UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

February 20, 2002

MEMORANDUM

Subject: D279123
Cutrine®- Ultra, EPA File Symbol 8959-LG

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

02-20-02

Through: Karen P. Hicks, Team Leader
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Product Science Branch
Antimicrobials Division (7510C)

2/20/02

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

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

BACKGROUND

The applicant, Applied Biochemists (as represented by an agent), has submitted a package for registration of the subject product, Cutrine®- Ultra. The package includes studies for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, eye irritation (two studies), skin irritation, and skin sensitization – MRID's 455332-05 through 455332-11, respectively. PSB reviews of the studies are attached to this memorandum.

The subject product, Cutrine®- Ultra, is a water treatment product for reservoirs, ponds, irrigation systems, etc. The product is labeled with copper (as elemental) as the active ingredient, from mixed copper-ethanolamine complexes in an emulsified formulation.

RECOMMENDATION

The submitted studies are acceptable. The test material identified in the study reports appears to represent the subject product. The resulting acute Toxicity Categories are listed in the table below.

Table: Acute toxicity regulatory status Cutrine®- Ultra

Data requirement	Means of support	Study result	Tox Category assigned to product
Acute Oral Toxicity	Submitted study, MRID 455332-05	Acceptable/ Tox Category III	III
Acute Dermal Toxicity	Submitted study, MRID 455332-06	Acceptable/ Category III	III
Acute Inhalation Toxicity	Submitted study, MRID 455332-07	Acceptable/ Category IV	IV
Eye Irritation	Submitted study, MRID 455332-08	Acceptable/ Category I (not corrosive)	II
Eye Irritation	Submitted study, MRID 455332-09	Acceptable/ Category II	
Skin Irritation	Submitted study, MRID 455332-10	Acceptable/ Category I, corrosive	I
Skin Sensitization	Submitted study, MRID 455332-11	Acceptable/ Non-sensitizer	Non-sensitizer

The second eye irritation study was presumably submitted to resolve the initial study's Tox Category indication, which could reasonably be considered ambiguous. (One of six animals in the Unrinsed group in the initial study had unresolved corneal opacity. If not for that animal, the results in other five of six would indicate Category III). The two studies considered together suggest Tox Category II.

Product labeling

In the proposed label (EPA Received date 10/30/2001), the following revisions are required in the "Hazards to Humans and Domestic Animals" section, as per the *Label Review Manual*:

- Change the word WARNING to DANGER.
- Add the statements, "Corrosive. Causes skin burns."
- Add the statement, "Wear protective clothing and [*] gloves." (*Specify type of gloves.)

On the label front panel, the word WARNING must be changed to DANGER.

The proposed First Aid statements are acceptable.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING

Attachment to 02/20/2002 Memorandum Regarding Data Package D279123
(Cutrine®- Ultra, EPA File Symbol 8959-LG)

Reviewer: W. Powell
Antimicrobials Division
Review date: 02/20/2002
Product No.: 8959-LG
DP Barcode: D279123
MRID No.: 455332-05
Report No.: 6009 (Study No.)
Study Completion: 05/22/1998
Author: George E. Moore

Conclusion:
LD_{50}: 910 mg/kg females (no C.L.),
970 mg/kg males (95% C.L. 800 mg/kg to 1240 mg/kg),
1000 mg/kg sexes combined (no C.L.)
Toxicity Category: III
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: None noted

Testing Facility: Product Safety Labs; 725 Cranbury Road, East Brunswick, New Jersey 08816

Test Material: Cutrine Ultra, Lot #GW1829A, a blue viscous liquid

Test Animal: Rat, Sprague-Dawley derived, albino
Age: Young adult
Weight: Males 198-240 g, Females 160-203 g
Source: Ace Animals, Inc. - Boyertown, PA

Test Method:

Three doses – 500, 1000, and 2000 mg/kg – of the test material undiluted were administered orally by gavage in single doses to fasted healthy rats, 5 per sex. Clinical observations were conducted at least once daily for the 14-day observation period or until mortality. Body weights were recorded on Day 0 prior to dosing, and on Days 7 and 14 or after death. Gross necropsy was conducted on all animals: thoracic and abdominal cavities were examined.

Results:

Mortality data is summarized in the table below. Median lethal dose can be observed to be between 500 and 2000 mg per kg body weight. This places the test substance in Tox Category III for acute oral toxicity (defined as 500 mg/kg < LD_{50} ≤ 5000 mg/kg). Estimated LD_{50} values were calculated at 910 mg/kg for the females (no confidence limits reportable), 970 mg/kg for the males (95% confidence limits 800 mg/kg to 1240 mg/kg), and 1000 mg/kg for sexes combined (no confidence limits reportable). All mortality in all three dose groups occurred between the Initial and Day 7 observations.

Table: Mortality Results

Dosage (mg/kg)	Number Dead/Number Tested		
	Males	Females	Total
500	0/5	1/5	1/10
1000	3/5	2/5	5/10
2000	5/5	5/5	10/10

Clinical signs in the 2000 mg/kg dose group observed at cage-side included hunched posture, hypoactivity, piloerection, signs of diarrhea, pronation. All surviving rats (500 and 1000 mg/kg dose groups) appeared to have normal weight gain during the study.

Necropsy observations in the 2000 mg/kg dose group included reddened lungs, discolored liver, extremely red gastrointestinal tract, gaseous distension of stomach. In the 500 mg/kg dose group, with the exception of moderately red lungs and red gastrointestinal tract in one female, necropsy observations were limited to slightly red lungs (which is often seen following the laboratory's CO_2 euthanasia procedure).

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING

Attachment to 02/20/2002 Memorandum Regarding Data Package D279123
(Cutrine®- Ultra, EPA File Symbol 8959-LG)

Reviewer: W. Powell
Antimicrobials Division
Review date: 02/20/2002
Product No.: 8959-LG
DP Barcode: D279123
MRID No.: 455332-11
Report No.: 6013 (Study No.)
Study Completion: 05/21/1998
Author: George E. Moore

Conclusion:
LD_{50}: 2460 mg/kg females (no C.L.),
5000 mg/kg males (observed),
Sexes combined: not applicable
Toxicity Category: III
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: None noted

Testing Facility: Product Safety Labs; 725 Cranbury Road, East Brunswick, New Jersey 08816

Test Material: Cutrine Ultra, Lot #GW1829A, a blue viscous liquid

Test Animal: Rat, Sprague-Dawley derived, albino
Age: Young adult
Weight: Males 223-283 g, Females 203-238 g
Source: Ace Animals, Inc. - Boyertown, PA

Test Method:

Three doses – 2000, 3000, and 5000 mg/kg – of the test material undiluted were applied to the dorsal and trunk area of 5 rats per sex (2000 and 5000 mg/kg dose groups) or 5 female rats (3000 mg/kg dose group). A gauze pad was applied and covered with a tape wrapping. This dressing was removed after a 24 hour exposure period, and the treatment site was then gently wiped with water and clean towel. The animals were observed for signs of toxicity at least once daily for 14 days. Body weights were recorded on Day 0 prior to dosing, and on Days 7 and 14 or after death. Gross necropsy was conducted on all animals: thoracic and abdominal cavities were examined.

Results:

Mortality data is summarized in the table below. Observed median lethal dose (LD_{50}) in the males was above 5000 mg per kg body weight. Estimated LD_{50} in the females was calculated at 2460 mg/kg (no confidence limits reportable). This places the test substance in Tox Category III for acute dermal toxicity (defined as 2000 mg/kg < LD_{50} ≤ 5000 mg/kg). LD_{50} for sexes combined was not calculated, based on significant difference in mortality in the males vs. in the females. All mortality (females only) in the three dose groups occurred between the Initial and Day 7 observations.

Table: Mortality Results

Dosage (mg/kg)	Number Dead/Number Tested		
	Males	Females	Total
2000	0/5	2/5	2/10
3000	(no test)	3/5	3/5
5000	0/5	4/5	4/10

Clinical signs in the 5000 mg/kg dose group observed at cage-side included hunched posture, reduced fecal volume, soft feces, irregular respiration, and eschar and erythema/edema present at dose site. All surviving rats gained weight during the study. 3/8 surviving rats in the 2000 mg/kg dose group and 2/6 survivors in the 5000 mg/kg group failed to gain weight over the first week of the 14-day observation period.

Necropsy observations noted in the study were limited to discolorations in the gastrointestinal tract (brown, green, red) and lungs (red or somewhat red).

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING

Attachment to 02/20/2002 Memorandum Regarding Data Package D279123
(Cutrine®- Ultra, EPA File Symbol 8959-LG)

Reviewer: W. Powell
Antimicrobials Division
Review date: 02/20/2002
Product No.: 8959-LG
DP Barcode: D279123
MRID No.: 455332-07
Report No.: 6048 (Study No.)
Study Completion: 05/19/1998
Author: Gary Wnorowski

Conclusion:
LC_{50}: > 2000 mg/L (Males, Females, and Combined), observed.
Toxicity Category: IV
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: None noted

Testing Facility: Product Safety Labs; 725 Cranbury Road, East Brunswick, New Jersey 08816

Test Material: Cutrine Ultra, Lot #GW1829A, a blue viscous liquid

Test Animal: Rat, Sprague-Dawley derived, albino
Age: Young adult
Weight (at study initiation): Males 250-296 g, Females 190-210 g
Source: Ace Animals, Inc. - Boyertown, PA

Test Method:

Following pre-test trials to determine a suitable test atmosphere, five rats per sex were exposed to an aerosol of the test material for 4 hours (plus an atmosphere equilibration period of 15 minutes). A whole body chamber was used. The exposure concentration was determined gravimetrically as 2.07 mg per liter of air, based on samples taken from the breathing zone at six intervals during the exposure period. Particle size distribution was assessed based on cascade impactor analysis of two samples taken from the breathing zone during the exposure period; a Mass Median Aerodynamic Diameter (MMAD) was determined for each sample. Chamber airflow, temperature, and relative humidity were monitored throughout the exposure period. Clinical signs were recorded at least once daily for a 14 day observation period. Body weights were recorded prior to exposure and again on Days 7 and 14. Gross necropsy was conducted on all animals.

Results:

There was no mortality. The study therefore places the test material in Category IV for acute inhalation toxicity (defined as LC_{50} > 2.0 mg/L) based on the observed LC_{50} > 2.07 mg/L.

Observations post-exposure typically included irregular respiration, dyspnea, hunched posture, hypoactivity, and facial staining. In addition, 1 animal had ocular discharge (red), corneal opacity (right eye), and reduced fecal volume. Necropsy findings were unremarkable, other than slight red lung discoloration in 10/10 animals. All animals gained weight during the study, though 1/10 lost weight during the first 7 days.

Exposure data are summarized in the table below.

Table: Exposure conditions

Exposure level (mg/L) – Gravimetric concentration (average of 6 values)	2.07
MMAD (µm) (average of 2 values)	3.1
GSD (µm) (average of 2 values)	1.6
Nominal chamber concentration (mg/L)	24.7
T_{99} – 99% atmosphere equilibration time (minutes)	15.1
Chamber total air flow (L/min) (average)	45.7 (range 45.6 to 45.9)
Chamber temperature (°F)	71 to 74
Chamber relative humidity (% RH)	47 to 65

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING

Attachment to 02/20/2002 Memorandum Regarding Data Package D279123
(Cutrine®- Ultra, EPA File Symbol 8959-LG)

Reviewer: W. Powell
Antimicrobials Division
Review date: 02/20/2002
Product No.: 8959-LG
DP Barcode: D279123
MRID No.: 455332-08
Report No.: 6011 (Study No.)
Study Completion: 05/26/1998
Author: George E. Moore

Conclusion:
Toxicity Category: I
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: None noted

Testing Facility: Product Safety Labs; 725 Cranbury Road, East Brunswick, New Jersey 08816

Test Material: Cutrine Ultra, Lot #GW1829A, a blue viscous liquid

Test Animal: Rabbit, New Zealand albino
Age: Adult
Weight: Not indicated
Source: Davidson's Mill Farm – South Brunswick, NJ

Test Method:

0.1 mL of the test substance was instilled undiluted into the conjunctival sac of one eye of each of 9 rabbits that were pre-screened for eye abnormalities. Upon instillation, eyelids of the treated eye were held together for approximately 1 second. The untreated eye served as a control. (Actually, both eyes were treated with anesthetic.) The treated eyes of 3 rabbits were rinsed with physiological saline 20-30 seconds after test substance instillation. This Data Review addresses this 'Unrinsed' group only. The treated eyes of the other 6 rabbits were not rinsed. Severity of ocular irritation was graded according to the Draize criteria at 1, 24, 48, and 72 hours after instillation and Days 4, 7, 10, 14, 17, and 21. Fluorescein dye was employed 24 hours after instillation and subsequently as needed to confirm reversal of corneal damage.

Results in the Unrinsed group:

The numbers of animals (in the "Unrinsed" dose group) having 'positive' irritation scores (as defined by EPA guidelines) at each observation time are indicated in the following table.

Table: Irritation incidence

Area observed	Number of 'positive'* irritation scores (Draize criteria) per no. of animals tested									
	1 Hour	24 Hrs	48 Hrs	72 Hrs	Day 4	Day 7	Day 10	Day 14	Day 17	Day 21
Cornea	0/6	6/6	5/6	2/6	2/6	1/6	1/6	1/6	1/6	1/6
Iris	1/6	5/6	3/6	2/6	1/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae: Redness	6/6	6/6	6/6	2/6	2/6	0/6	0/6	0/6	0/6	0/6
Swelling	5/6	6/6	3/6	2/6	2/6	2/6	1/6	0/6	0/6	0/6

* 'Positive' by EPA guidelines

Corneal opacity was limited to grade 1 (defined as covering scattered or diffuse area, details of iris clearly visible) but persisted in 1/6 animals through Day 21. Moderate iridal involvement was observed in as many as 5/6 animals, this occurring at 24 hours and subsiding in all affected animals by Day 7. 'Positive' conjunctival redness was observed in 6/6 animals through 48 hours, subsiding in all rabbits by Day 7. Maximum severity of conjunctival redness was grade 2 on the Draize scale (defined essentially as diffuse, crimson red but not beefy red, individual vessels not easily discernible). Maximum severity of conjunctival swelling was grade 2 on the Draize scale (defined as obvious swelling with partial eversion of lids, lids less than half closed).

The data place the test material in acute Toxicity Category I for eye irritation, based primarily on unresolved corneal opacity in 1/6 animals.

The age of the animals was not specified further than that they were adults. Body weight also was not indicated. However, this is not expected to affect the study outcome, as only healthy animals were said to be used.

The sexes of the animals were reported as 5 males and 4 females. Which of these were placed in the 'Unrinsed' dose group was not specified. However, this should not affect the study outcome.

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING

Attachment to 02/20/02 Memorandum Regarding Data Package D279123
(Cutrine®- Ultra, EPA File Symbol 8959-LG)

Reviewer: W. Powell
Antimicrobials Division
Review date: 02/20/02
Product No.: 8959-LG
DP Barcode: D279123
MRID No.: 455332-09
Report No.: 10992 (Study No.)
Study Completion: 09/06/2001
Author: Daniel J. Merkel

Conclusion:
Toxicity Category: II
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: None noted

Testing Facility: Product Safety Labs; 2394 Route 130, Dayton, New Jersey 08810

Test Material: Cutrine Ultra, Lot #1362919, a blue viscous liquid

Test Animal: Rabbit, New Zealand albino
Age: Young adult
Weight: Not indicated
Source: Davidson's Mill Farm – South Brunswick, NJ

Test Method:

0.1 mL of the test substance was instilled undiluted into the conjunctival sac of one eye of each of 6 rabbits (2 per sex) that were pre-screened for eye abnormalities. Upon instillation, eyelids of the treated eye were held together for approximately 1 second. The untreated eye served as a control. Severity of ocular irritation was graded according to the Draize criteria at 1, 24, 48, and 72 hours after instillation and Days 4, 7, 10, 14, and 17. Fluorescein dye was employed 24 hours after instillation and subsequently as needed to confirm reversal of corneal damage.

Results:

The numbers of animals with 'positive' irritation scores (as defined by EPA guidelines) at each observation time are indicated in the following table.

Table: Irritation incidence

Area observed	Number of 'positive'* irritation scores (Draize criteria) per no. of animals tested								
	1 Hour	24 Hrs	48 Hrs	72 Hrs	Day 4	Day 7	Day 10	Day 14	Day 17
Cornea	0/6	6/6	6/6	5/6	3/6	2/6	2/6	0/6	0/6
Iris	0/6	5/6	5/6	2/6	1/6	0/6	0/6	0/6	0/6
Conjunctivae: Redness	6/6	6/6	6/6	6/6	4/6	0/6	0/6	0/6	0/6
Swelling	6/6	5/6	5/6	5/6	2/6	0/6	0/6	0/6	0/6

* 'Positive' by EPA guidelines

Corneal opacity reached grade 3 (defined as having opalescent areas, no details of iris visible, size of pupil barely discernible) in 1/6 animals at Days 4 and 7 – and grade 2 in 1/6 animals at Days 4 and 7 – resolving in both animals by Day 14. Corneal opacity was limited to grade 1 (defined as covering scattered or diffuse area, details of iris clearly visible) in the other 4/6 animals, resolving by Day 4 in 1/6 and by Day 7 in 3/6 animals. Iridal involvement (grade 1 on the Draize scale) was observed in as many as 5/6 animals, this occurring at 24 and 48 hours and subsiding in all affected animals by Day 7. 'Positive' conjunctival redness was observed in 6/6 animals through 72 hours, subsiding in all animals by Day 7. Maximum severity of conjunctival redness was grade 2 on the Draize scale (defined essentially as diffuse, crimson red but not beefy red, individual vessels not easily discernible). Maximum severity of conjunctival swelling was grade 2 on the Draize scale (defined as obvious swelling with partial eversion of lids, lids less than half closed).

The data indicate acute Toxicity Category II for eye irritation, based on clearing of corneal opacity in all affected animals.

Animal body weights were not indicated. However, this should not affect the study outcome.

DATA REVIEW FOR PRIMARY DERMAL IRRITATION TESTING

Attachment to 02/20/02 Memorandum Regarding Data Package D279123
(Cutrine®- Ultra, EPA File Symbol 8959-LG)

Reviewer: W. Powell
Antimicrobials Division
Review date: 02/20/02
Product No.: 8959-LG
DP Barcode: D279123
MRID No.: 455332-10
Report No.: 6012 (Study No.)
Study Completion: 05/26/1998
Author: George E. Moore

Conclusion:
Toxicity Category: I
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: None noted

Testing Facility: Product Safety Labs; 725 Cranbury Road, East Brunswick, New Jersey 08816

Test Material: Cutrine Ultra, Lot #GW1829A, a blue viscous liquid

Test Animal: Rabbit, New Zealand albino
Age: Adult
Weight: Not indicated
Source: Davidson's Mill Farm – South Brunswick, NJ

Test Method:

0.5 gram of the undiluted test material was applied to a 6 cm^2 dose site on each of 6 rabbits (3 per sex) and covered with gauze and wrapping. After 4 hours, the dressing was removed and the dose site gently wiped. The test sites were observed for dermal effects at approximately 1, 24, 48, and 72 hours and Days 7, 10, and 14 after removal of the dressings. Severity of erythema and edema was scored using the Draize criteria.

Results:

The data indicate corrosiveness and Toxicity Category I for primary dermal irritation. This is notwithstanding the fact that the Primary Dermal Irritation Index for erythema and edema was calculated as 3.3, which is classified as moderately irritating. Severe erythema (grade 4 on Draize scale) was noted in 1/6 animals at

72 hours, in 2/6 on Days 7 and 10, and in 1/6 on Day 14. Eschar was noted at dose site in 1/6 animals at 72 hours, in 4/6 animals on Days 7 and 10, and in 1/6 on Day 14. Brown discoloration at dose site was noted in 3/6 animals at 72 hours. Blanching at dose site was noted in 1/6 animals at 24 and 72 hours and in 2/6 animals at 48 hours. Desquamation at dose site was noted in 2/6 animals on Days 7 and 10, and in 3/6 on Day 14.

The age of the animals was not specified other than that they were adult (and body weight was not indicated). This should not affect the study outcome, as the test animals were screened for health and for skin abnormalities.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING

Attachment to 02/20/02 Memorandum Regarding Data Package D279123
(Cutrine®- Ultra, EPA File Symbol 8959-LG)

Reviewer: W. Powell
Antimicrobials Division
Review date: 02/20/2002
Product No.: 8959-LG
DP Barcode: D279123
MRID No.: 455332-11
Report No.: 6013 (Study No.)
Study Completion: 05/21/1998
Author: George E. Moore

Conclusion:
Toxicity Category: Non-sensitizer
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: None noted

Testing Facility: Product Safety Labs; 725 Cranbury Road, East Brunswick, New Jersey 08816

Test Material: Cutrine Ultra, Lot #GW1829A, a blue viscous liquid

Test Animal:
Guinea pig, Hartley albino, male
Age: Young adult
Weight: 309-418 grams (at study initiation)
Source: Davidson's Mill Farms, South Brunswick, NJ

Positive Control: 1-chloro-2,4-dinitrobenzene (i.e., dinitrochlorobenzene, DNCB), light yellow to brown crystals

Test Method:

Following an initial screening to determine appropriate concentrations, 0.4 mL of 25% w/w test material in distilled water was applied to clipped sites in a test group of 10 male guinea pigs. Each treated site was occluded for 6 hours with a Hilltop Chamber. This procedure was repeated twice for a total of three induction applications, with the exception that the concentration was reduced from 25% to 15% for second and third inductions due to severe erythema and was relocated to an adjacent site. 13 days after third induction dose, 0.4 mL of 12% w/w test material in distilled water was similarly applied as a challenge to naive sites in the test group, and to a naive control group of 5 animals.

Observations for erythema at each test site were made at approximately 24 and 48 hours after each treatment. Reactions were scored according to the following scale of severity:

Table: Grading scale

Erythema	Score
No reaction	0
Very faint erythema, usually non-confluent	0.5
Faint erythema, usually confluent	1
Moderate erythema	2
Severe erythema with or without edema	3

A positive control study was also conducted in accordance with, and apparently concurrently with, the above procedure for the definitive study. 0.08% w/w DNCB in 80% aqueous ethanol was used for induction. 0.04% w/w DNCB in acetone was used for challenge.

Results:

The following table shows the average erythema scores (in accordance with the above grading scale) for each set of observations.

Table: Erythema reactions

Application	Test Material		Pos. Control	
	24 Hrs	48 Hrs	24 Hrs	48 Hrs
Induction #1	1.3	1.25	0.45	0.45
Induction #2	0.65	0.35	1.7	1.4
Induction #3	1.7	1.85	2.4	2.5
Challenge - test group	0.15	0.0	1.1	1.05
Naive Control Group	0.1	0.0	0.1	0.0

Test material:

In the definitive study (Cutrine Ultra test material), the concentrations selected for induction and challenge appear appropriate based on preliminary screening results. Reaction was severe in some animals after third induction, but this should not affect the study outcome (naive sites were used for challenge). Erythema reaction to

challenge in the test group was comparable to reaction in the naive control group; the study therefore **does not indicate dermal sensitization**.

Positive control:

In the positive control study with DNCB, erythema reaction to challenge in the test group was significantly greater than in the naive control group. The study therefore indicates a sensitization response to the DNCB and satisfies the historical positive control data requirement.