weight.

RECOMMENDATION

PSB concurs with the acute Toxicity Categories assigned in the attached study reviews. The Categories are listed in the table below.

In the acute inhalation toxicity study (MRID 449407-03), the temporary blockage of the atomizer (mentioned in the attached review) does not appear to invalidate the study. The blockage resulted in a reduction of the study's average atmospheric concentration. Without the blockage, the average concentration would have been close to 2.0 mg/L. With the blockage, it was 1.76 mg/L, which is in the middle of the Toxicity Category III range. The study is being treated in the same way that a limit test conducted at the Category III limit dose of 0.5 mg/L would be treated: the study indicates Category III or IV, and Category III is assigned for regulatory purposes.

In the dermal sensitization study report, the test material is classified as a mild sensitizer under the conditions of the study. However, the enclosed review classifies it as a non-sensitizer under the conditions of the study. PSB concurs with the enclosed review. Erythema response to the challenge dose in the naive control group was zero. Under the 75% w/v patch, though the test group response to challenge may have had significance as compared to zero response, it was arguably too mild to be significant in itself. It consisted of scattered mild redness, present in only 3/20 animals at 24 hours and in 1/20 at 48 hours. (Under the 50% w/v patch, used concurrently with the 75% patch on the test group animals at challenge, there was no response.)

The test material in each of the six studies was reported as "Bermuda", which the applicant's 10/01/99 letter indicated to be synonymous with the brand name of record for the proposed product.

Table: Acute Toxicity Categories for each effect

Data Requirement	Means of Support	Category
Acute Oral Toxicity	Submitted study, MRID 449407-01	III
Acute Dermal Toxicity	Submitted study, MRID 449407-02	III
Acute Inhalation Toxicity	Submitted study, MRID 449407-03	III
Primary Eye Irritation	Submitted study, MRID 449639-02	II
Primary Dermal Irritation	Submitted study, MRID 449407-04	IV
Dermal Sensitization	Submitted study, MRID 449407-05	Non-sensitizer

PRODUCT LABELING

The precautionary statements under the "Hazards to Humans and Domestic Animals" heading will be acceptable and in accordance with the *Label Review Manual* if modified as follows:

Add the statements: "Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash clothing before reuse."

Replace the statement, "Causes eye irritation," with the statement, "Causes substantial but temporary eye injury."

Add an instruction to wear protective eyewear (goggles, face shield, or safety glasses).

PSB has no objection to the inclusion of the optional statement, "May cause allergic skin reaction."

The following revisions are required in the "Statement of Practical Treatment" section:

In the "If Swallowed" instructions, add the statement, "Do not give anything by mouth to an unconscious person."

Replace the existing "If In Eyes" instructions with the statements, "IF IN EYES: Hold eyelids open and flush with a steady, gentle stream of water for 15 minutes. Get medical attention."

Add the instructions, "IF INHALED: Remove victim to fresh air. If not breathing, give artificial respiration, preferably mouth-to-mouth. Get medical attention."

DATA EVALUATION REPORT

POLY(IMINOIMIDOCARBONYLIMINOIMIDOCARBONYLIMINOHEXA ("BERMUDA")

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [870.1100 (81-1)]
MRID 44940701

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K0155

Primary Reviewer:
Susan Chang, M.S.
Signature: _____
Date: DEC 2 8 1999

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.
Signature: _____
Date: DEC 2 8 1999

Robert H. Ross, M.S., Group Leader
Signature: _____
Date: DEC 2 8 1999

Quality Assurance:
Lee Ann Wilson, M.A.
Signature: _____
Date: DEC 2 8 1999

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Wallace Powell, Ph.D. _____, Date _____
EPA Work Assignment Manager: Nader Elkassabany, Ph.D. _____, Date _____

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Rat [OPPTS 870.1100 (§81-1)]

DP BARCODE: D261351
P.C. CODE: 111801

SUBMISSION CODE: S571536
CASE NO.: 066322

TEST MATERIAL (PURITY): "Bermuda" (20.6% a.i.)

SYNONYMS: BAQUACIL Ultra Swimming Pool and Spa Sanitizer and Fungicide

CITATION: Brammer, A. (1999) "Bermuda": Acute oral toxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Study No. AR6764, April 20, 1999. MRID 44940701. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 44940701) groups of five male and five female fasted young adult Alpk:AP$_f$SD rats were given single oral 1000, 2000, or 3500 mg/kg doses of "Bermuda" (20.6%, a.i., Batch No. 1) and observed for 14 days.

All low-dose rats survived the study. Three males and four females in the mid-dose group and all high-dose rats died or were killed *in extremis* on day 1. Salivation was noted from four low-dose males on day 1 with recovery by day 2. No abnormalities were detected from other low-dose rats. Salivation, gasping, irregular breathing, prostration and/or moribundity, upward curvature of spine and/or decreased activity were noted from some of the decedents prior to death. Upward curvature of spine and decreased activity were also noted from some of the mid-dose survivors with recovery by day 2. One mid-dose female had her sides pinched in prior to death. All survivors had normal body weight gains. Stomachs with discolored/white fluid, mucosal folds raised and reddened, thin walls, and/or sloughing of the mucous layers were noted from most of the decedents. Creamy, discolored fluid contents were noted in the small intestines of some of the high-dose rats.

The oral LD_{50}s for males, females, and combined were 1831, 1617, and >1000 and < 2000 mg/kg for males, females, and combined, respectively.

"Bermuda" is in TOXICITY CATEGORY III based on the LD_{50}.

This acute oral study is classified as **Acceptable/Guideline** and satisfies the subdivision F guideline requirements for an acute oral study [870.110 (81-1)] in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: "Bermuda"

   Description: clear blue liquid
   Lot/Batch #: 1
   Purity: 20.6% w/w, a.i.
   Composition: not reported

2. Vehicle and/or positive control

   Deionized water

3. Test animals

   Species: rat
   Strain: Alpk:AP$_f$SD
   Age and/or weight at dosing: approximately 8-12 weeks; males: 294-342 g, females: 199-242 g
   Source: Rodent Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK
   Acclimation period: at least 5 days
   Diet: RM1 (supplied by Special Diet Services Limited, Witham, Essex, UK), *ad libitum*
   Water: mains water, *ad libitum*
   Housing: maximum of five/sex/cage suitable for animals of this strain
   Environmental conditions:
   Temperature: 22±3 °C
   Humidity: 30-70%
   Air changes: at 15/hour
   Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: February 15, 1999; end: March 4, 1999

2. Animal assignment and treatment

Following an overnight fast, groups of five rats/sex were given a single 1000, 2000, or 3500 mg/kg dose of the test material in deionized water by gavage. The animals were observed for clinical signs of toxicity twice post dosing and once daily thereafter for 14 days. They were weighed on study days 1, 8, and 15. All rats were necropsied.

TABLE 1. Doses, mortality/animals treated

Dose (mg/kg)	Males	Females	Combined
1000	0/5	0/5	0/10
2000	3/5	4/5	7/10
3500	5/5	5/5	10/10

Data taken from Table 1, p. 18, MRID 44940701.

3. Statistics

Calculation of the oral LD_{50} was by logistic regression using nominal dose values. Confidence limits were calculated using a likelihood ratio interval (Williams D.A., 1986, Interval Estimation of the Median Lethal Dose, Biometrics 42, 641-645).

II. RESULTS AND DISCUSSION

A. MORTALITY

Mortality is given in Table 1. None of the rats in the low-dose group died as a result of "Bermuda" toxicity. Three males and four females in the mid-dose group and five males and five females in the high-dose group died or were killed *in extremis* on day 1.

The oral LD_{50}s for males, females, and combined were 1831 (95% C.L. 1386-2420 mg/kg), 1617 (95% C.L. 1227-2131 mg/kg), and >1000 and < 2000 mg/kg for males, females, and combined[a], respectively. This places "Bermuda" in TOXICITY CATEGORY III.

[a] estimated by the reviewer

B. CLINICAL OBSERVATIONS

Salivation was noted from four low-dose males on day 1 with recovery by day 2. No abnormalities were detected from other low-dose rats. Salivation, gasping, irregular breathing, prostration and/or moribundity were noted from some of the decedents prior to death. Upward curvature of spine and decreased activity were also noted from some of

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the decedents and mid-dose survivors. The mid-dose survivors recovered by day 2. One mid-dose female had sides pinched in prior to death.

C. BODY WEIGHT

All survivors had normal body weight gains.

D. NECROPSY

Stomachs with discolored/white fluid, mucosal folds raised and reddened, thin walls, and/or sloughing of the mucous layers were noted from most of the decedents. Creamy, discolored fluid content was noted in the small intestines of some of the high-dose rats.

E. DEFICIENCIES

None

DATA EVALUATION REPORT

POLY(IMINOIMIDOCARBONYLIMINOIMIDOCARBONYLIMINOHEXA ("BERMUDA")

STUDY TYPE: ACUTE DERMAL TOXICITY - RAT [870.1200 (81-2)]
MRID 44940702

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K0155

Primary Reviewer:
Susan Chang, M.S.

Signature: _____
Date: DEC 2 8 1999

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: _____
Date: DEC 2 8 1999

Robert H. Ross, M.S., Group Leader

Signature: _____
Date: DEC 2 8 1999

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: _____
Date: DEC 2 8 1999

Disclaimer

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Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Wallace Powell, Ph.D. _____, Date _____
EPA Work Assignment Manager: Nader Elkassabany, Ph.D. _____, Date _____

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rat [OPPTS 870.1200 (§81-2)]

DP BARCODE: D261351
P.C. CODE: 111801

SUBMISSION CODE: S571536
CASE NO.: 066322

TEST MATERIAL (PURITY): "Bermuda" (20.6% a.i.)

SYNONYMS: BAQUACIL Ultra Swimming Pool and Spa Sanitizer and Fungicide

CITATION: Brammer, A. (1999) "Bermuda": Acute dermal toxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Study No. CR3498, April 20, 1999. MRID 44940702. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 44940702), a 7 cm x 7 cm dorso-lumbar region of five male and five female young adult Alpk:AP$_f$SD rats was dermally exposed to 2000 mg/kg (Limit Test) "Bermuda" (20.6%, a.i., Batch No. 1) for 24 hours. The animals were observed for 14 days.

None of the animals died during the study. No rats had any significant signs of systemic toxicity and all rats had normal body weight gains during the study. No treatment-related abnormalities were noted at necropsy.

The dermal LD_{50} for males, females, and combined was > 2000 mg/kg (Limit Test).

"Bermuda" is in TOXICITY CATEGORY III based on the LD_{50}.

This acute dermal study is classified as **Acceptable/Guideline** and satisfies the subdivision F guideline requirements for an acute dermal study [870.1200 (81-2)] in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: "Bermuda"

Description: clear blue liquid
Lot/Batch #: 1
Purity: 20.6% w/w, a.i.
Specific gravity: 1.136±0.002
Composition: not reported

2. Vehicle and/or positive control

None

3. Test animals

Species: rat
Strain: Alpk:AP$_f$SD
Age and/or weight at dosing: approximately 8-12 weeks; males: 299-350 g, females: 197-221 g
Source: Rodent Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK
Acclimation period: at least 5 days
Diet: RM1 (supplied by Special Diet Services Limited, Witham, Essex, UK), *ad libitum*
Water: mains water, *ad libitum*
Housing: individually in cages suitable for animals of this strain
Environmental conditions:
Temperature: 22±3 °C
Humidity: 30-70%
Air changes: a minimum of 15/hour
Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

Start: February 23, 1999; end: March 10, 1999

2. Animal assignment and treatment

The study was conducted as a limit test using five male and five female rats. Animals were given a single 2000 mg/kg dose of "Bermuda" applied to a 7 cm x 7 cm clipped area on the dorso-lumbar region of each animal. The application site was covered with a foil-backed patch held in place using a cohesive bandage and secured with

surgical tape. The covering was removed 24 hours later and the site cleaned with a damp cotton swab. The animals were observed for clinical signs of toxicity between one and four hours after treatment and once daily thereafter for 14 days. They were weighed prior to test material application (day 1), and on study days 8 and 15. All rats were sacrificed and necropsied.

3. Statistics

Calculation of the dermal LD_{50} was not required.

II. RESULTS AND DISCUSSION

A. MORTALITY

None of the rats died during the study.

The dermal LD_{50} for males, females, and combined was > 2000 mg/kg. This places "Bermuda" in TOXICITY CATEGORY III.

B. CLINICAL OBSERVATIONS

No significant signs of systemic toxicity were noted from any rats during the study.

C. BODY WEIGHT

All animals had normal body weight gains.

D. NECROPSY

No treatment-related abnormalities were noted at necropsy.

E. DEFICIENCIES

None

DATA EVALUATION REPORT

POLY(IMINOIMIDOCARBONYLIMINOIMIDOCARBONYLIMINOHEXA ("BERMUDA")

STUDY TYPE: ACUTE INHALATION TOXICITY - RAT [870.1300 (§81-3)]

MRID 44940703

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K0155

Primary Reviewer:
Susan Chang, M.S.

Signature: _____
Date: DEC 2 8 1999

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: _____
Date: DEC 2 8 1999

Robert H. Ross, M.S., Group Leader

Signature: _____
Date: DEC 2 8 1999

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: _____
Date: DEC 2 8 1999

Disclaimer

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Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Wallace Powell, Ph.D. _____, Date _____
EPA Work Assignment Manager: Nader Elkassabany, Ph.D. _____, Date _____

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - Rat [OPPTS 870.1300 (§81-3)]

DP BARCODE: D261351 SUBMISSION CODE: S571536
P.C. CODE: 111801 CASE NO.: 066322

TEST MATERIAL (PURITY): "Bermuda" (20.6% polyhexamethylene biguanide, a.i.)

SYNONYMS: BAQUACIL Ultra Swimming Pool and Spa Sanitizer and Fungicide

CITATION: Kilgour, J.D. (1999) "Bermuda": 4-Hour acute inhalation toxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Study No. HR2340, July 5, 1999. MRID 44940703. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 44940703), five male and five female young adult Sprague-Dawley rats were exposed nose-only to "Bermuda" (20.6% polyhexamethylene biguanide, a.i., Batch No. 1) for 4 hours at a concentration of 1.76 mg/L. The mass median aerodynamic diameter was estimated to be 1.84-1.98 μm and the geometric standard deviation was 2.00-2.04 μm. Approximately 63-78% of particles had an aerodynamic diameter $\leq$3.5 μm. The animals were observed for 14 days.

One male was found dead within three hours of the end of exposure. Salivation, irregular breathing, and auditory hypoaesthesia were noted from most of the rats during exposure. Wet fur, hunched posture, piloerection, stains around the nose, and chromodacryorrhoea were noted from most of the rats immediately after exposure. In addition, decreased activity, salivation, coldness to the touch, abnormal respiratory noise, and irregular breathing were observed from all females and most males. With the exception of one female that had abnormal respiratory noise through the end of the study, all surviving rats recovered by day 11. The decedent showed decreased activity, coldness to the touch, gasping, abnormal respiratory noise, reduced breathing rate, and increased breathing depth prior to death. With the exception of one male and one female that lost weight during the first week, all rats had normal body weight gains. The decedent had dark red mottled lungs, and a distended stomach. Two surviving males had red mottled lungs and one female had focal swelling on the uterus.

The LC_{50} for males, females, and combined was > 1.76 mg/L.

"Bermuda" is in TOXICITY CATEGORY III based on the LC_{50}.

This acute inhalation study is classified as **Acceptable/Guideline** and satisfies the subdivision F guideline requirements for an acute inhalation study [870.1300 (81-3)] in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: "Bermuda"

   Description: clear blue liquid
   Lot/Batch #: 1
   Purity: 20.6% a.i.
   Composition: not reported

2. Vehicle and/or positive control

   None

3. Test animals

   Species: rat
   Strain: Alpk:AP$_f$SD
   Age and weight at dosing: young adult (8-12 weeks); males: 330-370 g, females: 211-258 g
   Source: Rodent Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK
   Acclimation period: 9 days
   Diet: RM1 (supplied by Special Diet Services Limited, Witham, Essex, UK), *ad libitum*
   Water: mains water, *ad libitum*
   Housing: five/sex/cage in multiple rat racks suitable for animals of this strain
   Environmental conditions:
   Temperature: 22±3°C
   Humidity: 30-70%
   Air changes: at least 15/hour
   Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: April 22, 1999; end: May 6, 1999

2. Exposure conditions

Temperature and humidity were recorded at least three times during the four-hour exposure.

3. Animal assignment and treatment

Animals were assigned to the test groups noted in Table 1. Rats were exposed to "Bermuda" by nose-only exposure for four hours. They were observed frequently during exposure, at the end of exposure, and daily thereafter for 14 days. They were weighed prior to test material exposure and on days 1, 8, and 15. All rats were necropsied.

TABLE 1. Concentrations, exposure conditions, mortality/animals treated

Nominal Conc. (mg/L)	Grav. Conc. (mg/L)[a]	MMAD (μm)	GSD (μm)	Particles ≤3.5 μm (%)	Temp. (°C)	Humidity (%)	Male	Female	Combined
11.85	1.11	1.98, 1.84	2.00, 2.04	63-78	21.6-21.9	32-36	1/5	0/5	1/10

Data were taken from pp. 18, 19, 23, 24, 27, and 28, MRID 44940703.
[a]The analyzed "Bermuda" a.i. concentration was 0.36 mg/L, the % total particulate was 32.8%, and total formulation concentration was 1.76 mg/L.

4. Generation of the test atmosphere and description of the chamber

The exposure atmosphere was generated using a glass concentric - jet atomizer. The test material was warmed to 40°C, then pumped to the atomizer. Clean dry air was passed through the atomizer and carried the atmosphere to the exposure chamber. The nominal airflow was 15 liters/min and the nose-only exposure chamber volume was 27.6 L.

Time to equilibrium was not reported.

Analytical chemistry - Spectrophotometrical determination at 235 nm.

Test atmosphere concentration - Gravimetric samples were collected using polyvinyl chloride GLA 5000 filters eleven times from the breathing zone of the animals during exposure. Filters were weighed before and after collection to determine the mass collected. The value was divided by the total volume of air sampled to determine the chamber concentration. The average results are in Table 1 above.

Particle size determination - Particle size was determined using a Marple Cascade impactor twice during exposure. The test material concentration collected by each stage was determined gravimetrically. The aerodynamic mass median diameter and geometric standard deviation were determined graphically using a log/probit transform and a linear regression derived from the cumulative data. Results are in Table 1 above.

5. Statistics

Calculation of the inhalation LC_{50} was not required.

II. RESULTS AND DISCUSSION

A. MORTALITY

One male was found dead within three hours of the end of exposure.

The LC_{50} for males, females, and combined was > 1.76 mg/L. This places "Bermuda" in TOXICITY CATEGORY III.

B. CLINICAL OBSERVATIONS

Salivation, irregular breathing, and auditory hypoaesthesia were noted from most of the rats during exposure. Wet fur, hunched posture, piloerection, stains around the nose, and chromodacryorrhoea were noted from most the rats immediately after exposure. In addition, decreased activity, salivation, coldness to the touch, abnormal respiratory noise, and irregular breathing were observed from all females and most males. With the exception of one female that had abnormal respiratory noise through the end of the study, all surviving rats recovered by day 11. The decedent showed decreased activity, coldness to the touch, gasping, abnormal respiratory noise, reduced breathing rate, and increased breathing depth.

C. BODY WEIGHT

With the exception of one male and one female that lost weight during the first week, all rats had normal body weight gains.

D. NECROPSY

The decedent had changes of stained eyelids and nares, dark red mottled lungs, and distended stomach. Two surviving males had red mottled lungs and one female had focal swelling on the uterus.

E. DEFICIENCIES

Although the study was conducted as a limit test, due to blockage of the atomizer, the concentration was lower than target for 16 minutes towards the end of the exposure.

DATA EVALUATION REPORT

POLY(IMINOIMIDOCARBONYLIMINOIMIDOCARBONYLIMINOHEXA ("BERMUDA")

STUDY TYPE: PRIMARY EYE IRRITATION - RABBIT 870.2400 (81-4)] MRID 44963902

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K0155

Primary Reviewer:
Susan Chang, M.S.
Signature: S Chang
Date: DEC 2 8 1999

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.
Signature: H T Borges
Date: DEC 2 8 1999

Robert H. Ross, M.S., Group Leader
Signature: R H Ross
Date: DEC 2 8 1999

Quality Assurance:
Lee Ann Wilson, M.A.
Signature: L. A. Wilson
Date: DEC 2 8 1999

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Wallace Powell, Ph.D. _____, Date _____
EPA Work Assignment Manager: Nader Elkassabany, Ph.D. _____, Date _____

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit [OPPTS 870.2400 (§81-4)]

DP BARCODE: D261351
P.C. CODE: 111801

SUBMISSION CODE: S571536
CASE NO.: 066322

TEST MATERIAL (PURITY): "Bermuda" (20.6% a.i.)

SYNONYMS: BAQUACIL Ultra Swimming Pool and Spa Sanitizer and Fungicide

CITATION: Brammer, A. (1999) "Bermuda": Eye irritation study in rabbits. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Study No. FB5790, April 20, 1999. MRID 44963902. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 44963902) 0.1 mL of "Bermuda" (20.6% a.i., Batch No. 1) was instilled into the left conjunctival sac of three young adult female New Zealand white rabbits. The contralateral eye of all rabbits served as control. The eyes were scored for ocular irritation according to the Draize method 1, 24, 48, and 72 hours and 4, 7, 8, 10, 14 and 16 days after instillation and the irritation classified according to the method of Kay and Calandra.

Corneal opacity was found on 3/3 rabbits approximately one hour after test material instillation with resolution on 1/3 rabbits by day 2, on 1/3 rabbits by day 7, and on 1/3 rabbits by day 8. Iritis was noted on 3/3 rabbits approximately one hour after test material instillation with resolution on two rabbits by day 2 and on one rabbit by day 7. The test material induced positive conjunctival irritation on all three rabbits one hour after test material instillation that became negative by day 7. The highest maximum mean total score was 39.0, recorded approximately one hour after test material instillation.

In this study, "Bermuda" was moderately irritating and is in TOXICITY CATEGORY II for primary eye irritation.

This study is classified as **Acceptable/Guideline** and satisfies the subdivision F guideline requirements for a primary eye irritation study [870.2400 (81-4)] in the rabbit.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: "Bermuda"

Description: clear blue liquid
Lot/Batch #: 1
Purity: 20.6% a.i.
Composition: not reported

2. Vehicle

None

3. Test animals

Species: rabbit
Strain: New Zealand white
Age and weight at dosing: young adult; females: 2231-3540 g
Source: Charles River UK Limited, Margate, Kent, UK
Acclimation period: at least 5 days
Diet: STANBRA SQC, Special Diet Services Limited, Witham, Essex, UK, *ad libitum*
Water: mains water, *ad libitum*
Housing: individually in cages suitable for animals of this strain
Environmental conditions:
Temperature: 17±3°C
Humidity: 30-70%
Air changes: a minimum of 15/hour
Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

Start: February 15, 1999; end: March 5, 1999

2. Animal assignment and treatment

The test material (0.1 mL) was instilled into the left conjunctival sac of three female rabbits and the eye lids held together for approximately 1-2 seconds. The contralateral eye of all rabbits served as control. The animals were scored for ocular irritation approximately 1, 24, 48, and 72 hours and 4, 7, 8, 10, 14, and 17 days after instillation according to the Draize method and the degree of irritation classified according to the method of Kay and Calandra.

II. RESULTS AND DISCUSSION

A. Corneal opacity was found on 3/3 rabbits approximately one hour after test material instillation with resolution on 1/3 rabbits by day 2, on 1/3 rabbits by day 7, and on 1/3 rabbits by day 8. Iritis was noted on 3/3 rabbits approximately one hour after test material instillation with resolution on two rabbits by day 2 and on one rabbit by day 7. The test material induced positive conjunctival irritation on all three rabbits one hour after test material instillation that became negative by day 7. The highest maximum mean total score was 39.0, recorded approximately one hour after test material instillation.

This classifies the test material as moderately irritating. "Bermuda" is in TOXICITY CATEGORY II.

B. DEFICIENCIES

None

DATA EVALUATION REPORT

POLY(IMINOIMIDOCARBONYLIMINOIMIDOCARBONYLIMINOHEXA ("BERMUDA")

STUDY TYPE: PRIMARY DERMAL IRRITATION - RABBIT [870.2500 (81-5)]
MRID 44940704

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K0155

Primary Reviewer:
Susan Chang, M.S.

Signature: [signature]
Date: DEC 2 8 1999

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: [signature]
Date: DEC 2 8 1999

Robert H. Ross, M.S., Group Leader

Signature: [signature]
Date: DEC 2 8 1999

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: [signature]
Date: DEC 2 8 1999

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Wallace Powell, Ph.D. _____, Date _____
EPA Work Assignment Manager: Nader Elkassabany, Ph.D. _____, Date _____

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit [OPPTS 870.2500 (§81-5)]

DP BARCODE: D261351
P.C. CODE: 111801

SUBMISSION CODE: S571536
CASE NO.: 066322

TEST MATERIAL (PURITY): "Bermuda" (20.6% a.i.)

SYNONYMS: BAQUACIL Ultra Swimming Pool and Spa Sanitizer and Fungicide

CITATION: Brammer, A. (1999) "Bermuda": Skin irritation study in rabbits. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Study No. EB4827, April 20, 1999. MRID 44940704. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 44940704) three female adult New Zealand white rabbits were dermally exposed to 0.5 mL "Bermuda" (20.62% a.i., Batch 1) for 4 hours on the shorn flank. The animals were observed for 7 days. Irritation was scored by the method of Draize.

Very slight erythema were noted on 2/3, 2/3, 1/3, and 1/3 rabbits one hour, 2, 3, and 4 days following patch removal, respectively. Very slight or slight edema was noted on 3/3, 2/3, 2/3, 2/3, and 1/3 rabbits by one hour, 2, 3, and 4 days, respectively. By day 7, no irritation was noted on any rabbit. The primary irritation index was 1.3.

In this study, "Bermuda" was slightly irritating and is in TOXICITY CATEGORY IV for primary dermal irritation.

This study is classified as **Acceptable/Guideline** and satisfies the subdivision F guideline requirements for a primary dermal irritation study [870.2500(81-5)] in the rabbit.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: "Bermuda"

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Description: clear blue liquid
Lot/Batch #: 1
Purity: 20.6% a.i.
Composition: not reported

2. Vehicle

None

3. Test animals

Species: rabbit
Strain: New Zealand white
Age and weight at dosing: young adult; females: 2764-3203 g
Source: Charles River UK Limited, Margate, Kent, UK
Acclimation period: 5 days
Diet: STANRAB SQC (Special Diet Services Limited, Stepfield, Witham, Essen, UK), ad libitum
Water: mains water, *ad libitum*
Housing: individually in cages suitable for animals of this strain
Environmental conditions:
Temperature: 17±3 °C
Humidity: 30-70%
Air changes: a minimum of 15/hour
Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

Start: February 1, 1999; end: February 11, 1999

2. Animal assignment and treatment

Three female animals were given a single 0.5 mL dose of "Bermuda" applied to a 2.5 cm x 2.5 cm clipped intact site on the left flank. The application sites were covered with surgical gauze and secured with surgical tape. They were then covered by impermeable rubber sheeting and secured with adhesive impermeable polyethylene tape. The dressings were left in place for 4 hours, after which they were removed and the application sites cleaned with cotton wool soaked in clean warm water. The sites were scored for erythema and edema according to the Draize method 1, 24, 48, and 72 hours, and 4 and 7 days after patch removal.

II. RESULTS AND DISCUSSION

A. Very slight erythema were noted on 2/3, 2/3, 1/3, and 1/3 rabbits one hour, 2, 3, and 4 days following patch removal, respectively. Very slight or slight edema was noted on 3/3, 2/3, 2/3, 2/3, and 1/3 rabbits by one hour, 2, 3, and 4 days, respectively. By day 7, no irritation was noted on any rabbit. The primary irritation index was 1.3.

"Bermuda" is slightly irritating and is in TOXICITY CATEGORY IV.

B. DEFICIENCIES

None

DATA EVALUATION REPORT

POLY(IMINOIMIDOCARBONYLIMINOIMIDOCARBONYLIMINOHEXA ("BERMUDA")

STUDY TYPE: DERMAL SENSITIZATION - GUINEA PIG [870.2600 (81-6)]
MRID 44940705

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K0155

Primary Reviewer:
Susan Chang, M.S.

Signature: S. Chang
Date: DEC 2 8 1999

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: H T Borges
Date: DEC 2 8 1999

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: DEC 2 8 1999

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: DEC 2 8 1999

Disclaimer

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Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Wallace Powell, Ph.D. _____, Date _____
EPA Work Assignment Manager: Nader Elkassabany, Ph.D. _____, Date _____

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea Pig [OPPTS 870.2600 (§81-6)]

DP BARCODE: D261351
P.C. CODE: 111801

SUBMISSION CODE: S571536
CASE NO.: 066322

TEST MATERIAL (PURITY): "Bermuda" (20.6% a.i.)

SYNONYMS: BAQUACIL Ultra Swimming Pool and Spa Sanitizer and Fungicide

CITATION: Brammer, A. (1999) "Bermuda": Skin sensitization study in guinea pigs. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Study No. GG7259, April 20, 1999. MRID 44940705. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897

EXECUTIVE SUMMARY: In a dermal sensitisation study (MRID 44940705) with "Bermuda" (20.6% a.i., Batch No. 1), 30 young adult female Hartley guinea pigs were tested using the Buehler method.

Slight erythema was noted on 2/20 test animals 24 hours after the second induction with resolution by the third induction. Slight erythema was noted on 1/20 test animals 24 hours after the third induction. The control animals had no reactions. Scattered mild redness was noted on 3/20 test animals challenged with 75% w/v test material in deionized water 24 hours with resolution on two animals and persistence on one animal to 48 hours. The test animals challenged with 50% w/v test material in deionized water and the control animals had no reactions after challenge. The study report included a hexylcinnamaldehyde positive control study which was carried out within six months of the current study. The results were appropriate.

In this study, "Bermuda" was not a dermal sensitizer.

This study is classified as **Acceptable/Guideline** and satisfies the subdivision F guideline requirements for a dermal sensitization study [870.2600 (81-6)] in the guinea pig. **It should be noted that the study author stated the test material to be a mild sensitizer.**

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

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: "Bermuda"

Description: clear blue liquid
Lot/Batch #: 1
Purity: 20.6% a.i.
Composition: not reported

2. Vehicle and positive control

Vehicle: deionized water (challenge); positive control: hexylcinnamaldehyde (HCA) (historical data)

3. Test animals

Species: guinea pig
Strain: Dunkin Hartley
Age and weight at start of treatment: young adult; females: 292-339 g
Source: David Hall, Newchurch, Burton-on-Trent, Staffs, UK
Acclimation period: at least 5 days
Diet: FD1 (Special Diets Services, Witham, Essex, UK), *ad libitum*
Water: mains water, *ad libitum*
Housing: five per cage in cages suitable for animals of this strain
Environmental conditions:
Temperature: 20±3 °C
Humidity: 30-70%
Air changes: a minimum of 15/hour
Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

Start: January 28, 1999; end: March 4, 1999

2. Animal assignment and treatment

The animals were induced and challenged according to the method of Buehler. The scapular region of 30 female guinea pigs was clipped. For induction, 0.4 mL of undiluted test material was applied to a lint patch (approximately 2 cm x 2 cm), and then the patch was placed on the clipped area of the test animals for six hours. The application site was covered with an adhesive tape held in place by an adhesive elastic bandage and secured by a piece of PVC tape. This process was repeated for three

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times at an interval of 7 days. The control animals were treated as the test animals by omitting the test material from the patch. The test and control animals were left untreated for two weeks. The animals were challenged with 0.1-0.2 mL of 50% and 75% w/v test material in deionized water under occlusion to the clipped right and left flanks for six hours. Reactions were scored 24 hours after patch removal and immediately prior to the next induction and at 24 and 48 hours after patch removal after challenge.

II. RESULTS AND DISCUSSION

A. INDUCTION REACTIONS AND DURATION

Slight erythema was noted on 2/20 test animals 24 hours after the second induction with resolution by the third induction. Slight erythema was noted on 1/20 test animals 24 hours after the third induction. The control animals had no reactions.

B. CHALLENGE REACTIONS AND DURATION

Scattered mild redness was noted on 3/20 test animals challenged with 75% w/v test material in deionized water 24 hours following challenge with resolution on two animals and persistence on one animal to 48 hours. The test animals challenged with 50% w/v test material in deionized water and the control animals had no reactions after challenge.

"Bermuda" was not a dermal sensitizer.

C. POSITIVE CONTROL

The study report include a HCA positive control study which was carried out within six months of the current study. The results were appropriate.

D. ADDITIONAL TESTING

It is the reviewer's opinion that the study was conducted in a manner suitable to detect the sensitization potential of the test material. No additional testing is needed.

E. DEFICIENCIES

None

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DATA EVALUATION REPORT

POLY(IMINOIMIDOCARBONYLIMINOIMIDOCARBONYLIMINOHEXA ("BERMUDA")

STUDY TYPE: DERMAL SENSITIZATION - GUINEA PIG [870.2600 (81-6)]
MRID 44940705

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
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Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: H.T. Borges
Date: DEC 2 8 1999

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: DEC 2 8 1999

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: DEC 2 8 1999

Disclaimer

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Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Wallace Powell, Ph.D. _____, Date _____
EPA Work Assignment Manager: Nader Elkassabany, Ph.D. _____, Date _____

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea Pig [OPPTS 870.2600 (§81-6)]

DP BARCODE: D261351
P.C. CODE: 111801

SUBMISSION CODE: S571536
CASE NO.: 066322

TEST MATERIAL (PURITY): "Bermuda" (20.6% a.i.)

SYNONYMS: BAQUACIL Ultra Swimming Pool and Spa Sanitizer and Fungicide

CITATION: Brammer, A. (1999) "Bermuda": Skin sensitization study in guinea pigs. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Study No. GG7259, April 20, 1999. MRID 44940705. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897

EXECUTIVE SUMMARY: In a dermal sensitisation study (MRID 44940705) with "Bermuda" (20.6% a.i., Batch No. 1), 30 young adult female Hartley guinea pigs were tested using the Buehler method.

Slight erythema was noted on 2/20 test animals 24 hours after the second induction with resolution by the third induction. Slight erythema was noted on 1/20 test animals 24 hours after the third induction. The control animals had no reactions. Scattered mild redness was noted on 3/20 test animals challenged with 75% w/v test material in deionized water 24 hours with resolution on two animals and persistence on one animal to 48 hours. The test animals challenged with 50% w/v test material in deionized water and the control animals had no reactions after challenge. The study report included a hexylcinnamaldehyde positive control study which was carried out within six months of the current study. The results were appropriate.

In this study, "Bermuda" was not a dermal sensitizer.

This study is classified as **Acceptable/Guideline** and satisfies the subdivision F guideline requirements for a dermal sensitization study [870.2600 (81-6)] in the guinea pig. **It should be noted that the study author stated the test material to be a mild sensitizer.**

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

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: "Bermuda"

Description: clear blue liquid
Lot/Batch #: 1
Purity: 20.6% a.i.
Composition: not reported

2. Vehicle and positive control

Vehicle: deionized water (challenge); positive control: hexylcinnamaldehyde (HCA) (historical data)

3. Test animals

Species: guinea pig
Strain: Dunkin Hartley
Age and weight at start of treatment: young adult; females: 292-339 g
Source: David Hall, Newchurch, Burton-on-Trent, Staffs, UK
Acclimation period: at least 5 days
Diet: FD1 (Special Diets Services, Witham, Essex, UK), *ad libitum*
Water: mains water, *ad libitum*
Housing: five per cage in cages suitable for animals of this strain
Environmental conditions:
Temperature: 20±3°C
Humidity: 30-70%
Air changes: a minimum of 15/hour
Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

Start: January 28, 1999; end: March 4, 1999

2. Animal assignment and treatment

The animals were induced and challenged according to the method of Buehler. The scapular region of 30 female guinea pigs was clipped. For induction, 0.4 mL of undiluted test material was applied to a lint patch (approximately 2 cm x 2 cm), and then the patch was placed on the clipped area of the test animals for six hours. The application site was covered with an adhesive tape held in place by an adhesive elastic bandage and secured by a piece of PVC tape. This process was repeated for three

times at an interval of 7 days. The control animals were treated as the test animals by omitting the test material from the patch. The test and control animals were left untreated for two weeks. The animals were challenged with 0.1-0.2 mL of 50% and 75% w/v test material in deionized water under occlusion to the clipped right and left flanks for six hours. Reactions were scored 24 hours after patch removal and immediately prior to the next induction and at 24 and 48 hours after patch removal after challenge.

II. RESULTS AND DISCUSSION

A. INDUCTION REACTIONS AND DURATION

Slight erythema was noted on 2/20 test animals 24 hours after the second induction with resolution by the third induction. Slight erythema was noted on 1/20 test animals 24 hours after the third induction. The control animals had no reactions.

B. CHALLENGE REACTIONS AND DURATION

Scattered mild redness was noted on 3/20 test animals challenged with 75% w/v test material in deionized water 24 hours following challenge with resolution on two animals and persistence on one animal to 48 hours. The test animals challenged with 50% w/v test material in deionized water and the control animals had no reactions after challenge.

"Bermuda" was not a dermal sensitizer.

C. POSITIVE CONTROL

The study report include a HCA positive control study which was carried out within six months of the current study. The results were appropriate.

D. ADDITIONAL TESTING

It is the reviewer's opinion that the study was conducted in a manner suitable to detect the sensitization potential of the test material. No additional testing is needed.

E. DEFICIENCIES

None