These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

NDA20-532

AP Ltr

NA Ltr

FPL Sheet

MOR

STAT

Pharm/Tox

Bio

Chem

Micro

EA+Forsi

Memos

Co-Corres

Ap Ltr

NA Ltr

FPL Sheet

Division File
HFD 540

NDA 20-532

AUG 26 1996

EnviroDerm Pharmaceuticals, Inc..
Attention: Mr. Anthony A. Schulz
President
929 South Third Street
Louisville, KY 40203

Dear Mr. Schulz:

Please refer to your September 28,1994, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IVY BLOCK™ (bentoquatam, 5%).

Please also refer to our not approvable letter dated September 28, 1995. We acknowledge the receipt of your correspondence dated October 6 and 23, 1995; January 17, February 5 and 26, March 1(2), April 17 and 26, July 24, and August 2, 7, 13, 14, 15, 16, 21 (2), and 26, 1996.

This new drug application provides for the use of this drug product as a skin protectant against poison ivy, poison oak, and poison sumac.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the August 26, 1996, draft labeling. Accordingly, the application is approved effective on the date of this letter.

As agreed in the submission dated August 26, 1996, final printed labeling (FPL) will be identical to the August 26, 1996 draft labeling. Marketing the product with final printed labeling that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the final printed labeling a soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-532. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated April 17 and 26, and August 2, 14, 16, 21, and 26, 1996. These commitments, along with any completion dates agreed upon, are listed below:

1. To conduct a clinical study on the effectiveness and irritation potential of the drug product under actual field use conditions. Subjects in the field use study should include females and subjects over 65 years of age. The final protocol is to be submitted within 6 months of the date of this letter and you should not enroll subjects until we have approved the protocol.

2. To perform an antimicrobial preservative effectiveness test on the first three batches of IVY-BLOCK™ Lotion manufactured after approval of the NDA. The testing will be done at the time of manufacture and at the expiry date. Reports of results of this testing will be incorporated into the validation reports for these three batches.

3. An 18 month expiration dating period is currently approved based on the limited time and the limited number of manufactured Ivy Block lots packages which have been aged in the 4 oz. marketed container.

It is recommended you submit the following as a Phase 4 commitment:

Full shelf life data on 3 lots of Ivy Block in the 4 oz. bottles are required to extend the expiration dating period using an approved stability protocol. Alternatively, you may submit a supplemental application requesting such an extension. Prior approval would be required if you choose this route.

Protocols, data and final reports should be submitted to your IND for this product, and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

In addition, please submit three copies of the introductory promotional material that you propose

to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, MD 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.If you have any questions, please contact:

Harold Blatt
Consumer Safety Officer
(301) 827-2020

Sincerely yours,

MW 8/22/96

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure: Draft labeling, August 26, 1996

The reviewers of this application consisted of:

Peter Dionne, Microbiologist, DAIDP, HFD-520
Ralph Harkins, Division Director, DOB IV, HFD-725
Phyllis Huene, M.D., Medical Officer, DDDDP, HFD-540
James Vidra, Ph.D., Chemist, DNDC III, HFD-540
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPE III, HFD-880
Funmilayo Ajayi, Biopharmaceutist Ph.D., HFD-880
Amy Nostrandt, D.V.M., Ph.D., Pharmacologist/Toxicologist, HFD-540
Harold Blatt, D.D.S., Project Manager, HFD-540
Jean Raymond, DDMAC, HFD-40
Gerald Rachanow, J.D., Regulatory Officer, DOTCDP, HFD-560
Debra Bowen, M.D., Division Director, DOTCDP, HFD-560

Original NDA 20-532
HF-2/MedWatch (with labeling)
HFD-2/MLumpkin
HFD-80 (with labeling)
OFFICE FILE (with labeling)
HFD-540/ CLINICAL/ Huene 8/8/96
HFD-540/ CHEM/ Vidra DV 8/23/96
HFD-540/ PHARM/ Nostrandt 8/1/96
HFD-725/ STAT/ Harkins 8/1/96
HFD-880/ BIOPHARM/ Ajayi for 8/1/96
HFD-540/ PROJ MGR/ Blatt 8-1-96
HFD-520/ MICRO/ Dionne 8-2-96
HFD-40/ DDMAC/ Raymond
DIVISION FILE
HFD-240 with labeling)
HFD-613 (with labeling)
HFD-735/DBarash (with labeling)
DIVISION/drafter/date drafted

Concurrence:
HFD-105/ OFC DIR ODE V/ Weintraub
HFD-540/ DEP DIV DIR DDODP/ Katz
HFD-540/ DIV DIR DDODP / Wilkin
HFD-540/ SUPV PROJ MGR/ RCook
HFD-540/ SUPV PHARM/ Jacobs 8/1/96
HFD-725/ DIV DIR STAT/ Harkins 8/1/96
HFD-540/ SUPV CHEM/ DeCamp 8/2/96
HFD-880/ SUPV BIOPHARM/ Bashaw 8/1/96
HFD-520/ SUPV MICRO/ Sheldon 8/2/96
HFD-560/ DIV DIR DODP/ Bowen
HFD-85/DIVDIR,DNDC III/Sheinin GBS 8-26-96
APPROVAL
n20532ap.717

NDA 20-532

United Catalysts, Inc.
Attention: Mr. Anthony A. Schulz
Manager Business Development

SEP 28 1995

P.O. Box 32370
Louisville, KY 40232

Dear Mr. Schulz:

Please refer to your September 28, 1994, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IVY BLOCK (bentoquatam, 5%).

We acknowledge receipt of your amendments dated September 29, October 12, 26 (three), and 27, and November 4 (two), and 7, 1994; and January 3, 20, 23, and 24, February 24, March 27, April 12, May 18, August 10, 21, 24, and 25, and September 21, 1995.

We have completed our review of this application, as amended, and find that the information presented is inadequate, and the application is not approvable at this time.

Under section 505(d) of the Act and 21 CFR 314.125(b)(1) of the FDA implementing regulations, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

Specific deficiencies are as follows:

4. A valid analytical method for the determination of bentoquatam in the drug product should be developed. It is not acceptable to determine bentoquatam in the bulk drug substance, and then calculate its concentration in the finished product from this value, as appears to be done in method

5. An assay method for sodium dodecyl sulfate should be submitted. An assumption of 73.7% purity and 288.4 molecular weight is made without supporting data in method There is no evidence that this chemical is available as a primary standard.

6. The analytical method used for the stability studies does not indicate stability, as shown by your validation report. Please see volume 1.5, page 996. A stability-indicating method is needed.

7. Validation data for the determination of benzyl alcohol and methyl paraben by method are needed and should be submitted.

8. Regarding the Microbial Limits testing performed on the drug substance, it appears that preparatory testing as described in USP <61> to determine if organisms will grow in the product was not performed. Please perform preparatory testing to validate the utility of the method. In addition, it is recommended that when this test is performed, a limit of 100 cfu/g be utilized.

9. Regarding the Microbial Limits testing of the finished product:

   a. Before Microbial Limits testing is performed, preparatory testing, as described in USP <61>, should always be performed to show that test organisms will grow in the product. Microbial Limits testing of the finished product may not be necessary if it can be shown that the finished product does not support growth. If this testing is deemed necessary, it should be performed at least initially and at the end of the expiry on each lot of product.

   b. A rationale is needed as to why Microbial Limits testing is performed on the stability lots, and this test is not included in the tests and specifications listed for the finished product.

c. The product has specifications of not less than % of theory for both methylparaben and benzyl alcohol. Please demonstrate that the product formulated with the minimum amount of both of these ingredients will pass the USP <51> Antimicrobial Preservative Effectiveness Test (PET). If this is not done, then please show that each lot will pass the PET at both initial and end of expiry time periods.

10. A satisfactory response must be received regarding the deficiencies in DMF

In addition, when the application is resubmitted, the following are requested:

1. A commitment to perform an additional Phase 4 study

2. An update of the stability data submitted on September 29, 1994, for pilot lot HFCO, the market package. (At least 12 months of stability data should now be available.)

3. A confirmation that lot HFCO was packaged in the proposed market package, specifically, 4-oz white HDPE bottles with tapered oval base, 20/410 neck finish, from cap with flip-top feature, orifice, from and a 3 7/16" x 1 7/8" pressure-sensitive label with adhesive from

4. Current wastewater (see pages 62 and 66) and air (see pages 63 and 87) permits for (The EA should be updated to include current permit numbers and expiration dates. It is not necessary to include copies of the permits; a one-page Addendum to the EA with this information will be sufficient.)

5. Revised draft labeling for the drug product that is identical to the enclosed draft labeling. (Should additional information relating to the safety or effectiveness of this drug product become available, further revision of the labeling may be required.)

6. A safety update report in accordance with 21 CFR 314.50(d)(5)(vi)(b).

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact:

Joanne Holmes, M.B.A.
Project Manager
(301) 594-4877

Sincerely yours,

9/25/95

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

cc: Original NDA 20-532
HFD-500
HFD-540
CIN-DO
HFD-2/Lumpkin
HFC-130
HFD-82
HFD-800
HFD-240/Sherman
HFD-540/Derm File
HFD-007/CHEM/Maturu/8-21-95
HFD-520/MICRO/Dionne//8-11-95
HFD-540/PHARM/Sheevers/8-11-95
HFD-713/BIOSTAT SUPV/Harkins/8-11-95
HFD-426/BIOPHARM/Ajayi/8-14-95
HFD-540/MO/Huene/8-29-95
HFD-540/DIV DIR/Wilkin/9-6-95 9-w 9/26/95
HFD-540/PROJ MGR/Holmes/7-11-95
HFD-540/SMO/Chambers/9-3-95 WAC 9/25/95

Concurrence:
HFD-540/CHEM SUPV/De Camp/8-21-95/9-5-95
HFD-520/MICRO SUPV/Sheldon/8-11-95
HFD-540/PHARM SUPV/Jacobs/8-11-5
HFD-426/BIOPHARM SUPV/Pelsor/8-14-95
HFD-540/PROJ MGT SUPV/Cook/8-10-95
HFD-540/DEP DIR/Katz/9-5-95

drafted: jh/7-11-95
revised: jh/8-1-95;
mrrc/8-10-95; jh/8-10-95
wdc/8-22-95; smc/22-95
wac/8-24-95; jh/8-24-95
lr/9-11-95; jb/9-22-95
wac/9-23-95
jh/9-25-95
Revised LRipper/9-28-95 by addition of new #4 on page 3 per Nancy Sager email
NOT APPROVABLE (NA)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

MoR

AMENDMENT TO MEDICAL OFFICER'S REVIEW OF NDA 20-532

July 24, 1995

SPONSOR: United Catalysts, Inc.
Louisville, Kentucky

DRUG: Ivy Block

REASON FOR AMENDMENT: Review of labeling.

Consultations on the proposed Ivy Block labeling have been provided by Debra Bowen, M.D., and Gerald Rachanow, of the Office of OTC Drug Evaluation. With incorporation of their recommendations into the proposed labeling as revised by this medical officer, the labeling with recommended deletions and additions is as follows. (Recommended additions are shown by shading, and recommended deletions are shown by ~~single strikeout lines.~~)

Page 2
Deleted

Recommendations: The sponsor should be requested to revise the proposed labeling as specified. With submission of the revised labeling and a commitment to perform Phase 4 studies, the application should be approved.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA 20-532
HFD-540
HFD-540/MO/PHuene
HFD-540/Pharm/Sheevers
HFD-540/Chem/DeCamp
HFD-540/CSO/Holmes
HFD-540/Derm file

WRc 7/31/95

8/4/95

AMENDMENT TO MEDICAL OFFICER'S REVIEW OF NDA 20-532

August 8, 1996

SPONSOR: United Catalysts, Inc.
Louisville, Kentucky

DRUG: Ivy Block

REASON FOR AMENDMENT: Review of safety update of July 24, 1996.

For the safety update the sponsor has submitted a statement that there is no new or additional safety information regarding Ivy Block. No other information or data has been provided.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA 20-532
HFD-540
HFD-540/Huene
HFD-540/Blatt
HFD-540/Jacobs
HFD-540/DeCamp

APR 7 1996

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 20-532

540

March 25, 1996

SPONSOR: United Catalysts, Inc.
Louisville, Kentucky

DRUG: Ivy Block

ACTIVE INGREDIENT: Quaternium-18 bentonite
USAN: bentoquatam

CLINICAL INDICATION: Pre-exposure skin protectant against poison ivy and poison oak contact dermatitis.

DATE OF AMENDMENT: February 26, 1996

REASON FOR AMENDMENT: Response to the non-approvable letter of 9/8/95.

The clinical portion of the non-approvable letter of September 8, 1996 requested that the following be provided.

1. A commitment to perform an additional Phase 4 study on the irritation potential and effectiveness under actual field use conditions.

The sponsor provides a commitment to perform a Phase 4 study, and a protocol for this study. The protocol has been previously discussed with the sponsor, and it is acceptable.

2. Revised draft labeling that is identical to that enclosed in the letter.

The sponsor provides revised draft labeling that is identical to that in the non-approvable letter.

3. A safety update report.

The sponsor provides a safety update report. There have been no additional clinical data on the product since the submission of the NDA.

Conclusion and recommendations: From the clinical standpoint, the sponsor has provided an adequate response to the non-approvable letter. It is recommended that the application be approved.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA 3/26/96
HFD-540
HFD-540/Huene
HFD-540/Blatt 4/7/96
HFD-540/Jacobs
HFD-540/DeCamp

MEDICAL OFFICER'S REVIEW OF NDA 20-532
ORIGINAL SUBMISSION

March 28, 1995

SPONSOR: United Catalysts, Inc.
Louisville, Kentucky

DRUG: Ivy Block

ACTIVE INGREDIENT: Quaternium-18 bentonite
USAN: bentoquatam

PROPOSED CLINICAL INDICATION: Pre-exposure skin protectant against poison ivy and poison oak contact dermatitis.

FORMULATION:

Quaternium-18 bentonite	5.0%
Methyl paraben	%
Purified bentonite	%
Benzyl alcohol	%
Diisopropyl adipate	%
SD alcohol	%
Purified water	%

DATE OF SUBMISSION: September 28, 1994

MATERIAL REVIEWED: Original submission, submission of 2/24/95.

RELATED SUBMISSION: IND

PHARMACOLOGY AND CONTROLS REVIEWS: These are not as yet available.

Background

Quaternium-18 bentonite is an organoclay, a chemically modified clay, which is intended to serve as a barrier to the poison oak and poison ivy allergens (urushiols). In Ivy Block the clay is formulated into a lotion, which on application forms a visible whitish coating on the skin. It is theorized that rubbing the quaternium-18 bentonite formulation on the skin serves to arrange the organoclay particles so that a plate-like barrier is laid down which adheres to the skin. A second mechanism of action is also postulated, whereby the phenolic radical of urushiol is bound to the quaternium-18 bentonite surface.

Quaternium-18 bentonite has been used worldwide for more than 30 years as an ingredient in cosmetics. It is a GRAS compound for topical use.

A pressurized aerosol form of Ivy Block was marketed in 1985-6, but was subsequently withdrawn from the market at the request of the FDA, because it was considered to be a new drug requiring an approved NDA. Pre-marketing clinical trials on the aerosol form had been conducted on workers for the USDA Forest Service. In subsequent clinical trials conducted under IND it was found that the aerosol valve/nozzle combination did not deliver sufficiently precise doses for dose range studies, so the initial clinical studies were done with the aerosol concentrate, minus the gaseous propellant. Then the Forest Service made the determination that an aerosol formulation would no longer be acceptable for their needs because it might not be safe under fire conditions. For this reason, and the imprecision of dosing with the aerosol, the lotion was developed as an alternate dosage form, and studies with the aerosol were discontinued. The Phase I studies provided by the sponsor were performed on the lotion, and the Phase II studies were performed on the aerosol concentrate, as follows.

Phase I studies - lotion formulation

1. Cumulative irritancy.

This was conducted by on 25 subjects. The study was a comparison of Ivy Block lotion, Ban roll-on antiperspirant, and Oil of Olay lotion, applied five times weekly to the same skin site for 21 days, under conditions of occlusion and non-occlusion.

Each test product was applied to the skin of the lower back by four different procedures, which were as follows.

a. On a moistened pad, covered by an occlusive plastic dome.
b. Directly to the skin, covered by an occlusive plastic dome.
c. On a moistened Webril patch, held in place by tape.
d. Directly to the skin with no covering.

Applications were made daily on Mondays through Fridays, with the Friday application remaining in place until the following Monday, for three weeks. The skin sites were scored for reactions at each removal of the patch or dome, on the following scale:

0 = negative
0.5 = equivocal reaction
1 = erythema
2 = erythema and induration
3 = erythema, induration, and vesicles
4 = bullae

The results are provided as individual and summary scores. The summary score, representing the sum of the daily scores for all 25 subjects, was 8.5 for Ivy Block when applied by method a. above,

and 0 when applied by the other three methods. For Ban the summary score was 2 when applied by method a. and 0 when applied by the other three methods, and for Oil of Olay the summary score was 125 when applied by method a., 16 when applied by method b., and 0 when applied by methods c. and d.

The individual scores for Ivy Block show that 6 subjects had skin reactions. Two subjects had an 0.5 reaction on day 15, three subjects had an 0.5 reaction on days 14 and 15, and one subject had an 0.5 reaction on days 7 through 15.

2. Contact sensitization.

This was conducted by on 196 evaluable subjects. Ivy Block lotion was applied on a moistened patch under an occlusive plastic dome to the same skin sites on the upper back three times weekly, remaining in place for 48-72 hours, for nine applications. After a two week rest period a challenge patch was applied to a new skin site for 72 hours. Grading of the test sites for reactions was done at 24 hours after each patch removal on the following scale:

0 = negative
0.5 = equivocal reaction
1 = erythema
2 = erythema and induration
3 = erythema, induration, and vesicles
4 = erythema, induration, and bullae

210 subjects were enrolled in the study, of which 14 subjects dropped out for unknown reasons. The individual summary scores, representing the total of the daily scores for each subject, during the induction period were as follows.

Reaction scores Induction phase	
Score	# pts
0.5	3
1	8
1.5	5
2	4
2.5	1
3	1
3.5	1
4	1
6	1

The subject with a summary score of 6 had a score of 0.5 on days 3 and 9 and a score of 1 on days 4 through 8. The subject with a summary score of 4 had a score of 1 on days 2 through 4 and a score of 0.5 on days 5 and 6.

At challenge, the only reaction was a score of 0.5 in one subject.

Phase II studies - aerosol formulation

Two liquid formulations were used in these studies, which were as follows.

KE101

Quaternium - 18 bentonite	%
Cyclometicone 344	%
SD40A alcohol	%

KE102

Quaternium - 18 bentonite	%
Cyclometicone 344	%
SD40A alcohol	%

Protocols 7/88 and 8/88 used both formulas; Protocols 9/88 and 7/91 used formula KE101.

1. Dose response (Protocol 7/88).

This study, performed by evaluated the effectiveness of five dosages of the aerosol formulation of quaternium-18 bentonite in protecting against exposure to urushiol at levels previously shown to elicit moderate reactions in sensitive subjects.

Twelve subjects with a history of sensitivity to poison ivy, poison oak, or poison sumac were screened with graduated dosages of urushiol in acetone in order to select an exposure level that resulted in a moderate dermatitic reaction. After the screening reactions had subsided, the quaternium-18 bentonite aerosol formulation was applied to randomized test sites on the forearms at doses of 0.4, 0.8, 2.0, 4.0, and 8.0 mg of quaternium-18 bentonite per 8 cm^2. Four hours later the predetermined amount of urushiol was applied to each treated site and to one untreated control site. On days 3, 5, and 8 the severity of the resultant dermatitis was graded by a blinded observer.

It was found that there was a dose-related decrease in the mean dermatitis severity scores at all dose levels of quaternium-18 bentonite. The conclusion was that quaternium-18 bentonite at single doses of 2.0, 4.0, and 8.0 mg/8 cm^2, equivalent to 0.25 mg or more per cm^2, was statistically significantly more effective in the prevention of urushiol induced poison ivy than was no prior treatment.

2. Time course of protective activity (Protocol 8/88).

This study, performed by evaluated the effect of the pre-exposure time of application of the quaternium-18 bentonite aerosol on the prevention of urushiol dermatitis.

Twelve subjects with a history of sensitivity to poison ivy or poison oak were screened with graduated dosages of urushiol in alcohol in order to select an exposure level that resulted in a moderate dermatitic reaction. After the screening reactions had subsided, the quaternium-18 bentonite aerosol formulation was applied at a dose of 0.25 mg/cm^2 to five randomized test sites on the forearms at 6 hours, 4 hours, 1 hour, 30 minutes, and 15 minutes prior to a challenge with urushiol at the predetermined dose. At 2, 4, and 7 days after the application of urushiol the test sites and control untreated sites were graded for the severity of dermatitis by a blinded observer.

It was found that the average dermatitis severity scores for sites pre-treated with quaternium-18 bentonite at 15, 30, and 60 minutes and 4 hours prior to urushiol exposure were statistically significantly lower than at untreated sites through five days after urushiol exposure. It appeared that the optimal time of quaternium-18 bentonite application was between 15 and 60 minutes prior to urushiol exposure. The conclusion was that significant protection against urushiol dermatitis is provided by application of 0.25 mg/cm^2 of quaternium-18 bentonite in an aerosol formulation when applied at 15 minutes to 4 hours prior to urushiol exposure.

3. Influence of a topically applied insect repellent on the effectiveness of quaternium-18 bentonite (Protocol 9/88).

This study was performed by to evaluate the effect of the simultaneous application of the quaternium-18 bentonite aerosol formulation and the insect repellent DEET on the prevention of urushiol dermatitis.

Twenty-three subjects with a history of sensitivity to poison ivy or poison oak were screened with urushiol in alcohol to select an exposure level that produced a dermatitis. After the screening reactions had subsided the quaternium-18 bentonite aerosol formulation and the insect repellent were applied to five randomized test sites on the forearms at the following dose levels.

a. Q-18B formulation - 0.1 mg/cm^2
b. Q-18B formulation - 0.25 mg/cm^2
c. Q-18B formulation - 0.1 mg/cm^2 + DEET - 1.5 mg/cm^2
d. Q-18B formulation - 0.25 mg/cm^2 + DEET - 1.5 mg/cm^2
e. DEET - 1.5 mg/cm^2
f. No treatment control site.

One hour after application of the test products, the predetermined dose of urushiol was applied to all test sites. At 2, 5, and 7 days after the application of urushiol the test sites were graded for the severity of dermatitis by a blinded observer.

On the basis of statistical analysis of the data, the following conclusions were made: 1) quaternium-18 bentonite at single doses of 0.1 and 0.25 mg/cm^2, with or without the insect repellent, is significantly more effective than no treatment in preventing urushiol induced contact dermatitis, 2) among the doses studied, quaternium-18 bentonite shows a significant dose response relationship, with or without the insect repellent, and 3) Deet insect repellent and quaternium-18 bentonite exhibit significant interaction at days 5 and 8 following treatment, but not at day 3.

Reviewer's comments: The cumulative irritancy study shows that Ivy Block lotion produces little or no irritation under conditions of exaggerated exposure. There was also no contact sensitization with Ivy Block lotion when evaluated on a standard test for sensitization potential.

Effectiveness studies

Three studies were performed on the effectiveness of quaternium-18 bentonite lotion in the prevention or modification of urushiol induced contact dermatitis. The formulation used in these studies was designated as quaternium-18 bentonite lotion; this was identical in composition to Ivy Block lotion.

1) Protocol 7/91. This was performed by and was a comparison of the lotion and aerosol formulations.

Forty-six subjects with a history of sensitivity to poison ivy or poison oak were entered into the study, of which 38 were evaluable for efficacy. Screening tests for urushiol sensitivity were not

performed prior to treatment as was done in the previous studies, in order to minimize the possibility of reactions induced by antigenic stimulation from multiple urushiol applications in the screening phase. Applications of quaternium-18 bentonite aerosol and quaternium-18 bentonite lotion were made to randomized test sites on opposite forearms at a dose of 0.25 mg/cm^2 of the active ingredient. Each forearm also had a randomly assigned untreated test site. One hour later patches moistened with a standardized dose of urushiol were applied to the treated and untreated test sites. Four hours later the patches were removed and the test sites were washed. Evaluation for skin reactions was done on days 3, 5, and 8 by a blinded observer on a scale of from 0 for no reaction to 7 for a very severe reaction, using an integer scale except that a score of 0.5 was included.

Thirty-eight subjects were considered to be evaluable for efficacy. To be considered evaluable, the subjects were to have had a reaction at the untreated test site. However, the reviewing statistician elected to include any subject with a positive test site reaction in the efficacy analysis, regardless of whether there was an untreated test site reaction. In this analysis four subjects were included who did not have a untreated test site reaction.

The distribution of reaction scores at the treated and untreated test sites were as follows.

Lotion reaction scores									
	0.0	0.5	1.0	2.0	3.0	4.0	5.0	6.0	7.0
Day 3									
Lotion	36	1	0	1	0	0	0	0	0
Control	10	0	3	14	9	0	1	1	0
Day 5									
Lotion	31	1	0	2	2	0	0	1	0
Control	2	1	1	2	7	4	4	15	1
Day 8									
Lotion	30	1	0	1	5	0	0	1	0
Control	5	2	0	0	6	4	4	16	1

Quaternium-18 bentonite lotion was significantly superior to the untreated control at day 3 ($p=0.0001$), day 5 ($p=0.0001$), and day 8 ($p=0.0001$). Sixty-eight percent of the lotion test sites were completely protected from urushiol dermatitis and showed no reaction.

Although the results with the aerosol formulation are not reproduced here, the results were equivalent to those with the lotion formulation.

2) Protocols 1/92 and 2/92. These studies used identical protocols, and were designed to be the pivotal studies to demonstrate the effectiveness of Ivy Block lotion in the prevention or modification of urushiol induced contact dermatitis.

The investigators under Protocol 1/92 were as follows.

James Marks, M.D.
Professor of Medicine, Division of Dermatology
College of Medicine
Pennsylvania State University
Hershey, PA

Joseph Fowler, M.D.
Division of Dermatology
University of Louisville
Louisville, KY

The investigators under Protocol 2/92 were as follows.

Elizabeth Sherertz, M.D.
Associate Professor of Dermatology
Bowman Gray School of Medicine
Winston-Salem, NC

Robert Rietschel, M.D.
Chairman, Department of Dermatology
Ochsner Clinic
New Orleans, LA

The conduct of the study was as follows.

1) Study objective: The objective was to measure the effectiveness of quaternium-18 bentonite lotion in preventing or modifying urushiol induced reactions.

2) Study design: Subjects with a history of susceptibility to poison ivy contact dermatitis were pretreated with quaternium-18 bentonite lotion and then exposed to poison ivy antigen (urushiol). A comparison of randomized treated and untreated test sites was made at specific time periods after exposure by a blinded investigator.

3) Subject selection: Those selected were healthy males and females, between the ages of 18 and 65, with a history of at least two episodes of poison ivy, and at least one episode in the previous five years.

4) Subject exclusions: Subjects with the following conditions or medication usage were excluded from the study.

a. Use of any systemic or topical antihistamine, corticosteroid, anti-inflammatory or analgesic product, with the exception of acetaminophen, concurrently or within one week prior to study participation.

b. Use of any other topical product, such as insect repellent, sunscreen, creams, or lotions, on the arms concurrently or within one week prior to study participation.

c. Pregnancy or lactation.

d. Presence of significant dermatological conditions which could interfere with the study determinations.

e. Presence of any significant medical condition which could alter immune responses or contraindicate exposure to poison ivy antigen, specifically ARC or AIDS, rheumatoid arthritis, systemic lupus or any autoimmune disease, conditions being treated with systemic corticosteroids, diseases treated with chemotherapy, diseases or conditions requiring dialysis on a regular basis, and terminal conditions.

f. History of extreme allergies or extremely strong reactions to poison ivy toxin.

g. Alcoholism or drug dependency.

5) Test procedure: Test sites A and B were demarcated with a marking pen on the volar surfaces of both forearms, in accordance with a randomization table. On one forearm an area of 50 cm^2 was designated to be the treated area. Onto this area 0.35 ml of quaternium-18 bentonite lotion was applied, and was spread by the subject as evenly as possible within the defined area using the fingers of the opposite hand, to produce a film of quaternium-18 bentonite at a concentration of approximately 0.25 mg/cm^2. The other forearm served as an untreated control site.

The treated site was allowed to dry for one hour prior to the urushiol challenge. Patches treated with a standardized amount of urushiol were then applied to the center of each of the test sites. At four hours after application of urushiol, the patches were removed and the forearms were washed, with care taken to clean each test site individually to prevent cross-contamination.

6) Evaluation of dermatitis: At days 2, 5, and 8 after application of the urushiol patches the sites were graded on the following scale.

0	=	no reaction.
+/-	=	questionable reaction (erythema with or without edema and without itching).
1+	=	erythema with itching.
2+	=	erythema with edema and itching.
3+	=	erythema, edema, and beginning vesiculation, involving less than 25% of the test site.
4+	=	as in 3+. but vesicles involving 25 to 50% of the treatment site.
5+	=	as in 3+. but vesicles involving 50 to 75% of the treatment site.
6+	=	as in 3+. but vesicles confluent in a circular pattern over the test site.
7+	=	erythema, edema, and vesiculation, plus evidence of ulcerative breakdown.

The area of dermatitis was also measured, and the forearms were photographed.

Results of the study under Protocol 1/92 were as follows.

1) Subject enrollment and evaluability: 116 subjects were enrolled into the study, of which 85 subjects were evaluable for efficacy. Thirty-one subjects were classified as unevaluable either because of noncompliance or because neither test or control site showed a reaction by day 5. Of the 85 evaluable subjects, 7 subjects were dropouts with reaction score data only at days 2 and 5.

Of the 116 subjects enrolled, 45 (39%) were males and 71 (61%) were females.

2) Efficacy evaluation: The primary efficacy variable was the reaction scores. The sponsor performed two analyses using this efficacy variable. The primary analysis utilized a 9 point ordinal scale and assigned a value of 1 to the +/- score, and values of 2 through 8 to the scores of 1+ through 7+, respectively. Then, in accordance with the monitor's determination that scores of 0 and +/- were clinically indistinguishable, a secondary analysis was done, in which a value of 0 was assigned to both the 0 and +/- scores, with values of 1 through 7 assigned to the reaction scores of 1+ through 7+. The primary analysis was as follows.

The mean reaction scores for the evaluable subjects at each visit were as follows.

Mean reaction scores (± = 1)			
	# pts	Q188 lotion Mean (range)	Control Mean (range)
Day 2	85	0.36 (0 - 4)	2.05 (0 - 7)
Day 5	85	1.08 (0 - 7)	4.31 (0 - 8)
Day 8	78	1.49 (0 - 8)	4.72 (0 - 8)

Statistical analysis was apparently not performed on the differences in mean reaction scores.

The frequency distribution of the reaction scores at each visit was as follows.

Distribution of reaction scores # pts (%) (± = 1)						
Reaction score	Day 2		Day 5		Day 8	
	Q188	Control	Q188	Control	Q188	Control
0	66 (78%)	25 (29%)	50 (59%)	10 (12%)	42 (54%)	5 (6%)
1	12 (14%)	20 (24%)	13 (15%)	7 (8%)	9 (12%)	4 (5%)
2	3 (3.5%)	5 (6%)	6 (7%)	5 (6%)	8 (10%)	2 (3%)
3	3 (3.5%)	13 (15%)	4 (5%)	9 (11%)	5 (6%)	16 (21%)
4	1 (1.2%)	12 (14%)	9 (11%)	12 (14%)	8 (10%)	13 (17%)
5	0	5 (6%)	1 (1.2%)	11 (13%)	1 (1.3%)	6 (8%)
6	0	3 (3.5%)	0	7 (8%)	0	6 (8%)
7	0	2 (2.4%)	2 (2.4%)	15 (18%)	1 (1.3%)	14 (18%)
8	0	0	0	9 (11%)	4 (5%)	12 (15%)
# pts	85	85	85	85	78	78

There was a statistically significant difference in reaction scores between the quaternium-18 bentonite lotion sites and the untreated control sites at all three time points ($p = 0.0001$).

The within subject comparison of reaction scores at each visit was as follows.

Within subject comparison of reaction scores (± = 1)			
	Day 2	Day 5	Day 8
Lower reaction score at Q188 site	56 (66%)	72 (85%)	67 (86%)
No difference	22 (26%)	6 (7%)	9 (12%)
Lower reaction score at control site	7 (8%)	7 (8%)	2 (3%)
# pts	85	85	78

Statistical analysis was apparently not performed on the within subject comparison of reaction scores.

The number of subjects that never developed a reaction, and the time to development of a reaction in the remaining subjects was as follows.

Time to reaction (± = 1)		
	Q188 lotion	Control
No reaction	41 (48%)	4 (5%)
Reaction by day 2	19 (22%)	60 (71%)
Reaction by day 5	20 (24%)	20 (24%)
Reaction by day 8	5 (6%)	1 (1.2%)
Total # pts	85	85

In the subsequent healing of the dermatitis, 114 subjects were classified as having normal healing, one subject had slow healing due to extreme urushiol sensitivity, and information was missing for one subject.

In the secondary analysis, in which a score of ± was assigned a value of 0, 71 subjects were evaluable for efficacy; results were as follows.

The mean reaction scores at each return visit were as follows.

Mean reaction scores (± score = 0)			
	# pts	Q188 lotion Mean (range)	Control Mean (range)
Day 2	71	0.17 (0 - 3)	1.61 (0 - 6)
Day 5	71	0.80 (0 - 6)	4.10 (0 - 7)
Day 8	70	1.14 (0 - 7)	4.11 (0 - 7)

The frequency distribution of the reaction scores at each visit was as follows.

Distribution of reaction scores (± score = 0)						
Reaction score	Day 2		Day 5		Day 8	
	Q188	Control	Q188	Control	Q188	Control
0	64 (90%)	31 (44%)	49 (69%)	3 (4%)	43 (61%)	4 (6%)
1	3 (4%)	5 (7%)	6 (9%)	5 (7%)	8 (11%)	2 (3%)
2	3 (4%)	13 (18%)	4 (6%)	9 (13%)	5 (7%)	14 (20%)
3	1 (1.4%)	12 (17%)	9 (13%)	12 (17%)	8 (11%)	12 (17%)
4	0	5 (7%)	1 (1.4%)	11 (16%)	1 (1.4%)	6 (9%)
5	0	3 (4%)	0	7 (10%)	0	6 (9%)
6	0	2 (3%)	2 (3%)	15 (21%)	1 (1.4%)	14 (20%)
7	0	0	0	9 (13%)	4 (6%)	12 (17%)
# pts	71	71	71	71	70	70

There was a statistically significant difference in reaction scores between the quaternium-18 bentonite lotion sites and the untreated control sites at all three time points ($p = 0.0001$).

The within subject comparison of reaction scores at each visit was as follows.

Within subject comparison of reaction scores (± score = 0)			
	Day 2	Day 5	Day 8
Lower reaction score at Q188 site	39 (55%)	65 (92%)	60 (86%)
No difference	28 (39%)	1 (1.4%)	8 (11%)
Lower reaction score at control site	4 (6%)	5 (7%)	2 (3%)
# pts	71	71	70

The number of subjects that never developed a reaction, and the time to development of a reaction in the remaining subjects was as follows.

Time to reaction (± score = 0)		
	Q188 lotion	Control
No reaction	41 (58%)	1 (1.4%)
Reaction by day 2	7 (10%)	40 (56%)
Reaction by day 5	15 (21%)	29 (41%)
Reaction by day 8	8 (11%)	1 (1.4%)
Total # pts	71	71

The conclusion by the sponsor's statistician was that there is a statistically significant difference in the reaction score assessments between the quaternium-18 bentonite lotion treated sites and the untreated control sites at days 2, 5, and 8, which suggests that the test product induced lower scores against poison ivy reactions as compared with the corresponding untreated control at all three timepoints. Both the primary and the secondary efficacy analyses had corroborating results.

4) Adverse events: One subject had a mild contact urticaria which was considered by the investigator to be possibly related to the quaternium-18 bentonite lotion. This appeared as a slightly pruritic, erythematous rash around the site of the lotion application immediately after application; it had disappeared by

the time of the urushiol application. On day 8 the subject was challenged with an application of the quaternium-18 bentonite lotion on a site adjacent to the original application. Within five minutes a mild urticarial ring appeared around the application site, which then faded over the next 20 minutes.

All other reported adverse events do not appear to be related to the urushiol patch or the quaternium-18 bentonite lotion.

Results of the study under Protocol 2/92 were as follows.

1) Subject enrollment and evaluability: 110 subjects were enrolled into the study, of which 79 subjects were evaluable for efficacy. Thirty subjects were classified as unevaluable because neither test nor control site showed a reaction by day 5, and one subject was considered to be unevaluable because he was over age 65, which violated the selection criteria. Of the 79 evaluable subjects, 1 subject was a dropout with reaction score data only at days 2 and 5.

Of 106 subjects enrolled, 39 (37%) were males and 67 (63%) were females; apparently this information was not available on the other 4 subjects.

2) Efficacy evaluation: The primary efficacy variable was the reaction scores. As for study 1/92, the sponsor performed two analyses using this efficacy variable. The primary analysis utilized a 9 point ordinal scale and assigned a value of 1 to the +/- score, and values of 2 through 8 to the scores of 1+ through 7+, respectively. In accordance with the monitor's determination that scores of 0 and +/- were clinically indistinguishable, a secondary analysis was done, in which a value of 0 was assigned to both the 0 and +/- scores, with values of 1 through 7 assigned to the reaction scores of 1+ through 7+. The primary analysis was as follows.

The mean reaction scores for the evaluable subjects at each visit were as follows.

Mean reaction scores (± = 1)			
	# pts	Q188 lotion Mean (range)	Control Mean (range)
Day 2	79	0.19 (0 - 4)	2.91 (0 - 8)
Day 5	79	0.76 (0 - 7)	5.61 (0 - 8)
Day 8	78	1.09 (0 - 7)	5.81 (0 - 8)

Statistical analysis was apparently not performed on the differences in mean reaction scores.

The frequency distribution of the reaction scores at each visit was as follows.

Distribution of reaction scores # pts (%) (± = 1)						
Reaction score	Day 2		Day 5		Day 8	
	Q188	Control	Q188	Control	Q188	Control
0	70 (89%)	15 (19%)	60 (76%)	2 (3%)	49 (63%)	1 (1.3%)
1	6 (8%)	19 (24%)	8 (10%)	5 (6%)	13 (17%)	7 (9%)
2	1 (1.3%)	7 (9%)	1 (1.3%)	1 (1.3%)	3 (4%)	1 (1.3%)
3	1 (1.3%)	7 (9%)	1 (1.3%)	3 (4%)	2 (3%)	2 (3%)
4	1 (1.3%)	10 (13%)	3 (4%)	10 (13%)	3 (4%)	6 (8%)
5	0	2 (3%)	3 (4%)	5 (6%)	4 (5%)	5 (6%)
6	0	8 (10%)	1 (1.3%)	13 (17%)	0	10 (13%)
7	0	10 (13%)	2 (3%)	36 (46%)	4 (5%)	39 (50%)
8	0	1 (1.3%)	0	4 (5%)	0	7 (9%)
# pts	79	79	79	79	78	78

There was a statistically significant difference in reaction scores between the quaternium-18 bentonite lotion sites and the untreated control sites at all three time points ($p = 0.0001$).

The within subject comparison of reaction scores at each visit was as follows.

Within subject comparison of reaction scores (± = 1)			
	Day 2	Day 5	Day 8
Lower reaction score at Q188 site	63 (80%)	73 (92%)	70 (90%)
No difference	15 (19%)	4 (5%)	4 (5%)
Lower reaction score at control site	1 (1.3%)	2 (3%)	4 (5%)
# pts	79	79	78

Statistical analysis was apparently not performed on the within subject comparison of reaction scores.

The number of subjects that never developed a reaction, and the time to development of a reaction in the remaining subjects was as follows.

Time to reaction (± = 1)		
	Q188 lotion	Control
No reaction	42 (53%)	0
Reaction by day 2	9 (11%)	64 (81%)
Reaction by day 5	15 (19%)	15 (19%)
Reaction by day 8	13 (17%)	0
Total # pts	79	79

In the subsequent healing of the dermatitis, 91 subjects were classified as having normal healing; this information was lacking for the remaining subjects.

In the secondary analysis, in which a score of ± was assigned a value of 0, 73 subjects were evaluable for efficacy; results were as follows.

The mean reaction scores at each return visit were as follows.

Mean reaction scores (± score = 0)			
	# pts	Q188 lotion Mean (range)	Control Mean (range)
Day 2	73	0.08 (0 - 3)	2.27 (0 - 7)
Day 5	73	0.56 (0 - 6)	5.01 (0 - 7)
Day 8	73	0.77 (0 - 6)	5.14 (0 - 7)

The frequency distribution of the reaction scores at each visit was as follows.

Distribution of reaction scores (± score = 0) # pts (%)						
Reaction score	Day 2		Day 5		Day 8	
	Q188	Control	Q188	Control	Q188	Control
0	70 (96%)	28 (38%)	62 (85%)	1 (1.4%)	57 (78%)	4 (6%)
1	1 (1.4%)	7 (10%)	1 (1.4%)	1 (1.4%)	3 (4%)	0
2	1 (1.4%)	7 (10%)	1 (1.4%)	3 (4%)	2 (3%)	2 (3%)
3	1 (1.4%)	10 (14%)	3 (4%)	10 (14%)	3 (4%)	6 (8%)
4	0	2 (3%)	3 (4%)	5 (7%)	4 (6%)	5 (7%)
5	0	8 (11%)	1 (1.4%)	13 (18%)	0	10 (14%)
6	0	10 (14%)	2 (3%)	36 (49%)	4 (6%)	39 (53%)
7	0	1 (1.4%)	0	4 (6%)	0	7 (10%)
# pts	73	73	73	73	73	73

There was a statistically significant difference in reaction scores between the quaternium-18 bentonite lotion sites and the control sites at all three time points ($p = 0.0001$).

The within subject comparison of reaction scores at each visit was as follows.

Within subject comparison of reaction scores (± score = 0)			
	Day 2	Day 5	Day 8
Lower reaction score at Q188 site	45 (62%)	69 (95%)	64 (88%)
No difference	28 (38%)	2 (3%)	5 (7%)
Lower reaction score at control site	0	2 (3%)	4 (6%)
# pts	73	73	73

The number of subjects that never developed a reaction, and the time to development of a reaction in the remaining subjects was as follows.

Time to reaction (± score = 0)		
	Q188 lotion	Control
No reaction	57 (78%)	0
Reaction by day 2	3 (4%)	45 (62%)
Reaction by day 5	9 (12%)	28 (38%)
Reaction by day 8	4 (6%)	0
Total # pts	73	73

The conclusion by the sponsor's statistician was that there is a statistically significant difference in the reaction score assessments between the quaternium-18 bentonite lotion treated sites and the untreated control sites at days 2, 5, and 8, which suggests that the test product induced lower scores against poison ivy reactions as compared with the corresponding untreated control at all three timepoints. Both the primary and the secondary efficacy analyses had corroborating results.

4) Adverse events: There were no adverse events which were related to the quaternium-18 bentonite lotion.

Reviewer's comments: The studies under Protocols 1/92 and 2/92 are felt to have been well designed and conducted to evaluate the effectiveness of Ivy Block lotion in the prevention or amelioration of artificially induced poison ivy contact dermatitis. Both studies have demonstrated a highly significant effect of the lotion in this regard.

Uncontrolled studies - lotion formulation

Protocol 7/92 was an open label study designed to evaluate the practical aspects of the application of Ivy Block lotion, such as patterns of usage and product acceptability, under conditions of clinical usage. It was not designed nor intended as an evaluation of the effectiveness in the protection of poison ivy/oak dermatitis. The study population was U.S. Forest Service workers, as they performed field work in three national forests in Texas, Louisiana, and Arkansas. The investigator was David Buddrus, M.D., and the study was performed by lay safety officers at the field locations.

The Forest Service workers were screened by questionnaires as to past occurrences of poison ivy/oak and willingness to participate in the study. Each subject was to keep daily records on a questionnaire for a total of 20 days when field work was performed and exposure to poison ivy/oak might have occurred. There was no requirement that these be consecutive days. Days 1 through 10 were control days on which at least four hours of forest work were performed and Ivy Block was not used. Days 11 through 20 were comparable field days on which Ivy Block was applied each morning, and re-applied throughout the day as needed when the coating wore off. The subjects were to report on possible poison ivy/oak exposure on each of the 20 days, their experience with the lotion, and the occurrence of poison ivy/oak dermatitis.

The subjects selected were between 18 and 65 years of age, with a history of at least two occurrences of poison ivy dermatitis, with at least one occurrence within the previous five years. Subjects were excluded if they had a significant chronic dermatologic condition such as psoriasis, atopic dermatitis, etc., involving skin areas where the lotion would be applied which could interfere with the study determinations.

The subjects enrolled were instructed not to use oral or topical anti-inflammatory agents or analgesics other than acetaminophen, or any other topical products on the arms during the course of the study. They were also cautioned not to carelessly or intentionally expose themselves to poison plants while at work.

Fifty-two subjects were enrolled in the study, of which 40 recorded some study days, and 33 provided data for both control and treatment periods. None of the dropouts were related to usage of

Ivy Block. In the majority of instances the forest work days were not consecutive, due to rotation of work assignments, weekends, holidays, and time off for various reasons. For all the subjects, there were 183 instances of single daily applications, 34 more days on which two or three applications were made, and 4 days on which the lotion was applied more than three times. It was necessary to re-apply the lotion on 38 days of the total of 219 lotion use days; the principal reason for re-application was that the subject had washed the lotion off. In a smaller number of cases there was a need for re-application because the visible coating had been rubbed off, and in a few cases the coating had been removed by perspiration.

Eight subjects developed poison ivy dermatitis during the control period and four subjects developed poison ivy dermatitis during the treatment period. Among the 33 subjects with data in both control and treatment periods, there were 26 reported exposures to poison ivy in the control phase and 18 reported exposures in the treatment phase.

Adverse experiences were burning of the face in one subject who was also using Retin-A to the face for actinic keratoses, and some local discomfort in two subjects, who, however, both continued to use the product.

Reviewer's comments: This study was not designed to evaluate effectiveness under conditions of consumer use, and as such is inadequate in this regard. The study was poorly supervised and controlled, due primarily to the nature of the study population and their work schedules and recreational activities, possible exposure to poison ivy after treatment or without treatment was poorly documented, and the study population was small. It is felt that no conclusions as to the effectiveness under clinical usage conditions can be drawn from this study.

Labeling review

The labeling is for OTC use. The labeling indication and directions for use are as follows. Recommended additions are shown by shading. Recommended deletions are shown by ~~single strikeout lines.~~

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-532 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF_____ Trade (generic) name/dosage form: IVY-BLOCK (bentoquatam) Action: (AP) AE NA

Applicant EnvironDerm Therapeutic Class 1P

Indication(s) previously approved none

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application prevention of poison ivy, oak and sumac

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

✓ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

✓ b. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing.

(2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

✓ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Richard Bloot

Signature of Preparer and Title (PM, CSO, MO, other)

8-2-96

Date

cc: Orig NDA/PLA # 20-532

HFD-540 /Div File

NDA/PLA Action Package

HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

Janet Wilson 8/19/96

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

395

An outline of a protocol has been submitted but without such detail that a firm opinion as to the adequacy of the protocol cannot be rendered at this time. Please refer to cf. correspondence from sponsor of 4/17/96.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-532 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF_____ Trade (generic) name/dosage form: IVY-Block (bentoquatam) Action: AP AE (NA)

Applicant United Catalysts Therapeutic Class 1P

Indication(s) previously approved none

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application prevention of poison ivy, oak, and sumac

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Joanne M Holmes — 9/26/95

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA #_____
HF_____/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

PATENT INFORMATION

United States Patent [19]

Powell, Jr. et al.

1200

[11] **Patent Number: 4,861,584**

[45] **Date of Patent: Aug. 29, 1989**

[54] **ALLERGEN ABSORBENT AND BLOCKING AEROSOL COMPOSITION**

[75] Inventors: **Thomas W. Powell, Jr., Las Vegas, Nev.; Anthony A. Schulz, Floyds Knobs, Ind.; Gary W. Beall, Fairfield, Ky.**

[73] Assignee: **United Catalysts, Inc., Louisville, Ky.**

[21] Appl. No.: **99,960**

[22] Filed: **Sep. 23, 1987**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 940,946, Dec. 12, 1986, abandoned, which is a continuation-in-part of Ser. No. 785,167, Oct. 7, 1985, abandoned.

[51] Int. Cl.[4] A61K 31/14; A61K 31/74

[52] U.S. Cl. 424/79; 424/45; 514/642; 514/770; 514/862; 514/949

[58] Field of Search 514/642, 770, 862, 949; 424/79, 45

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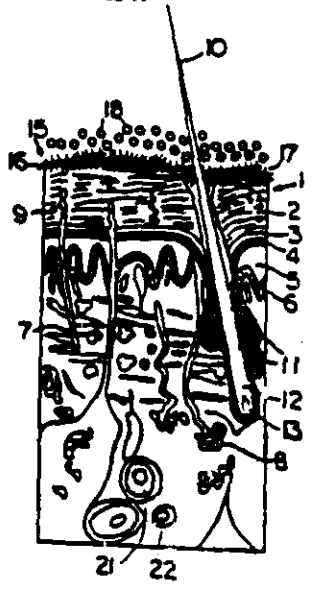
Primary Examiner—Leonard Schenkman

Attorney, Agent, or Firm—Vorys, Sater, Seymour and Pease

[57] **ABSTRACT**

An allergen absorbent and blocking aerosol composition for topical application to the skin comprises a highly activated organophilic clay of the smectite type, ion exchanged with a quaternary ammonium compound having aryl or alkyl groups in the range of from 10 to 22 carbon atoms, and a vehicle comprising one or more long-chain hydrocarbons or volatile silicone oils. The composition is preferably in the form of an aerosol composition additionally comprising an aerosol propellant. The composition is applied to the skin, preferably by spraying, to block and absorb the allergenic oils of toxic plants such as poison ivy and the like.

9 Claims, 2 Drawing Sheets



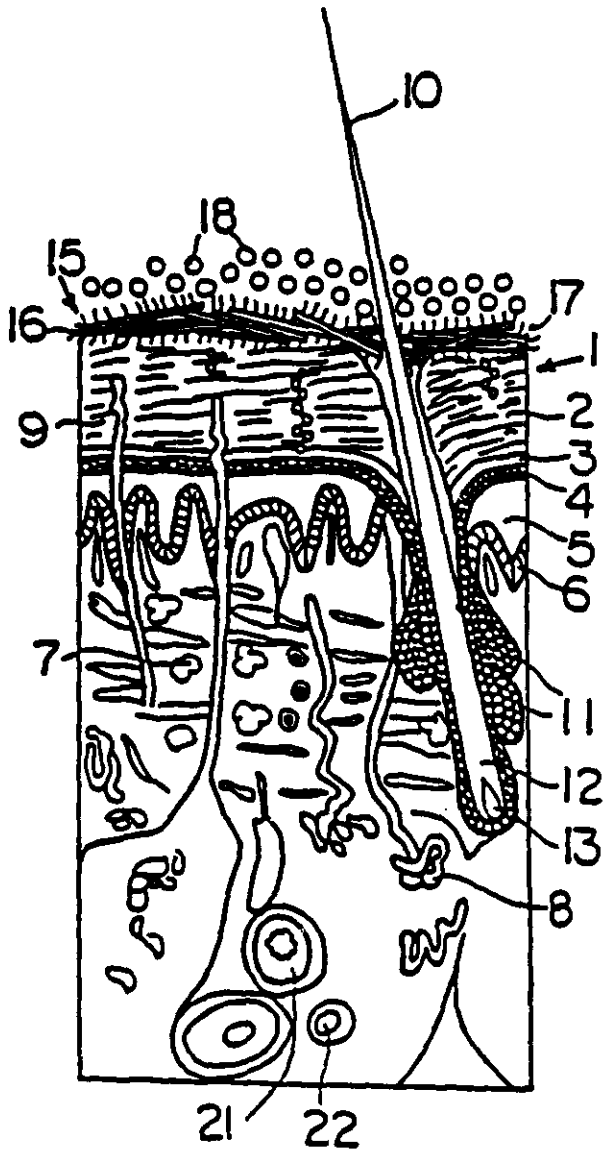


FIG 1

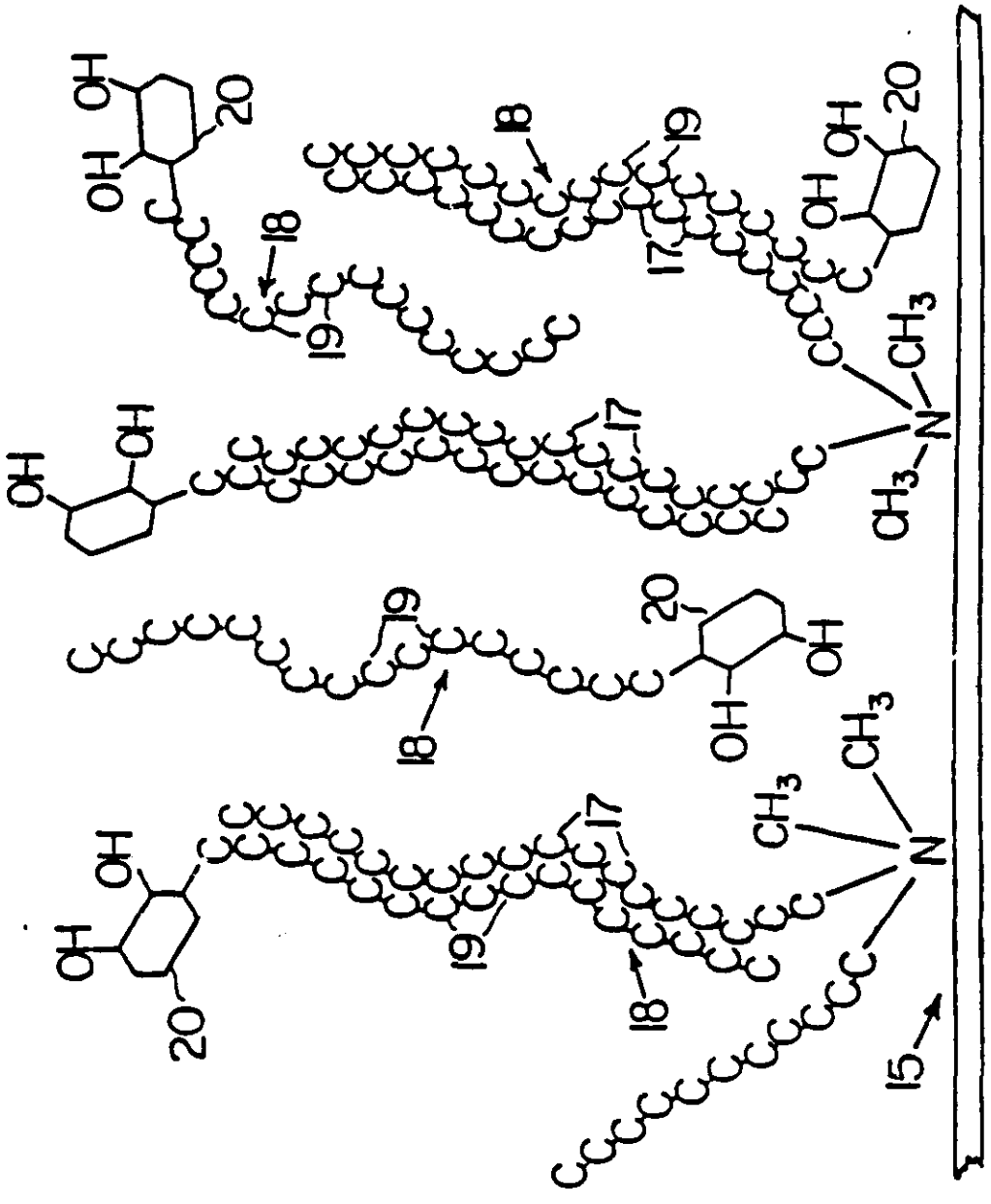


FIG 2

ALLERGEN ABSORBENT AND BLOCKING AEROSOL COMPOSITION

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending application Serial No. 940,946, filed Dec. 12, 1986, now abandoned which is a continuation-in-part of, Ser. No. 785,167, filed Oct. 7, 1985, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to an allergen absorbent and blocking aerosol composition for topical application to the skin to prevent allergic skin reactions of persons due to contact with poison ivy, poison oak or poison sumac.

2. Description of the Prior Art

Poison ivy and poison oak are two of the major causes of allergic contact dermatitis in the United States today. According to Dr. William Epstein, as reported in the Smithsonian, Volume 16, Number 5, dated August, 1985 by Noel Vietmeyer:

"Poison ivy and oak are by far the major causes of allergic contact dermatitis in the United States. More people suffer from them than from all the other allergic skin diseases combined . . . No one counts the number of cases, but there are probably at least ten million a year, nationwide. Poison oak and poison ivy are possibly the greatest cause to workmen's disability in the nation; each year may bring more than 140,000 cases in the workplace, causing perhaps more than 152,000 lost work days."

According to Kligman *AMA Archives of Dermatology*, Vol. 77, February, 1958, p. 149, et seq.,) the first significant advance in Rhus biochemistry was made by Majima (Ber. Deutsch Chem. Ges. 40:4390, 1907 and 50:172, 1922), working with urushiol. Urushiol is a yellow oil extracted from the Japanese lac tree. Later, McNair (J. Am. Chem. Soc. 43:159, 1921), studied poison oak and concluded that the active principle (lobinol) was a catechol with an unsaturated side chain, whose position and structure were not identified. Hill and his collaborators (J. Am. Chem. Soc. 56:2736, 1934) later hydrogenated poison ivy urushiol. They obtained a product identical with Majima's hydrourushiol from Japanese lac. They therefore wrongly concluded that the antigenic compounds in the American and Japanese plants were identical.

According to Kligman, however:

"The sole chemical difference between Japanese lac and poison ivy is the position of one of the unsaturated bonds of the triolefin."

Strangely, however, the allergen urushiol does not appear to affect animals and household pets. Cats and dogs can be exposed and actually play in the area without being affected, but can infect their owners by brushing up against their skin and transferring the urushiol on their coats to the unexposed areas of the human anatomy. According to Dr. Epstein, Ibid.:

"Between 15 and 25% of us are essentially immune, 25% are mildly sensitive and don't normally develop severe reactions, 25 to 30% are moderately sensitive and break out significantly with the amount of urushiol found in one leaf and 10 to 20% are so exquisitely sensitive that less than one leaf produces intense dermatitis . . . ."

The oily substance urushiol, when in contact with the skin, penetrates the outer skin layers and begins to chemically bind to the skin cells. The body sees the combination of the urushiol in chemical combination with a skin cell as a foreign intruder. The immune system immediately rushes large white cells called macrophages and T-lymphocytes to destroy the affected skin cells. Dr. Epstein explains, Ibid:

"It's the body's own over-reaction that causes the complications. In sensitized persons, the area fills up with the white blood cells and they release so much cell-destroying toxins that they tear apart even the skin itself. That's what produces the blisters and suppurating sores."

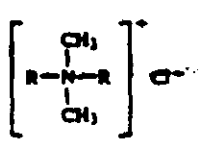
Many folk remedies have been proposed for use after contact with urushiol. These include morphine (topically), bromine, kerosene, gun powder, iodine, aqua regia, buttermilk, cream and marshmallows. Additionally, innumerable botanicals, such as snake root, coffee, gelisium, hellebore, ipecac, lobelia, mustard, opium, strychnine, veratrum, etc., have been suggested.

A major problem as to the contact with urushiol from poison oak, poison sumac and poison ivy is encountered by the foresters of the U.S. Forestry Service. This is particularly severe in the case of forest fires, where the soot and gases from the burning flames contain urushiol, which can get into the foresters fighting the fire and even into their respiratory system. This is further complicated by the fact that the urushiol coats fomites, such as clothing, utensils, even carbon and soot in the area of forest fires and can therefore provide another method of contact, even outside the area of the plants themselves.

Prior to this invention, Dr. Edward E. Waali, working under contract with the U.S. Forestry Service, tested many materials in an effort to find a chemical which would absorb or somehow chenically bind urushiol. Waali tested solid absorbents, such as silica gel, alumina and activated charcoal. Additionally, he saturated samples of cloth and mordanted them with salts of aluminum, copper and chromium.

Dr. William L. Epstein, also working under contract with the U.S. Forestry Service, became aware of Dr. Waali's work and tested a wide variety of agents, including Sure® antiperspirant and Drysol™, both of which contain the antiperspirant aluminum chlorohydrate. The Sure® antiperspirant, in the spray form, contains aluminum chlorohydrate, cyclomethicone, quaternium-18 hectorite, perfume, ethanol, isobutane and propane. This composition is reported to contain from 1 to 5% quaternium-18 hectorite. See, for example, *Clinical Toxicology of Commercial Products*, Gosselin, et al, 5th edition, William and Watkins, 1984, PV-633.

Quaternium-18 hectorite is a reaction product of hectorite and quaternium-18 is commercially available as Bentone 38 (NL Chemicals). Quaternium-18 (CAS Number 61789-80-8) is predominantly (90 to 100%) a quaternary salt that conforms generally to the formula:



where R represents hydrogenated tallow fatty radicals.

Quaternium-18, quaternium-18 hectorite and quaternium-18 bentonite are generally considered safe as cos-

metic ingredients and have been widely used as suspending agents for antiperspirants. See "Final Report on the Safety Assessment of Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite," *Journal of the American College of Toxicology*, Vol. 1(2), 1982, pp. 71–83.

Accordingly, a need has continued to exist for an effective and cosmetically acceptable material to protect humans from the effects of contact with poison ivy and similar poisonous plants.

SUMMARY OF THE INVENTION

This goal has now been achieved by an allergen absorbent and blocking composition comprising a highly-activated organophilic clay gel and a long-chain hydrocarbon or volatile silicone fluid vehicle. The organophilic clay gel consists of layered platelets of smectite clay having a cation exchange capacity in excess of 50 milliequivalents per 100 grams of clay, which has been ion exchanged with a quaternary ammonium compound having at least one alkyl group containing from about 10 to 22 carbon atoms. It is essential that the smectite clay and quaternary ammonium compound be highly activated, and this is accomplished by high-shear mixing in a colloid mill or other known mechanisms. Additionally, low molecular weight polar activators, such as methanol, may be used.

According to this invention, the allergen absorbent and blocking composition is topically applied to the skin and clothes and thereby effectively blocks the skin and adjacent cloth from contact with urushiol and absorbs the urushiol and holds it away from the skin until it is washed off with soap and water. The highly-activated gel, consisting of platelets of the smectite clay, forms a barrier on the skin and clothes, possibly through contact of the active tallow tails of the organic material with the lipids of the skin and by absorption of the urushiol in the organic alkyl groups. It is felt, therefore, that there is a partitioning effect which effectively blocks and absorbs the oil phase urushiol from aqueous phase perspiration and the like, allowing the urushiol to be held away from the skin and held in chemical combination with the reactive alkyl chains of the organo-treated clay, while allowing the aqueous phase materials to pass through the clay barrier.

Accordingly, it is an object of the invention to provide a skin-protective composition.

A further object is to provide a protective composition capable of screening against poison ivy and the like.

A further object is to provide a composition which is effective for protecting skin from the effects of contact with poison ivy and which can be applied by spraying.

A further object is to provide an absorbent composition for urushiol.

Further objects of the invention will become apparent from the description of the invention which follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagrammatic view of the skin's surface and the organophilic clay platelets acting as a barrier to the invading urushiol droplets.

FIG. 2 is a diagrammatic view of an individual clay platelet with the alkyl groups attached thereto.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

It has been known for a long time that organic compounds which contain a cation will react under favorable conditions by ion exchange with clay platelets which contain a negative layer-lattice and exchangeable cations to form organophilic organic-clay products. If the organic cation contains at least one alkyl group containing at least 10 carbon atoms, then such organo-clays have the property of swelling in certain organic liquids. See, for example, U.S. Pat. No. 2,531,427 and U.S. Pat. No. 2,966,506, both of which are incorporated herein by reference. See also the book *Clay Mineralogy*, Second Edition, 1968, by Ralph E. Grim (McGraw-Hill Book Co., Inc.), particularly Chapter 10, "Clay-Mineral-Organic Reactions," pp. 336–368-"Ionic Reactions, Smectite;" and pp. 392–401-"Organophilic Clay-Mineral Complexes." Since the commercial introduction of these organo-clays in the early '50's, it has become well-known to gain maximum gelling (thickening) by adding a low molecular weight polar organic compound to the composition. Such polar organic compounds have been variously called activators, dispersion aids, solvating agents, and the like. See, for example, U.S. Pat. Nos. 2,677,661, O'Halloran; 2,704,276, McCarthy, et al; 2,833,720, Stratton; 2,979,229, Reeder et al.; and 3,294,683, Stansfield, et al, which are incorporated herein by reference. The most efficient and accepted polar materials for use as activators have been found to be low molecular weight alcohols and ketones, particularly methanol and acetone. The activators, however, have very low flash points and require the use of flameproof apparatus. Higher-boiling activators, having higher flash points, such as propylene carbonate, may also be used. Clays used to prepare the allergen absorbent and blocking compositions of this invention are the smectite-type clays, having a high cation exchange capacity. The cation exchange capacity of the smectite clay should equal or exceed 50 milliequivalents per 100 grams of clay. The preferred range of milliequivalent capacity should be about 100–120 milliequivalents per 100 grams of clay. Particularly desirable types of clay are the naturally-occurring Wyoming variety of swelling bentonite and like clays, as well as hectorite, a swelling magnesium-lithium silicate clay. Suitable bentonite clays are also found in Europe, particularly in the Moosburg section of Bavaria. Smectite clays can be also prepared synthetically by either a pneumatolytic or preferably a hydrothermal synthesis process. Representative hydrothermal processes for preparing synthetic smectites are described in the following U.S. Patents, which processes are incorporated herein by reference: U.S. Pat. No. 3,252,757, Granquist; U.S. Pat. No. 3,586,478, Neumann; U.S. Pat. No. 3,666,407, Orelemann; U.S. Pat. No. 3,671,190, Neumann; U.S. Pat. No. 3,844,978, Hickson; U.S. Pat. No. 3,844,979, Hickson; U.S. Pat. No. 3,852,405, Granquist; and U.S. Pat. No. 3,855,147; Granquist.

As has been previously indicated, the invention relates to the discovery that organo-treated clays of the smectite type, which are highly activated, produce allergen absorbents and blocking gels for topical application to the skin to prevent contact of the skin with the allergens produced by poison ivy, poison oak or poison sumac. The smectite-type clays, which have sufficient cation exchange capacity to be ion exchanged with

organic compounds having a cation and one or more alkyl chains, having at least 10 carbon atoms naturally occur in Wyoming and in the Moosburg section of Bavaria, in the vicinity of Munich, Germany. The clays are of the bentonite type and are usually of the sodium form. However, if they are not already in the sodium form, they can be converted by passing an aqueous clay slurry through a bed of cation exchange resin in the sodium form. Alternately, the smectite clay can be mixed with water and a soluble sodium compound, such as sodium carbonate, or sodium hydroxide, and sheared at high shear in a colloid or pug mill or extruder. Representatives of such smectite clays are the following:

Montmorilloníte:

$((Al_{4-x}Mg_x)Si_8O_{20}(OH)_{4-f}F_f)\cdot xR^+$ where $0.55 \leq x \leq 1.10$, $f \leq 4$ and R is selected from the group consisting of Na, Li, NH_4, and mixtures thereof;

Bentonite:

$((Al_{4-x}Mg_x)(Si_{8-y}Al_y)O_{20}(OH)_{4-f}F_f)\cdot(x+y)R^+$ where $10.0 \leq x \leq 1.10$, $0 \leq y \leq 1.10$, $0.55 \leq (x+y) \leq 1.10$, $f \leq 4$ and R is selected from the group consisting of Na, Li, NH_4, and mixtures thereof;

Beidellite:

$((Al_{4+y})(Si_{8-y}Al_y)O_{20}(OH)_{4-f}F_f)\cdot xR^+$, where $0.55 \leq x \leq 1.10$, $0 \leq y \leq 0.44$ and R is selected from the group consisting of Na, Li NH_4, and mixtures thereof;

Hectorite:

$((Mg_{6-x}Li_x)Si_8O_{20}(OH)_{4-f}F_f)\cdot xR^+$ where $0.57 \leq x \leq 1.15$, $f \leq 4$ and R is selected from the group consisting of Na, Li, NH_4, and mixtures thereof;

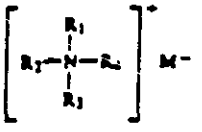
Saponite:

$((Mg_{6-y}Al_y)(Si_{8-x-y}Al_{x+y})O_{20}(OH)_{4-f}F_f)\cdot xR^+$ where $0.58 \leq x \leq 1.18$, $0 \leq y \leq 0.66$, $f \leq 4$ and R is selected from the group consisting of Na, Li, NH_4, and mixtures thereof;

Stevensite:

$((Mg_{6-x}Al_x)Si_8O_{20}(OH)_{4-f}F_f)\cdot 2xR^+$ where $0.28 \leq x \leq 0.57$, $f \leq 4$ and R is selected from the group consisting of Na, Li, NH_4, and mixtures thereof.

These smectite clays may be synthesized hydrothermally by forming an aqueous reaction mixture in the form of a slurry containing mixed hydrous oxides or hydroxides of the desired metals with or without, as the case may be, sodium (or alternate exchangeable cation or mixture thereof) fluoride in the proportions defined in the above formulas and preselected values of x, y, and f for the particular synthetic smectite desired. The slurry is then placed in an autoclave and heated under autogenous pressure to a temperature within the range of approximately 100° to 325° C., preferably 275° to 300° C. for a sufficient period of time to form the desired product. Formulation times of 3 to 48 hours are typical at 300° C., depending on the particular smectite being synthesized and the optimum time can be readily determined by pilot trials. The organic compounds useful in this invention are quaternary and ammonium salts containing at least one methyl radical and a mixture of alkyl radicals, having from 14 to 20 carbon atoms, preferably wherein 20 to 35% have 16 carbon atoms and 5% have 18 carbon atoms on a 100% basis. Additionally, quaternary ammonium compounds containing at least one methyl and one benzyl radical may be utilized. The anion is preferably selected from the group consisting of chloride and bromide and mixtures thereof and is preferably a chloride. However, other anions, such as acetate, hydroxide, nitrite, etc., may be present in the ammonium salt. The methyl or benzyl trialkyl ammonium salt may be represented as follows:



The preferred quaternary amine for use in the practice of this invention is dimethyl dihydrogenated tallow ammonium chloride. R_1 can be methyl or benzyl. R_2 can be methyl or C_{10} to C_{18}. R_3 can be methyl or C_{10} to C_{18}. R_4 can be C_{10} to C_{18}. Commercially-prepared hydrogenated tallow typically analyzes 2.0% C_{14}, 0.5% C_{15}, 29.0% C_{16}, 1.5% C_{17}, 66.0% C_{18} and 1.0% C_{20} alkyl radicals.

Nevertheless, the alkyl radicals may be derived from other natural oils, including various vegetable oils, such as corn oil, soybean oil, cottonseed oil, castor oil and the like, as well as various animal oils and fats. Additionally, the alkyl radicals may be petrochemically derived, as from alpha olefins.

We hve found that is is essential that the organophilic clay compounds be highly activated. Activation of the organophilic clays may be accomplished by use of organic polar materials of low molecular weight (which are known as activators). These activators, dispersion aids and the like have previously been described.

PREPARATION OF THE ORGANOPHILIC CLAYS

The organophilic clays are prepared by admixing the smectite clay, the quaternary ammonium compound and water together, preferably at temperatures within the range of 100° to 171° F. (38° to 77° C.) for a period of time sufficient for the organic compound to coat the smectite clay platelets, followed by filtering, washing, drying and grinding. In using the organophilic clays in emulsions, the drying and grinding steps can be eliminated. When the smectite clay and quaternary ammonium compound and water are mixed together in such concentrations that a slurry is not formed, then the filtration and washing steps are eliminated. Preferably, however, the smectite clay is dispersed in water at a concentration of from about 3 to 7% and the slurry is optionally centrifuged to remove nonclay impurities. Thereafter, the slurry is agitated and heated to a temperature in the range of 140° to 171° F. (60° to 77° C.). The quaternary amine salt is added in the proper milliequivalent ratios, preferably as a liquid in isopropanol. The amount of the quaternary ammonium salt added to the smectite clay for purposes of this invention must be sufficient to impart to the organo-philic clay the enhanced dispersion characteristics desired. Milliequivalent ratio is defined as the number of milliequivalents of the organic compound in the organo-clay per 100 grams of clay, on a 100% active clay basis. The organophilic clays preferably have a milliequivalent ration of from 100 to 120. A milliequivalent ratio of at least 50 is required to be effective. If polar organic activators are utilized, the lower milliequivalent ratios of 50 to 100 can be utilized without affecting the resultant gel system disadvantageously. The smectite clay and quaternary ammonium compound are admixed with known vehicles, as for example, long-chain hydrocarbons, such as isopropyl palmitate or isopropyl myristate, or volatile silicone vehicles, such as cyclomethicone or dimethicone or hexamethyldisiloxane. The entire admixture is

subjected to a high-shear mixing in a colloid mill, a pug mill or the like. Generally speaking the concentration of the organo-treated clay is in the ratio of from 5 to 15% by weight. Therefore, the vechicle for the resulting gel makes up the balance of the mixture in the weight concentration of from about 95 to 85%.

If the gel is utilized in the form of an aerospray, the admixture of organo-treated clay forming the gel is in a weight concentration of from 5 to 15% and the hydrocarbon or silicone liquid vehicle forms the remaining 95 to 85%. The total gel makes up about 10 to 50% by weight of the contents of the can, with the rest of the material being a propellant.

AEROSOL PROPELLANTS

Aerosol propellants are well known in the art and have been described in some detail, as for example, in U.S. Pat. No. 3,835,896, to Smrt. Generally, with the banning of the chlorinated hydrocarbon propellants, the propellants used in the United States today are hydrocarbons. These are blends of isobutane and propane. According to Smrt:

"Isobutane is a colorless, easy-liquefiable gas which is generally shipped as a liquefield gas under its own vapor pressure. The vapor pressure of isobutane is 30.7 psig at 70° F. Propane is a gas at atmospheric pressure and normal temperatures and is colorless, both in its gaseous and liquid phases. Propane is also generally shipped as liquefied gas under its own vapor pressure, which-is 110 psig at 70° F. The blends of hydrocarbon propellants are generally indentified by the vapor pressure of the blend at 70° F. Thus, for example, a 90-10 blend consists of 90% isobutane and 10% propane by weight and this blend has a pressure of 40 psig at 70° F. Blend 84-16 consists of 84% isobutane and 16% propane by weight and this blend has a vapor pressure of 46 psig at 70° F."

Therefore, the trade designation "A-46" relates to the vapor pressure of the propellant at 70° F.

Margolis goes further so state, in U.S. Pat. No. 3,568,394, that the low-boiling, liquefied alkanes, useful as propellants, are those which, alone or as mixtures at 70° F., have a vapor pressure of at least 20 pounds per square inch, but generally not more than 70 pounds per square inch. He lists alkanes, having vapor pressures in excess of 40 pounds per square inch as hexane, propane, pentane and butane. These, of course, can be mixed with alkanes having a lower vapor pressure to produce a desired pressure which is dependent upon the proportion of each of the specific alkanes present in the mixture. Such proportions are readily determined by methods which are well known to those skilled in the art.

Additionally, according to Bartlett, in U.S. Pat. No. 4,595,522, it is possible to utilize azeotropic mixtures of monochlorodifluoromethane and dimethyl ether in admixture with butane or isobutane to produce useful aerosol propellants with a vapor pressure in the range of 50 to 60 psig. Even noble gases, such as helium, neon, argon, krypton or mixtures thereof, have been proposed and have been used by some as propellants for an aerosol product. Thus, Wittenhorst, in 4,380,505, proposes their use so that the problems of chlorofluorohydrocarbon propellants are not encountered, since the noble gases do not apparently affect the ozone belt surrounding the earth.

AEROSOL FILLING

There are three different methods generally employed for filling assorted aerosol containers. These are described by Cunningham in U.S. Pat. No. 3,857,422, and are incorporated herein by reference. According to Cunningham, Column 1, lines 20 through 68 and Column 2, lines through 8:

"One is termed the "cold fill" method of filling. The product and liquefied propellant are individually refrigerated prior to their introduction into an open container. This refrigeration lowers the propellant vapor pressure so that it can be handled in the liquid state. This delays liquid to vapor transition of the propellant for a period sufficient to permit insertion and crimping of a valve assembly in the container to effect closure of the can. The cold fill method is not satisfactory for some products, due to the product formulation. For example, water base products freeze in the refrigeration step of the filling operation. Additionally, it has been found that some propellant is wasted in this type of filling operation in that some propellant will vaporize and escape from the container before closure of the container can be completed.

A second method employed for filling aerosol type containers is commonly referred to as the "under cap" method. In this operation, the product (at room temperature) is initially introduced into the container by a conventional liquid product filling machine and a valve is loosely inserted into the can. Generally, a vacuum is then drawn on the container, after which a liquid propellant is injected therein at high pressure (e.g., approximately 750 psig). Subsequently, the valve cup is crimped to the container by means of an internally expanding collet. However, in the time between the injection of the propellant into the container and the subsequent crimping operation, a portion of the liquid propellant is trapped between dual seals contacting the container and valve cup and around the curl of the can opening and valve cup over-lip. This propellant is lost in the filling operation. The loss of propellant for a single can is in excess of 5 grams . . . .

A third method employed for filling aerosol containers is known as "pressure filling." In this operation, the product is put into a container at room temperature, after which a valve assembly is inserted, a vacuum may be drawn, and the valve crimped. A propellant injector machine is then mated with the valve pedestal and propellant is supplied at high pressure and forced into the container through the valve assembly. The primary advantage of the pressure-filled method is a reduced loss of the propellant, as compared to either of the previously described methods of filling."

DESCRIPTION OF THE DRAWINGS

Referring now to FIG. 1, there is illustrated a diagrammatic section of the skin after a diagram of *Gray's Anatomy*. As will be noted, the skin is made up of an epidermis 1 and a dermis 7. The epidermis consists of five layers, the stratum corneum 2, the stratum lucidum 3, the stratum granulosum 4, the stratum mucosum 5, which terminates in the stratum germinativum 6. The sudoriferous gland 8 is located in the dermis. However, the ducts 9 extend through the epidermis to the outer layer of the skin. Additionally, the shaft of the

hair 10 extends through duct 14 and terminates at the bulb 12. The hair follicle is surrounded by sebaceous glands 11, which discharge into the duct 14 to keep the hair shaft lubricated. Additionally, the dermis 7 contains a great deal of adipose tissue 20 and some relatively deep-lying arteries 21 and nerves 22.

According to the drawing, the organo-treated clay 15, made up of platelets 16 and the depending tallow tails 17 form as a layer over the skin with the tallow tails reacting to some extent with the lipids of the skin's surface. This allows the platelets to align themselves to act somewhat as a shield against the invading urushiol droplets 18. Stroking of the platelets manually appears to orient the platelets so as to lie parallel with the epidermal cells of the skin. The quaternium bentonite or quaternium hectorite appears somewhat muddy when initially applied to the skin. However, as the quaternium-18 bentonite gel is stroked onto the skin, the muddy appearance disappears. The urushiol droplets, in order to reach the skin, must pass through the barriers or blockers formed by the platelets 16 without being absorbed by the reactive organic alkyl groups in the form of tallow tails 17. It is believed that the tallow tails, through the van-der Waal forces, tend to absorb chemically the urushiol droplets and hold the urushiol droplets and thus prevent their contact with the skin (see FIG. 2). Any urushiol droplets which might escape the first row of tallow tails are blocked by the clay platelets 16 and then encounter succeeding alkyl groups where absorption takes place. Additionally, the oragnophilic clay aerosol composition can be sprayed onto the clothes or tools, so as to suspend and inactivate the allergen until the clothes or tools can be laundered. Otherwise, there is some danger that other persons can be exposed to the allergen when these are laundered or that the worker himself may be reexposed by contact with the unwashed clothes at a later time.

Urushiol 18 is diagrammatically illustrated in FIG. 2, according to its chemical formula. As will be noted, the urushiol compound consists of a phenyl group 20 with two hydrogen groups and a long hydrocarbon chain of 15 to 17 carbons, designated as 19.

Additionally, the quaternary ammonium compounds are designated with the alkyl groups 17, consisting of 16 to 18 carbons. Some of the quaternary ammonium compounds contain a benzyl compound 21 and one alkyl chain and two methyl groups, while the other quaternary ammonium compounds consist of two alkyl hydrocarbon chains 17 and two methyl groups. The van der Waal bonding of the hydrocarbon chain 19 of the urushiol compound 18 is diagrammatically shown with the long-chain alkyl group 17 of the organophilic clay 15. Additionally, it is felt that the phenyl group 20 of the urushiol compound may have some affinity for the active surface of the platelet 16 of the organophilic clay. This is shown diagrammatically in the right-hand portion of FIG. 2.

It should be understood that this explanation is somewhat hypothetical. However, it is supported by data, as will hereinafter be shown. The fact of the matter is that absorption apparently is not the major mechanism in this instance, since materials with higher surface areas do not provide the protection that is provided by the organo-treated clays. It is felt, therefore, that the organic surface area is of major importance while the inorganic surface area formed by the pores of the clay platelets perform only a secondary function relative to the absorptive function performed by the reactive alkyl groups of the organic clays.

The invention will be better understood by reference to the following examples which are intended to be illustrative and not limiting.

EXAMPLE 1

A batch of organophilic clay is prepared by admixing finely milled sodium bentonite with sufficient quaternary ammonium compound so as to provide 85 milliequivalents of quaternary ammonium compound per 100 grams of clay. The quaternary ammonium compound is obtained from hydrogenated tallow and contains two alkyl groups containing from 16 to 18 carbons in length and 2 methyl groups. This is commonly referred to as quaternium-18. The quaternary ammonium compound was mixed with sufficient water and the sodium bentonite so as to produce a slurry containing about 4% by weight of clay. The temperature of the slurry was maintained at 170° for a period of about 30 minutes. This allowed the quaternary ammonium compound to ion exchange with the clay paticles. The slurry was then spray dried into a fine powder. This product is known in the cosmetic industry as quaternium-18 bentonite. The powdered organo-clay was admixed with about 4.3% by weight of an SD-40 alcohol and about 84% by weight of cyclomethicone (Dow-Corning 344) as a vehicle. This then produced a gel containing 11.3% organo-clay, 84% cyclomethicone and 4.3% SD-40 alcohol. The gel was then loaded into an aerosol container at room temperature. A valve assembly was inserted into the container and the valve was crimped. An A-46 mixed hydrocarbon propellant was then introduced through the valve assembly under pressure to produce an aerosol composition within the can of 30:70 weight ratio of gel to propellant. As previously mentioned, the A-46 propellant is 84% isobutane and 16% propane by weight and has a vapor pressure of 46 psig at 70°F.

EXAMPLE 2

The materials prepared as in Example 1 was tested for effectiveness in a procedure carried out under a grant from the U.S. Forestry Service under the supervision of Dr. William Epstein of the University of California Medical School at San Francisco. The test procedure involved the application of Sure® deodorant, as a comparison composition, and the organophilic clay of Example 1, by spraying onto the skin of the forearm, and subsequent challenge at 1, 4 and 24 hours after application by the application of dilutions of purified urushiol in acetone in a double-blind fashion. Three samples concentrations of urushiol in acetone were made up, with five microliter samples of the solution of urushiol in acetone containing amounts of urushiol ranging from 0.25 micrograms to 0.005 micrograms. The samples of urushiol in acetone were then applied to the patch test sites. The patch test sites were read two to five days later and recorded from N to 4 as follows:

N = Normal
1 = Erythema and edema involving half the test
2 = Erythema and edema plus small vesicles involving the entire site
3 = Full involvement of the test site with erythema and edema and large vesicles
4 = Bullae.

A − 1 score signifies a definite positive reactive which involves less than ½ of the test site and a ± score signi-

fies a questionable reaction which is subsequently read as either + or −.

The results of these tests are shown in Table I.

TABLE I

Average Protective Effect of SURE ® and Example 1 Compared to the Control

Pretreatment Time	Micrograms Dilutions of Urushiol			
	0.25	0.1	0.05	0.025
1 hour				
Sure ®	1	1.3	1.2	1.0
Example 1		Not Done		
4 hours				
Sure ®	1.5	0.9	0.9	0.5
Example 1	3.0	2.0	1.5	1.3
24 hours				
Sure ®	0	0.75	1.0	0.4
Example 1	1.5	0.9	0.9	1.5

Table I shows that pretreatment with the Sure ® deodorant does reduce the patch test reaction to dilutions of urushiol. However, Sure ® is not able to prevent the reactions completely, but simply reduce them. The material of Example 1, on the other hand, was more effective at reducing the reactions and this was particularly noticeable at 4 and 24 hours after applications, as compared to Sure ®. This table averages overall responses.

EXAMPLE 3

A second preliminary study was carried out, comparing the results of pretreatment with Sure ® to pretreatment with Drysol TM (a 20% w/v concentrate of aluminum chloride hexahydrate in alcohol; a solution of aluminum chloride (hexahydrate) 20% w/v in anhydrous ethyl alcohol (S.D. alcohol) 93% v/v." *Physicians Desk Reference*, 36th Ed., 1982. Medical Economics Co., Inc., 1982). The pretreatment time was 4 hours. The patch tests were urushiol and the patch test readings were the same as described above.

This preliminary study, comparing the high concentration of the aluminum salt (Drysol TM) to Sure', indicated that the alcoholic solution was less effective than Sure ®.

EXAMPLE 4

In the next series of experiments, the subjects were pretreated with breakdown products of Sure ® that either were missing the aluminum chlorohydrate or the suspending agents (bectorite and propylene carbonate). The patch tests with urushiol and the patch test readings were the same as described above.

These experiments compared the blocking effect of Sure ® with its ingredients, i.e. without fillers and without aluminum chlorohydrate. In one instance, Sure ® was compared to the aluminum compound containing preparation without the fillers, i.e. the quaternium-18 hectorite, and the two were equal on two occasions. Sure ® was more effective in one and definitely more effective in four instances. In no instance was the aluminum salt more effective than Sure ®. Sure ®, containing only the fillers and no aluminum, was compared to Sure ® and the two preparations were equal on two occasions. Sure ® was more effective than the filler preparations on two occasions and much more effective on one occasion. On the other hand, the filler was more effective than Sure ® on two occasions. Finally, in direct comparison of the filler versus the aluminum preparation, the filler was more effective than the aluminum salt on two occasions and much more effective in four additional trials. In one instance, the aluminum salt was more effective than the filler preparations.

EXAMPLE 5

The tests, as previously described, were carried out with three particularly sensitive individuals. These are shown in Tables II, III and IV.

As can be seen, after the second day, the control showed a normal reaction for the patch test for the low concentration, but a 2 reaction as to any concentration of urushiol above 0.05 micrograms. Sure ®, on the other hand, provided some protection at 0.05 micrograms and reduced the size of the reaction as to the concentration above 0.1. The material of Example 1, however, showed full protection 4 hours after application for all concentrations of the material. Essentially the same results were obtained after Day 4. Except with the control, the severity of the reactions increased. The severity of the reaction of the high concentration of urushiol increased with the Sure ® application, by the material of Example 1 gave full protection throughout the total range of concentration. Twenty-four hours after application, essentially the same results were obtained on Day 2. On Day 4, the severity of the reaction was greater with the control and with the Sure ® sample and there was a 1 range of reaction for the Example 1 after 24 hours.

TABLE II

Micrograms Urushiol	Day 2			Day 4		
	Control	Sure ®	Ex. 1	Control	Sure ®	Ex. 1
Urushiol applied 4 hours after application of protective composition:						
0.25	2	−1	N	3	3	N
0.1	2	1	N	2	1	N
0.05	2	N	N	2	N	N
0.025	N	N	N	N	N	N
0.01	N	N	N	N	N	N
Urushiol applied 24 hours after application of protective composition:						
0.25	2	1	N	3	3	1
0.1	2	1	N	2	1	1
0.05	2	N	N	2	N	N
0.025	N	N	N	N	N	N
0.01	N	N	N	N	N	N

TABLE III

Micrograms Urushiol	Day 2			Day 4		
	Control	Sure ®	Ex. 1	Control	Sure ®	Ex. 1
Urushiol applied 4 hours after application of protective composition:						
0.25	2	2	N	4	2	N
0.1	2	2	N	3	2	N
0.05	1	−1	N	2	1	N
0.025	−1	N	N	N	N	N
Urushiol applied 24 hours after application of protective composition:						
0.25	2	2	2	4	2	2
0.1	2	2	2	3	2	2
0.05	1	1	N	2	1	N
0.025	−1	N	N	N	N	N

TABLE IV

Micrograms Urushiol	Day 2			Day 4		
	Control	Sure ®	Ex. 1	Control	Sure ®	Ex. 1
Urushiol applied 4 hours after application of protective composition:						
0.05	2	2	N	3	2	−1

TABLE IV-continued

Micrograms	Day 2			Day 4		
Urushiol	Control	Sure ®	Ex. 1	Control	Sure ®	Ex. 1
0.025	N	N	N	1	N	N
0.01	N	N	N	N	N	N
Urushiol applied 24 hours after application of protective compounds:						
0.05	2	1	1	3	2	2
0.025	N	−1	N	1	N	N
0.01	N	N	N	N	N	N

Table III, for a completely different individual, who was extremely sensitive, demonstrated a more severe reaction with both the control sample and the Sure ® sample, after Day 2 and Day 4, as compared to Table II. However, the quaternium-18 bentonite of Example 1 provided good protection, both for Day 2 and Day 4 throughout the entire range of urushiol concentrations. The severity of the reactions increased across the board after application and even the material of Example 1 showed a moderate grade 2 reaction for the higher concentrations on the second and fourth days. The superiority of the material of Example 1 over the control and over the Sure ® is shown, however, throughout.

Table IV demonstrates in like manner the protection afforded to the individual throughout a smaller range of urushiol concentrations. On the fourth day, when the urushiol was applied 4 hours after the protective composition, the material of Example 1 showed a positive reaction, as indicated by −1. In like manner, the table demonstrates that even when the urushiol is applied 24 hours after the protective composition there is protection against the low concentrations of urushiol by the organophilic clay of Example 1 on the second and fourth days following application.

A further series of tests was performed to compare the effectiveness of the composition of this invention with other compositions containing clays which have not been treated with a long-chain quaternary ammonium compound. Three compositions were prepared according to the procedures in the following Examples 6, 7 and 8.

EXAMPLE 6

An aerosol sample was prepared in the same manner as described in Example 1, except that only the cyclomethicone and alcohol were added to the aerosol can prior to charging with the A-46 mixed hydrocarbon propellant. The vehicle to propellent ratio, therefore, was 30:70. This sample did not contain any organo-clay in the form of quaternium-18 bentonite, and served as a control.

EXAMPLE 7

Another sample was prepared identically with the sample of Example 1, except that the sodium bentonite was not ion exchanged with a quaternary ammonium compound. Therefore, the the can contained a gel consisting of 11.3% bentonite (without the quaternary ammonium compound), 4.3% SD-40 alcohol and 84% cyclomethicone, and was pressure charged with the A-46 propellent in a weight ratio of 30:70, gel to propellant.

EXAMPLE 8

Example 8 was prepared in the identical method as Example 7, except that kaolin was substituted for the sodium bentonite. The composition, then, of the gel was 11.3% kaolin, 84% cyclomethicone and 4.3% alcohol. This gel was then charged with an A-46 propellant in a weight ratio of 30:70, gel to propellant.

These materials were tested as follows:

Screening:

Thirty-seven healthy male and female volunteers were screened with serial dilutions of purified urushiol in acetone and applied in 5 microliter aliquots ranging from 1.25 to 0.005 micrograms to determine their level of sensitivity and their end-point dilution. Of this group, 28 were entered into the test protocol.

Test method:

Subjects were randomly sprayed on the volar aspect of each forearm with one of the four test preparations of Examples 1, 6, 7 and 8, by a technician; 4 hours later the treated sites were exposed to 5 microliters of a solution of urushiol in acetone in 2 to 4 dilutions that clearly included the predetermined end-point dilution for each subject. The test sites were evaluated in 2 and 5 days and scored on a scale from 0 to 4 in which:

0 = no reaction
1 = erythema edema involving more than half the test area
2 = erythema, edema and small vesicles involving the full test area
3 = erythema, edema and significant vesiculation
4 = bullae

Positive reactions that affected less than half the test area were scored as −1 and questionable reactions, usually seen on the first observation period, were scored ±. Subjects were tested every 10 to 14 days after the previous test sites had healed so that comparative, sequential data was obtained in a number of persons.

Results:

In this study, it was possible to analyze the data in two distinct ways. The first evaluation method consisted of a direct comparison of 2 preparations applied to the same subject on the same day. So long as at least one test site gave a positive reaction, the materials could be scored as better than or equal to each other on that single occasion. If both test sites were scored completely negative for poison ivy dermatitis, it was considered a null event and no comparison was recorded. The results of that evaluation are listed in Table V. It can be seen that there were 37 valid comparison events and that the composition of Example 1, according to the invention, on 16 occasions scored better than the compositions of Examples 6, 7, or 8; whereas on only one occasion did one of the compositions of Examples 6, 7 or 8 score better than the composition of Example 1. On the other hand, comparisons of the compositions of Examples 6, 7 and 8 amongst each other gave mixed results, so that none of those three preparations were seen to have a distinct advantage over the others.

The second evaluation method involved 16 subjects who were tested at least twice so that in most instances, all four materials, of Examples 1, 6, 7 and 8, were tested in the same subject but on different occasions. This data is presented in Table VI. Examination of this table indicates that all of the test substances (Examples 1, 6, 7 and 8) had some protective effect, and on some occasions, the effect was impressive. Nevertheless, a careful examination of this table indicates that preparation 1 always produced optimal protection, whereas the other preparations sometimes did but at other times did not.

It is clear that by both methods of evaluating the considerable amount of data obtained, that the composition of Example 1 is the most effective as a topical protection against experimental poison ivy dermatitis in this rather stringent test method which uses an acetone solution of purified urushiol. None of the compositions of the three Examples, 6, 7 and 8 can be distinguished as being more effective than the others. However, the composition of Example 1 is unquestionably superior to the compositions of Examples 6, 7 and 8 in the test system used.

TABLE V

Direct comparison of Topical Protective Effect

Composition of Example	Number of Instances Superior to Composition of Example			
	1	6	7	8
1 (invention)	—	4	7	5
6	1	—	2	0/6
7	0	2	—	3
8	0	5/6	2	—

TABLE VI

Subject	Pretreatment: Composition of Example	Amount of Urushiol (micrograms) 1.25	0.5	0.25	0.1	0.05	0.025	0.01	0.005
#1	1						0	0	0
	6						1	0	0
	7						2	0	0
	8						2	1	0
#2	1								
	6	1	±	0	0				
	7	1	0	0	0				
	8	1	0	0	0				
#3	1			0	0	0	0		
	6			1	−1	0	0		
	7			0	0	0	0		
	8			0	0	0	0		
#4	1	0	0	0	0				
	6	2	1	−1	0				
	7	2-3	−1	−1	1				
	8	0	0	0	0				
#5	1	0	0	0	0				
	6	1	0	0	0				
	7								
	8	−1	0	0	0				
#6	1				0	0	0		
	6								
	7				0	0	0		
	8				0	0	0		
#7	1		1	−1	0	0			
	6		2	1	0	0			
	7		0	0	0	0			
	8		1	1	0	0			
#8	1		0	0	0	0			
	6								
	7	1	−1	+	0				
	8	−1	+	0	0				
#9	1								
	6				1	0	0		
	7				+	0	0		
	8								
#10	1			0	0	0	0		
	6			2	0	0	0		
	7			2	0	0	0		
	8			1	0	0	0		
#11	1			−1	0	0	0		
	6			1	+	0	0		
	7			1	0	0	0		
	8			1-2	−1	0	0		
#12	1	0	0	0	0				
	6	2	1	−1	0				
	7	−1	0	0	0				
	8	2	1	−1	0				
#13	1			0	0	0	0		
	6			2	−1	0	0		
	7			2	−1	+	0		
	8			2	1	0	0		
#14	1				1	0	0	0	0
	6					2	1-2	2	0
	7				1	2	2	1	0
	8					2	2	1	0
#15	1					0	0		
	6					0	0		
	7					1	0		
	8					+	0		
#16	1		0	0	0	0			
	6		1	2	0	0			
	7		1	1	−1	0			

TABLE VI-continued

Subject	Pretreatment: Composition of Example	Amount of Urushiol (micrograms) 1.25	0.5	0.25	0.1	0.05	0.025	0.01	0.005
	8		0	0	0	0			

It is believed that the long C_{18} chain of the urushiol molecule is absorbed through alkyl groups of the organophilic smectite clays. Additionally, it is felt that the phenyl group of the urushiol may have some affinity for the active su face of the clay platelet itself. The material is preferably applied in aerosol from onto the skin and clothes, prior to encountering the urushiol-producing plants, such as poison ivy, oak or sumac. The comparative study, however, has clearly shown that the organophilic smectite clays of this invention are more effective than any material heretofore known in the prevention of experimentally-induced poison oak or ivy dermatitis.

The invention having now been fully described, it should be understood that it may be embodied in other specific forms or variations without deparing from its spirit or essential characteristics. Accordingly, the embodiments described above are to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are intended to be embraced therein.

We claim:

1. A method of protecting the skin from contact with an allergen comprising applying to the skin of a subject in need thereof a barrier composition consisting essentially of

(1) from about 5% to about 15% by weight of a smectite clay having an ion exchange capacity of at least 50 milliequivalents per 100 grams, said clay having been ion exchanged with at least 50 milliequivalents per 100 grams of said clay of a quaternary ammonium compound having at least one alkyl group containing more than 10 carbon atoms, and

(2) from about 95% to about 85% by weight of a pharmaceutically acceptable non-toxic vehicle.

2. The method of claim 1 wherein said barrier composition further comprises a polar acuvator for said smectite clay in a proportion of from about 1% to about 4% by weight.

3. The method of claim 1 wherein said ion exchanged smectite clay is quaternium-18 bentonite.

4. The method of claim 1 wherein said ion exchanged smectite clay is quaternium-18 hectorite.

5. The method of claim 1 comprising the additional step of manually stroking the area of the skin to which said barrier composition has been applied, whereby platelets making up the structure of said clay are oriented to lie parallel with the surface of the skin.

6. The method of claim 1 wherein said barrier composition is applied by spraying.

7. The method of claim 1 wherein said barrier composition contains about 11.3% of said smectite clay.

8. A method of preventing contamination of clothes and utensils with an allergen comprising applying to said clothes and utensils a barrier composition consisting essentially of

(1) from about 5% to about 15% by weight of a smectite clay having an ion exchange capacity of at least 50 milliequivalents per 100 grams, said clay having been ion exchanged with at least 50 milliequivalents per 100 grams of said clay of a quaternary ammonium compound having at least one alkyl group containing more than 10 carbon atoms, and

(2) from about 95% to about 85% by weight of a pharmaceutically acceptable non-toxic vehicle.

9. The method of claim 8 wherein said barrier composition contains about 11.3% of said smectite clay.

* * * * *

PATENT CERTIFICATION

United Catalysts Inc
P.O. Box 32370
Louisville, KY 40232 USA
Telephone 502-634-7500
Business Office 502-634-7727 (Fax)
Technical Center 502-634-7720 (Fax

Patent Certification Statements

The following relate to statements required under the referenced codes.

Statement under 21 U.S.C. 355(b) (1)

U. S. Patent 4,861,584, issued August 29, 1989, to Thomas W. Powell, Jr. et al., assigned to United Catalysts, Inc., claims a method of using the active ingredient of the allergen blocking lotion for which the applicant is submitting this New Drug Application. U. S Patent 4,861,584 expires on August 29, 2006, barring an extension.

Statement under 21 U.S.C. 355 (b) (2)

Applicant believes that no certification under 21 U.S.C. 355(b) (2) is necessary because the investigations under 21 U.S.C. 355(b) (1) (a) which are relied upon by applicant for approval of this application were conducted by or for the applicant.

1214

United Catalysts Inc
P.O. Box 32370
Louisville, KY 40232 USA
Telephone 502-634-7500
Business Office 502-634-7727 (Fax)
Technical Center 502-634-7720 (Fax)

September 28, 1994

Food and Drug Administration
Center for Drug Evaluation and Research
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

NOTICE REGARDING ASSIGNMENT OF MARKETING EXCUSIVITY FOR
NDA 20-532 IVY-BLOCK™

Dear Colleague:

NDA 20-532 is for a product which includes an active ingredient not previously approved by FDA for drug use. This ingredient, quaternium-18 bentonite (Q18-B; proposed USAN - benquatamine) has been widely utilized in cosmetic preparations but has not previously been approved as an active drug ingredient.

In the present formulation Q18-B is an active drug ingredient which forms a barrier to protect skin against the allergenic oil produced by poison ivy and poison oak. Nine clinical studies, including well-controlled clinical studies, have been performed to support NDA approval of IVY-BLOCK and we therefore intend to request the agency assign a five (5) year marketing exclusivity to the file.

In the event additional information is needed at this time please contact me.

Sincerely,

Anthony A. Schulz
Manager Business Development

United Catalysts, Inc.

AAS/ts

Stat

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 31, 1995

From: Ralph Harkins, Ph.D., Group 7 Leader, SERB, Biometrics Division, HFD-713

Subject: NDA 20-532; Ivy Block

To: Joanne Holmes, HFD-540

Apparently I failed to give you a completed, final copy of the Ivy Block 45-day review. The finalized copy is attached for your files.

I had several problems with the Ivy Block submission. However, since it was a single indication submission, with very little data, these problems were not insurmountable. I talked to company people when I had problems. They were able to tell me what I needed to know. It was easier and faster to handle these problems this way than to have them send additional volumes, etc. Clearly, had this been a large or multi-indication NDA, it would not have been possible to handle the noted problems in this manner.

The problems noted in my 45-day review were mentioned during the filing meeting. However, I also noted that the submission was small, that I had already been in contact with the company and had settled my problems satisfactorily. There was nothing to include in your deficiency letter to them.

FEB 7 1995

Statistical Review and Evaluation

NDA#: 20-532

Applicant: United Catalysts, Inc.

Name of Drug: Ivy Block

Documents Reviewed: Volumes 1.10, 1.11 and 1/12 dated September 28, 1994

Indication: Skin Protectant against allergenic oil produced by poison oak and poison ivy when applied prior to exposure.

Medical Input: Dr. Phyllis Huene, HFD-540

A. INTRODUCTION

These trials were designed prior to our requirements for gender and age to be considered in the evaluation process. As a result one of the exclusion criteria was that any subject 65 years of age or greater, was excluded. Even though both males and females were enrolled, gender was not recorded in conjunction with the efficacy and safety data. As a result it is not possible to determine if there are potential differences in gender effects.

There currently is no product on the market for prevention of poison ivy/oak. This product, if shown to be safe and effective, would be of great benefit to those who make their living in environments infested with poison ivy and poison oak as well as to those who visit the woods for recreational purposes.

B. EVALUATION

B.1 EFFICACY

STUDY UDF 07/91

Study UDF 07/91 was a randomized, investigator blinded, paired site, four arm trial to compare effectiveness of Q-18B lotion to Q-18B aerosol and each to its respective vehicle. Forty-six subjects were randomized to treatment. Eight were dropped from analysis due to no response for any of the four treatments. The aerosol lotion was applied and a glass rod was used to spread it evenly over the randomly assigned area. Since it was not applied as an aerosol, these results may not extrapolate to the aerosolized product.

Reaction readings, on a 9 point scale (0 = no reaction, +/- = questionable reaction, and 7 = maximum reaction), were taken at day 2, 5 and 8 after application of formulations.

Hypotheses to be tested were: A) Is the Q-18B lotion equally effective to the aerosol? B) Does the lotion and aerosol each beat their vehicle? In addition, I was interested in whether there is any difference in duration in protection between the lotion and aerosol formulations.

In testing whether the two formulations are equivalent, I used two approaches. The first was to compare the number of "0" readings for all three days for each formulation and test if these are statistically different. This is a paired comparison.

In 70.5% of the readings the aerosol was a success compared to 86.4% of the lotion readings. This difference of 15.9% is statistically significant in favor of the lotion formulation. $p < .02$, 95% CI (-.28,-.06).

The second is to compare the mean response rate for the two formulations. The mean response rates for lotion and aerosol respectively at day 2 are 0.05 and 0.32, at day 5 they are 0.37 and 0.82 and at day 8 they are 0.62 and 0.98. All are statistically significant at the $p <= 0.05$ level. The lotion was superior to the aerosol formulation at day 2 and held this relative position for the duration of the trial. However, there is no statistically significance in duration of protection, i.e., the relative difference in response rates did not vary significantly between the two formulations over time.

Each of the formulations was statistically superior to its vehicle, $p < .0001$ and the two vehicles are not statistically different.

Although both men and women were enrolled, subject gender is not provided, therefore gender analysis is not possible. Similarly, subject age is not provided so no age comparisons can be made.

STUDY UDF 01/92

Study UDF 01/92 was a randomized, investigator blinded, matched pair, two arm trial to compare effectiveness of 5% Q-18B lotion to an untreated control site. One-hundred sixteen male and female subjects were randomized to treatment. Sixteen were dropped from analysis due to no response for either product, fifteen were non-evaluable due to administrative non-compliance (which is not explained) and one was dropped due to failure to comply with the protocol. Eighty-five were evaluable.

Reaction readings, on a 9 point scale (0 = no reaction, +/- = questionable reaction, and 7 = maximum reaction), were taken at day 2, 5 and 8 after application of formulations.

Hypotheses to be tested were: A) Is the 5% Q-18B lotion superior to the untreated control area? In addition, I was interested in whether there is any difference in duration in protection.

At day 2 the number of positive readings for 5% Q-18B and its control are respectively (22% and 77%), at day 5, (41% and 88%), and at day 8, (46% and 94%). The 5% Q-18B is statistically superior to its control at each time point, $P < .0001$ in each case.

Duration of protection was not as good in study 1/92 as it was in 7/91. In study 1/92 only 54% failed to develop a response compared to 86.4% of the lotion subjects in study 7/91.

Although both men and women were enrolled, subject gender is not provided, therefore gender analysis is not possible. Similarly, subject age is not provided so no age comparisons can be made.

STUDY 2/92

The protocol for study 2/92 is identical to that of 1/92. One-hundred ten subjects were enrolled. Thirty subjects failed to develop an allergic reaction on the control site, therefore were not included in the final evaluation. One subject was disqualified due to being over age 65. Since this is a matched pair design, I included the 30 dropped due to no reaction at either site in my analysis. The statistical evaluation shows the Q-18B to be statistically superior to its control, $p < .0001$ with the 95% CI on the difference in protection rates being (.56,.70).

Although 39 subjects were male and 67 were female, no analyses by gender were done because this information is not provided on a per subject basis.

STUDY 7/92

This was a field trial to demonstrate the effectiveness of Q-18B under actual field conditions. There are a number of problems with the design of this trial, such as, the time of the trial relative to activity of poison ivy/oak may not have been optimal, the enrollment practices are not explained, all subjects were followed for 10 days without any treatment then those left were treated and followed 10 more days and actual monitoring of participants in the study seems to have been somewhat lax.

A total of 40 male and female forest service personnel who were reactive to poison ivy/oak were enrolled. For the first ten days of the 20 day trial no protection was used. For the last ten all participants used Q-18B as often during the day as necessary to maintain an intact coating on exposed skin. Eight subjects dropped after the first ten days of the trial. During the first 10 days 26/40 (65%) subjects reported being exposed to poison ivy or oak and 9 (35%) developed poison-ivy/oak rash. During the second 10 day period 18/32 (56%) subjects reported being exposed to poison oak or ivy and 4 (22%) developed a poison ivy/oak rash. The p value comparing these groups, based on StatXact is greater than .05 and the 95% CI is (-.16, .41). This indicates the ivy block is not effective. A better comparison it that comparing the rate of reaction for those at risk, i.e., 9/40 versus 4/32. This also shows ivy block is non effective.

The two laboratory trials indicate about 15% of subjects who are reactive to poison ivy/oak will not develop it every time they are exposed. In this trial the sponsor lost 8 of 9 subjects who developed a reaction in the ten day non ivy block use period. As a result they have a less reactive population available for the ten day trial period when the ivy block is being used. This biases the results in favor of ivy block.
These data fail to statistically support the sponsors claim that ivy block provides protection against poison ivy/oak under actual field working and exposure conditions.

B.2 SAFETY

The adverse event data for all trials shows no serious safety problems. However, there were only 40 subjects exposed to ivy block on areas other than intact forearm skin. In the text of study 7/92 there is the note that one subject with acne withdrew due to exacerbation of his condition. Another with some type rash experienced some difficulty. If this product is to be used by subjects who do not have intact skin, then this needs to be further investigated. This could also be handled by proper labeling.

RECOMMENDATIONS

In the laboratory experiments, ivy block proved to be quite effective. The one field trial was poorly designed, undersized, inadequately monitored and conducted and inconclusive. It should not be used to deny approval of what may be a good product for the prevention of poison ivy/oak. However, I do not believe we can give it clear approval either. Therefore, I recommend that the company be required to do at least one adequate, well-controlled field trial in an effort to provide evidence of ivy block's effectiveness under actual field use conditions. This trial may be a Phase III or IV trial, depending on the Division's judgement.

If an additional trial is allowed, it should include, and identify, males and females, elderly and other age groups, and different racial groups in sufficient numbers to generate evidence relative to these factors as concerns safety as well as efficacy.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

The two experimental trials demonstrate that ivy block is effective in preventing development of poison ivy/oak under well controlled laboratory conditions. However, such conditions are not always indicative of the agent's effectiveness under actual field use conditions. The trial to demonstrate the safety and effectiveness of ivy block under actual field use conditions failed to demonstrate effectiveness. Unfortunately, this trial was improperly designed and inadequately monitored. Therefore, it's failure to demonstrate effectiveness may be due to the ivy block not being effective or simple due to inadequacies of the trial itself. One can not say.

There is some indication that use of ivy block on acne or otherwise non-intact skin may cause problems. Therefore, it is to be used only on healthy skin areas.

In view of the absence of any product that can be used prophylactically for poison ivy/oak, ivy block could be conditionally approved with the proviso that an adequate, well-controlled Phase IV field trial be conducted. A second option is to have them do an adequate, well-controlled Phase III trial to attempt to support their claims. Obviously, if this trial fails to support the safety and effectiveness claims, then the approval would be withdrawn or not given.

Ralph Harkins, Ph.D. 1/6/95

Ralph Harkins, Ph.D. Group Leader
Biomedical Statistician, Group 7

Concur: Dr. Satya D. Dubey 2-7-95

cc:
Orig. NDA-20-532
HFD-540
HFD-540/Dr. Wilkin
HFD-540/Dr. Chambers
HFD-540/Dr. Huene
HFD-540/Ms. Holmes
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-344/Dr. Lisook
Chron.
This review contains 5 pages.

Bio

MAY 2 1995

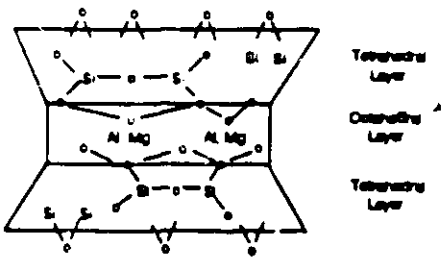
NDA: 20,532 **SUBMISSION DATE:** Oct. 26, 1994.
Quarternium-18 Bentonite, 5% lotion (Ivy Block)

United Catalysts, Inc. **REVIEWER:** Funmilayo O. Ajayi, Ph.D
P.O. Box 32370
Louisville, KY 40232 **TYPE OF SUBMISSION:** Original NDA **Code:** 2 P

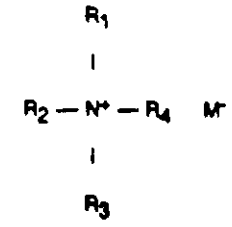
SYNOPSIS: The application is submitted for quarternium-18 bentonite which is being proposed for use as a protective barrier to reduce the risk of developing poison ivy/oak dermatitis. The sponsor is proposing topical application of the lotion at 4-hourly intervals until out of the risk zone. The sponsor did not carry out any formal systemic bioavailability or percutaneous penetration study. However, the sponsor-provided information from preclinical studies revealed little or no safety concerns.

BACKGROUND: Quarternium-18 bentonite (Q-18 B) is a chemically modified clay. The structural formula for Q-18 B is not known to be published, and has not been elucidated by the applicant. The general structural configuration for sodium bentonite and Q-18 B are represented below. Q-18 B has been used worldwide as a component of cosmetics for about 3 decades. The clay serves as a barrier to poison ivy and poison oak allergen thereby interfering with the development of poison ivy/oak dermatitis. An aerosol formulation was marketed briefly in 1985 to 1986. Ivy block is not currently marketed anywhere in the world. However, toxicological studies which include skin and eye irritation as well as dermal sensitization in animals have shown this compound to be safe as cosmetic agent up to 10%. The LD_{50} obtained following oral administration to animals is > 8g/Kg (the highest dose). No toxicity is expected from diisopropyl adipate and SD alcohol 40-2. Bentonite has been used, up to 5%, as a suspending agent in pharmaceutical formulation.

SODIUM BENTONITE



QUATERNIUM - 18



Where: R_1 and R_2 are methyl groups, R_3 and R_4 are hydrogenated tallow; M^- is typically a chloride anion

FORMULATION:

Composition	% Volume
Quarternium-18 Bentonite	5.0
Bentonite, NF	
S.D. Alcohol 40-2	
Diisopropyl adipate	
Benzyl alcohol, NF	
Methylparaben, NF	
Purified water, USP	

RECOMMENDATION: In view of the long time experience with this agent in cosmetics, the Division of Biopharmaceutics recommends that a waiver of the requirement to demonstrate systemic bioavailability be granted.

Fajayi 4/20/95
Funmilayo O. Ajayi, Ph.D
Pharmacokinetic Evaluation Branch

Biopharm Day (4/10/95): Ludden, M. Chen, Fleischer, Hepp, Ajayi.

FT initialed by Frank Pelsor, PharmD F. Pelsor

cc: NDA 20,532 HFD-540 (Clinical Division), HFD-426 (Fleischer), HFD-427 (M. Chen,Pelsor,Ajayi), Chron, Drug, FOI, Reviewer, HFD-540(Hsh)

Pharm/Tox

Review and Evaluation of Pharmacology and Toxicology Data
Division of Topical Drug Products, HFD-540

NDA#: 20,532

Date Submitted: 9/28/94
Date CDER Received: 9/30/94
Date Assigned: 10/14/94
Date Review Completed: 11/1/94
Date Accepted by Supervisor: 11/10/94

Sponsor:

United Catalysts Inc.
PO Box 32370
Louisville, KY 40232

Name of Drug: IVY-BLOCK 5% w/w
Generic Name: Benquatamine (name awaiting USAN approval)
Chemical Name: Quaternium-18 Bentonite

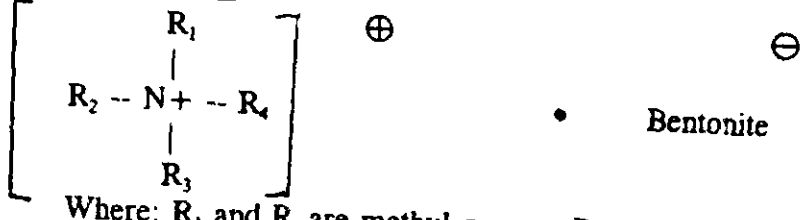
Pharmacological Category/Indication: Protective coating to prevent poison ivy/oak rash

Route of Administration: Topical dermal lotion

Recommended Dosage: Lotion is to be spread over areas at risk of exposure to poison ivy, oak, or sumac

Related IND: IND

Structural Formula:



Where: R_1 and R_2 are methyl groups, R_3 and R_4 are hydrogenated tallow

Formulation:

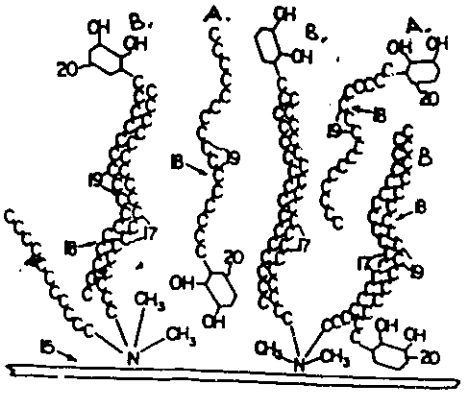
Ingredient	% w/w
Q-18 B	5.0
Purified Bentonite	
Methyl Paraben	
SD Alcohol 40-2	
Benzyl alcohol	
Diisopropyl Adipate	
Purified water	

Index of Preclinical Studies:

Acute Inhalation Study
Ocular/Mucosal Membrane Irritation Study
Sensitization Study
Subchronic Study

Introduction:

Poison ivy, oak, and sumac cause allergic contact dermatitis due to an oil, urushiol, which is contained in the leaves of the plant. On contact, urushiols pass through the skin and bind to proteins, which form allergens and elicit an immune response. IVY BLOCK is designed as a preventive coating made up of bentonite (clay) with Quaternium 18. The urushiol molecule in poison ivy has a long carbon chain (15-17 C long) that is thought to interact by Van-der-Waals forces with the fatty chains (alkyl groups) of the organophilic clay. Additionally, it is thought that the phenyl group of the urushiol may have some affinity for the active surface of the clay platelet. (See diagram below.) This product was marketed previously , but was withdrawn from the market when the FDA notified the manufacturer that the formulation was being manufactured as an unapproved, new drug requiring an NDA.



The figure portrays free urushiols (A) and urushiols bound to the product (B), IVY BLOCK. 15 = organo-treated clay, 17 = tallow "tails" of IVY BLOCK, 18 = urushiol, 19 = the 15-17 carbons of urushiol, 20 = the phenyl group of urushiol

Preclinical Studies

Several of the studies reviewed below are 10-35 years old and would likely not be acceptable under today's GLP standards. The studies are included for completeness.

Previously reviewed studies contained in the original IND are attached in Appendix A.

Acute Inhalation Toxicity

The study was performed by Ten rats (5/sex) were exposed to the test article for 1 hour (200 mg/L) Animals were observed at 1, 3, 6, and 24 hours, and then daily for 14 days total. One female died on study. The report stated that based on the results the test article is not toxic to rats by inhalation under conditions of the study. (According to the laboratory performing this study, a compound is considered an inhalation toxin if 50% or more animals die on study.)

Ocular/Mucous Membrane Toxicity

This study was performed by
The irritation of mucous membranes was evaluated. Bentonite and Bentone 34 (the reaction product of bentonite and dimethyl distearyl ammonium chloride; apparently the same or similar to 18-Q bentonite, although the sponsor does not state this clearly) were placed into the eyes of the same rabbits used above in the inhalation test in a 10% solution of Bentone 34 (test eyes) or bentonite (control eyes). Test eyes were completely negative; control eyes showed mild irritation of the conjunctiva which cleared by the second day.

Sensitization

This study was performed by
Bentone 34 was administered intracutaneously into 12 guinea pigs as a 0.1% suspension in physiological saline solution 3 times per week for a total of ten doses. The first dose was 0.05 ml; subsequent doses were 0.1 ml. After two weeks, 0.05 ml doses were again injected. The laboratory reported no hypersensitivity reactions, and that Bentone 34 is non-allergenic to guinea pigs.

Subchronic Toxicity

This study was performed by
Moistened Bentone 34 and bentonite (0.5 g) were placed on the depilated skin of 20 rabbits (10/group) for 90 days. Bentonite served as the control to Bentone 34. At the end of 90 days (65 exposures) blood hemoglobin and blood counts were made; livers, kidneys, and skin from the treated area were evaluated histopathologically following necropsy.

Two rabbits in the control group died, and there was an outbreak of diarrhea of all remaining rabbits in the third month of study. No skin irritation was noted. Blood values were comparable between groups except for a high proportion of eosinophils, which the report theorized was probably associated with diarrhea. In the histologic examination, most livers were found to have increased levels of glycogen storage, and focal collections of cells thought to be associated with a parasitic infection. Two rabbits in the Bentone 34 group had lesions in the kidney that were also thought to be associated with parasitic infection. Skin findings included some thinning, possibly associated with mechanical abrasion, and a few changes in the dermis. Overall, the histopathologist found no evidence of systemic or toxic reaction to the compounds.

Review by the American College of Toxicology

The American College of Toxicology (ACT) in its review entitled: Journal of the American College of Toxicology 1 (2), 71-83 (1982), *Final Report on the Safety Assessment of Quaternium-18 Hectorite and Quaternium-18 Bentonite*, indicated that Quaternium-18 is safe as a cosmetic ingredient. (A copy of the toxicology section is included in Appendix B.) Several of the studies in the article appear to be identical to studies submitted by the sponsor.

Acute Studies: Oral toxicity of Quaternium-18 (Q-18), as measured by LD50, was in excess of 0.5 to 10 g/kg in several reviewed studies (i.e. relatively non-toxic). Q-18 was negative as an irritant at low concentrations (5%), but positive at a 75% concentration. In another study, concentrations of 1.5-10% were found to be a mild irritant to the skin of rabbits in a 21-day study. Q-18 Bentonite at 0.5 g caused no reaction to rabbit skin after 5 days. In a guinea pig skin sensitization study, no reaction was noted. Eye irritation studies of Q-18 were negative at 5%, but in a study using a 4% concentration, slight temporary conjunctival irritation was noted.

Subchronic Studies: Q-18 given orally caused toxicity at 1 g/kg/day in guinea pigs after 12 days of treatment (exact findings not stated). Dogs and rats fed Q-18 up to 2800 ppm for 90 days had no abnormalities. Q-18 bentonite (1, 5, and 25%) was given to weanling rats revealed no toxicity except that reduced food efficiency at the highest dose.

Q-18 bentonite (0.5 g) applied to the abraded skin of 10 rabbits caused no local or systemic toxicity.

Summary and Evaluation

The sponsor has submitted a variety of studies in support of the NDA for a IVY BLOCK. The sponsor submitted evaluations of acute, subchronic, and inhalation toxicity potential in the original studies submitted for this NDA (i.e. not including the review material in the ACT article), or for the IND

In acute toxicity, no dermal toxicity was noted in rabbits at 0.5 g of Q-18 bentonite. Acute

oral toxicity as measured by LD50 was 5-8 g/kg in rats. Q-18 bentonite was negative in a guinea pig sensitization assay. Ocular studies indicated that the compound was a slight-to-moderate, but reversible, eye irritant.

In subchronic studies, moistened Bentone 34 and bentonite (0.5 g) was negative for toxicity when placed on the depilated skin of rabbits for 90 days. Weanling rats given 1-25% compound orally were not negatively affected by the compound.

According to the ACT article cited above, Q-18 bentonite is only a slight irritant that exhibits little or no systemic toxicity. The article also states that "There is no reported information concerning any of the Quaternium-18 compounds with respect to absorption, metabolism, storage, excretion, teratology, mutagenesis or carcinogenesis." Although such data would be helpful, it was not addressed when the original IND was reviewed in 1989, at least partly because the compound has a long history of use in cosmetics. In addition, given the charge of this molecule, uptake and resultant systemic effects are highly unlikely.

Recommendations:

Approval.

Hilary V. Sheevers, Ph.D.

Hilary V. Sheevers, Ph.D.

cc:
HFD-340
HFD-540
HFD-540/PHARM/HSHEEVERS
HFD-540/MO/HUENE
HFD-540/CHEM/DECAMP
HFD-540/PMS/HOLMES

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Concurrence Only:
HFD-540/DD/JWilkin 11/2/94
HFD-540/SPHARM/SALAM 11/14/94

APPENDIX B

1289

SECOND REPORT OF THE COSMETIC INGREDIENT REVIEW EXPERT PANEL

JOURNAL OF THE

AMERICAN COLLEGE OF TOXICOLOGY

SPECIAL ISSUE

results in an in vitro study which used skin from the abdomen of human infants; DDAC did not penetrate this material.[9]

The FDA has proposed that Bentonite clay be granted GRAS status as a direct food ingredient. Upon oral administration, very little (if any) Bentonite clay is absorbed. As much as 3% in the diet of experimental animals had no negative effects.[10]

Animal Toxicology

Acute Studies

Oral toxicity

Acute oral toxicity studies have been conducted on all three Quaternium compounds and on a variety of cosmetic formulations in which they appear.

Quaternium-18: A 5% aqueous dispersion of this ingredient was administered to male rats by intragastric intubation. Six rats each received 5 g/kg of the dispersion and four received 10 g/kg. No deaths occurred in either group. The LD50 of the dispersion was estimated to be in excess of 10 g/kg. The estimated LD50 of Quaternium-18 is somewhat greater than 0.5 g/kg, since the dispersion contained only a 5% concentration of this ingredient.[11]

In another study, a 4% aqueous dispersion was given orally in doses of 5, 10, and 20 ml/kg to groups of six rats. None of the rats died during the 14-day observation period that followed dosing. The LD50 was reported as greater than 20 ml/kg of the 4% dispersion, which allows the LD50 of the ingredient to be calculated as greater than 0.8 g/kg.[12]

A 75% aqueous suspension administered orally to rats at two dose levels (doses or number of rats were not specified) was described as having an LD50 of 7000 mg/kg. This reflects an oral LD50 of the ingredient of 5250 mg/kg.[13]

Doses varying from 1 g/kg to 10 g/kg of a 70% solution of Quaternium-18 in isopropanol were given orally to 98 rats. The doses below 5 g/kg were further diluted with isopropanol. The resultant LD50 was 6.35 g/kg. (This LD50 included the effect of the isopropanol, which was not tested separately).[14]

Quaternium-18 Hectorite: In an acute oral toxicity study, five groups of five rats each were given a 50% (w/v) aqueous suspension by gavage; the doses ranged from 1.25–20 g/kg. No deaths occurred during the 14-day observation period. The oral LD50 of the suspension is greater than 20 g/kg or greater than 10 g/kg of the ingredient.[15]

Products that include relatively small amounts of the ingredient were tested for oral toxicity. When an eyeshadow formulation containing 10 percent Quaternium-18 Hectorite was evaluated in rats, the product's LD50 was calculated to be greater than 5 g/kg.[16] Three personal cleanliness formulations were each given to 10 rats in 1 g/kg oral doses; for each formulation tested, the LD50's were greater than 1 g/kg.[17]

When a fingertip powder blusher (10% Quaternium-18 Hectorite) was administered orally to 10 rats via stomach intubation at a single dose of 25 g/kg, no mortalities resulted. The LD50 of the product was reported as greater than 25 g/kg.[18]

Quaternium-18 Bentonite: This ingredient was given orally, as a suspension in cottonseed oil in doses of 8 g/kg, to twenty rats. No deaths occurred in two weeks following dosing. The suspension was difficult to manipulate, so no higher doses were given. Available data indicate that the LD50 is greater than 8 g/kg.[19]

Skin irritation

Quaternium-18: An aqueous dispersion containing 3% of this ingredient was applied to one intact and one abraded area of the skin of each of six rabbits. To each area, 0.5 ml was applied and covered by a gauze patch which was removed after 24 hours; then the remaining dispersion was washed off. At 24 and 72 hours after application, the reaction was graded; no irritation was found.[111]

Tested with a similar procedure, a 4% aqueous dispersion gave comparable results.[112]

A more concentrated (75%) sample of the ingredient was tested according to the Draize method. The Primary Irritation Index (PII) was calculated to be 1.92 out of a possible maximum of 8. Examination of the scores showed that erythema had increased at the 72-hour observation period, indicating that there had been a delayed irritant reaction.[119]

Another commercial 75% aqueous dispersion of Quaternium-18 was studied at concentrations of 2%, 5% and 10%. The actual concentrations of the ingredient were 1.5, 3.7, and 7.5%. Patches containing 0.05 g of the suspensions were applied to the skin of rabbits and allowed to remain there for 21 days, after which the patches were removed and the irritation at the sites graded. The dispersion was determined to be a mild irritant at the concentrations used.[113] This same product was also tested at 10 percent to determine its ability to irritate mucosa: 0.2 ml of the commercial product was applied to the penile mucosa of rabbits. Grading of the irritation gave a score of 0.43 out of a possible maximum of 4, showing this product had a mild ability to irritate mucosa.[113]

Quaternium-18 Hectorite: A Federal Hazardous Substance Act skin irritation test was conducted with this compound, using a dose of 0.5 g of a 50% suspension in water on each of six rabbits. When it came in contact with intact or abraded skin, this material did not produce any irritation.[118]

Quaternium-18 Bentonite: The undiluted ingredient was applied in quantities of 0.5 g to both intact and abraded rabbit skin. After contact was maintained for six hours per day for five consecutive days, there were 10 days of rest and then five more days of exposure. No reaction was found, and the test material was considered to be inert.[124]

Skin sensitization

Quaternium-18 Bentonite: The ability of this ingredient to produce allergic reaction on the skin of guinea pigs was studied by intracutaneous injection. Twelve guinea pigs were given an initial injection of 0.05 ml of the test sample (0.1% in physiological saline). Then, three additional injections of 0.1 ml were made each week for the next three weeks, after which there was a two-week rest period. At the end of this time, challenge doses of 0.05 ml were injected. Increased reaction to the challenge dose over the induction dose would have indicated a sensitization. However, the challenge doses gave less reaction than the induction dose, indicating no sensitization.[114]

Eye irritation

Quaternium-18: One-tenth of a milliliter of a 5% aqueous dispersion of this ingredient was instilled in one eye, the other remaining untreated as a control; six rabbits were used. Cornea, iris and conjunctiva were all found free of irritation during the 72-hour observation period.[111]

A 4% dispersion of the ingredient was tested by the same procedure. No cor-

neal or iridial irritation occurred, but some conjunctival irritation, which disappeared with time, was reported.[12]

A product containing a 75% suspension of the ingredient was also tested in the rabbit eye. The product was diluted to 10% (making the test material a 7.5% dispersion), and 0.1 ml of this was placed in the conjunctival sac. Readings were made at 24 and 48 hours after instillation. The eye irritation score was reported to be 11.7 out of a possible 110, making the 7.5% dispersion a minimal irritant.[13]

Quaternium-18 Hectorite: A rabbit eye irritation test was performed according to the Draize method with 0.1 ml of a 50% aqueous suspension; no irritation was produced.[15]

Quaternium-18 Bentonite: Instillation of 0.1 ml of a 10% suspension in physiological saline was made into one eye of each of 10 rabbits. Twenty-four hours after instillation, the "test eyes" were completely negative for irritation.[14]

Acute inhalation toxicity

Quaternium-18 Hectorite: An inhalation toxicity study evaluated a one-hour exposure of 10 rats to a mist containing the ingredient. Quaternium-18 Hectorite was mixed with isopropyl myristate to facilitate spraying (concentration not stated). One hundred forty-three grams of the mixture were atomized in the one-hour period; the nominal concentration was calculated to be 202 mg/l. In the 14 days following exposure, no toxic manifestations were noted and no deaths occurred.[11]

Subchronic Studies

Oral toxicity

Quaternium-18: This material was fed at varying concentrations to guinea pigs for 12 days. Uniform doses of 10 ml/kg were administered daily to two animals at each concentration. The lowest dose level that produced signs of toxicity appeared to be 1 g/kg/day.[12] Quaternium-18 was also fed to dogs and rats at subacute dietary levels of 2800 ppm for 90 days. No abnormalities were found in food consumption, body weight, reaction, mortality, or urinalysis, or in hematologic, blood chemistry, gross pathologic, or histopathologic studies.[13]

Quaternium-18 Bentonite: Groups of 12 weanling rats were fed diets containing 1%, 5%, or 25% of the ingredient for 12 weeks. Two similar groups were fed the basic diet and served as controls. The gain in weight per unit of diet consumed was practically the same for groups consuming up to 5%, while a reduction of food efficiency occurred in the 25% group. At the end of 12 weeks, hematology, organ weights, gross pathology, and micropathology were essentially the same in all groups, and there was no indication that any subchronic oral toxicity was produced by the ingredient.[14]

Dermal toxicity

Quaternium-18 Hectorite: Aqueous suspensions containing 50%, 25%, 12.5%, or 0.0% of this ingredient in quantities of 4 g/kg were applied to the exposed skin of rabbits three times a day, five days per week for three weeks. Each application, spread over at least 20% of the body surface, was allowed to remain on the skin for two hours, after which the remaining material was washed off, the skin dried, and the next dose applied. Six rabbits were used for each concentration, three with intact skin and three with the skin abraded. During the study,

general health, appetite, and activity did not differ among the groups. Weight gain, hematological elements, and gross and micropathology were similar in all groups. Some animals, including controls, had inflammatory lesions in the heart, brain, liver, kidney, and lung. These were attributed not to the test materials, but to protozoan infection, which was reported to be common in rabbits obtained from commercial suppliers. The local effects on the skin consisted of mild drying and scaling of the upper layers in the early days of the study. Continued exposure did not produce involvement of the deeper layers.[18]

Quaternium-18 Bentonite: Ten rabbits were depilated (15 × 18 cm) on their dorsa and exposed under occlusion to 0.5 g of Quaternium-18 Bentonite for six hours per day for 90 days. Ten control animals were also used. Exposure sites were scored for irritation according to the Draize criteria at the end of such exposure and at the beginning of the next. Hematological and gross pathological findings were normal for both groups. Micropathology revealed minor liver and kidney abnormalities in both experimental and control groups; chronic protozoan infection was implicated. No evidence of local or systemic toxicity of Quaternium-18 Bentonite was found.[30]

Clinical Assessment of Safety

Skin Irritation and Sensitization

Quaternium-18

This ingredient was investigated for its skin irritating and sensitizing characteristics on 25 men and 25 women (Caucasian) varying in age from 18 to 35. The repeated insult, occluded patch test was employed. Patches (1.5 in^2) were saturated with sample (7.5%, unspecified diluent) and applied for 24 hours to the volar aspect of the arm; 24 hours elapsed between each scoring and application, which totalled 15 per person. Ten days after the last induction exposure, a 24-hour challenge application of sample was made to each subject. The results and accompanying analysis can be found in Table 2. Six out of the 50 subjects reacted 13 times to the 750 induction exposures. Only two of the 13 reactions were level-2 reactions. Two of the 50 subjects reacted to the challenge exposure; there were no other reactors. The mean primary skin irritation index (PSI) for all test subjects was calculated to be 0.26 out of a maximum of 8. The

TABLE 2. Repeated Insult and Skin Sensitization Human Studies—Quaternium-18.[a]

		No. of subjects	No. of applications	Intensity of reactions				
				4	3	2	1	0
Primary Skin Irritation	Male	25	375	0	0	2	7	366
	Female	25	375	0	0	0	2	373
	Total	50	750	0	0	2	9	739
Skin Sensitization	Male	25	25	0	0	1	0	24
	Female	25	25	0	0	1	0	24
	Total	50	50	0	0	2	0	48

[a]Data from Ref. 43.

CONCLUSION

On the basis of the available information presented in this report, the Expert Panel concludes that Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite are safe as cosmetic ingredients in the present practices of use and concentration.

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*Available upon request: Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Ave., N.W., Washington, DC 20005

Chem

DIVISION OF TOPICAL DRUG PRODUCTS HFD-540
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-532 with user fees due date 9.29.95.

REVIEW # 2

DATE REVIEWED: 9.25.95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	8.10.95	8.11.95	

NAME & ADDRESS OF APPLICANT:
United Catalysts Inc
1227 South 12th Street
Louisville, KY 40210
Tel 502-634-7531
Mr. Anthony A. Schultz.

DRUG PRODUCT NAME
Proprietary: IVY BLOCK
Established: BENTOQUATAM (USAN - 12.28.1994); Quaternium-18 Bentonite (CTFA); Q-18B; Organoclay generic name; Tixogel VP (applicants cosmetic use ingredient).
Code Name/#: CAS# 1340-69-8 (USAN); and CAS# 68911-87-5 (Tixogel VP).
Chem.Type/Ther.Class: 1P

PHARMACOL. CATEGORY: Barrier for the prevention of allergic contact dermatitis; Poison ivy and poison oak skin protectant.

DOSAGE FORM: Lotion
STRENGTHS: 5% Q-18B w/w
ROUTE OF ADMINISTRATION: Topical
DISPENSED: 4 oz white HDPE bottle

___ Rx _X_ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
Quaternium-18 Bentonite.
See enclosed structural formula adopted by USAN.

REMARKS:

Amendment dated 8.10.95 was a 7 page response to FDA 483 report of 7.27.95. The following issues were raised in 483:

characterization of impurities in quaternium-18 bentonite, calibration of FTIR instrument, documented investigation of failed batches (lots Q1000 and Q1002), second review of the batch records, review and approval of starting raw material (Bentonite lot 59365 dated 7.5.94), x-ray spectral approval procedure for 12 bentonite lots prior to the addition of quaternium, lack of a SOP to periodically verify suppliers COA, missing COA for bentonite lot 59365, acid wash cleaning procedure for the equipment, centrifuge

feed tank log disagreement between SOP and actual practice.

CONCLUSIONS & RECOMMENDATIONS:

I recommend to concur with the judgement of the FDA Cincinnati District. Field had concluded that the submitted response was acceptable. EER was signed as acceptable by Ms. Ferguson dated 9.7.95.

cc:
Orig. NDA 20-532
HFD-540/Division File
HFD-007/PMaturu
HFD-540/WDeCamp, JHolmes

filename: N20532.795

P. Maturu
P.Maturu, Primary Review Chemist

Wilson A. DeCamp, Ph.D. 9/27/95
W.DeCamp, Supervisory Review Chemist

NAI 9/29/25/95

ENCLOSURES (6):

1. X-ray diffraction peak comparison for quaternium-18 bentonite lots Q1000, Q1002, etc.
2. FTIR spectrums for quaternium-18 bentonite lots Q1000 and Q1002.
3. X-ray fluorescence elemental analysis for quaternium-18 bentonite lots Q1000, Q1002, etc.
4. X-ray fluorescence elemental analysis of quaternium-18 bentonite lot 59365.
5. Calibration of FTIR by ASTM method E 1421-91.
6. Acceptable EER dated 9.7.95.

X-Ray Diffraction Peak Comparison Table
Quaternium-18 Bentonite Samples
July 1994 Production Run

Sample Identification

Q1000	Q1001	Q1002	Q1003	Q1004	Q1005
3.354	3.329	3.346	3.354	3.329	3.354
4.048	3.614	3.623	3.633	3.643	3.623
4.267	4.024	4.036	4.048	4.036	4.048
4.481	4.451	4.481	4.481	4.466	4.496
12.461	12.461	12.580	12.824	12.461	12.701
29.356	25.402	26.418	26.418	25.900	26.418

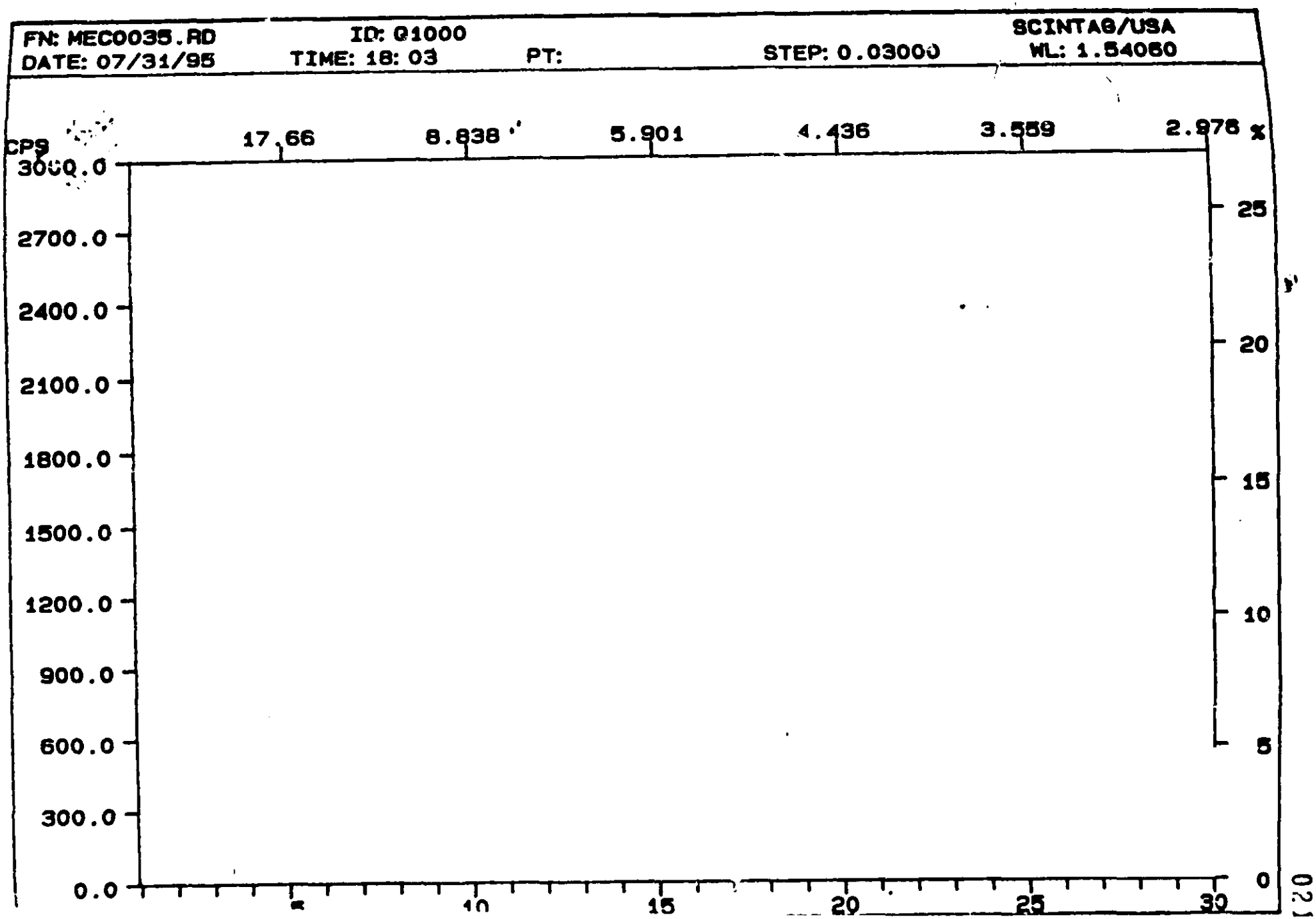
The shaded areas represent d-spacings that vary as a function of the quaternium-18 amine treatment. This effect results from amine intercalation that effectively increases the spacing between the bentonite (montmorillonite) platelets.

XRD REFERENCE DATA - RAW BENTONITE (MONTMORILLONITE) and Q-18 B PRIMARY D-Spacings

PEAK - ANGSTROMS	IDENTITY
15.250	MONTMORILLONITE
~25-29.5	" (Expanded by Quat)
~12-13	"
4.496	"
4.265	QUARTZ
4.049	CRISTOBOLITE (OPALINE)
3.764	CLINOPTOLITE
3.350	QUARTZ
3.182	FELDSPAR
3.025	CALCITE

Note:

These data represent internally-developed control values supported by extensive studies.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DATE: 07/31/95
ID: Q1000
TIME: 18: 03
PT:
STEP: 0.03000
SCINTAG/USA
WL: 1.54060
CPS
17.66
8.838
5.901
4.436
3.559
2.976
3000.0
2700.0
2400.0
2100.0
1800.0
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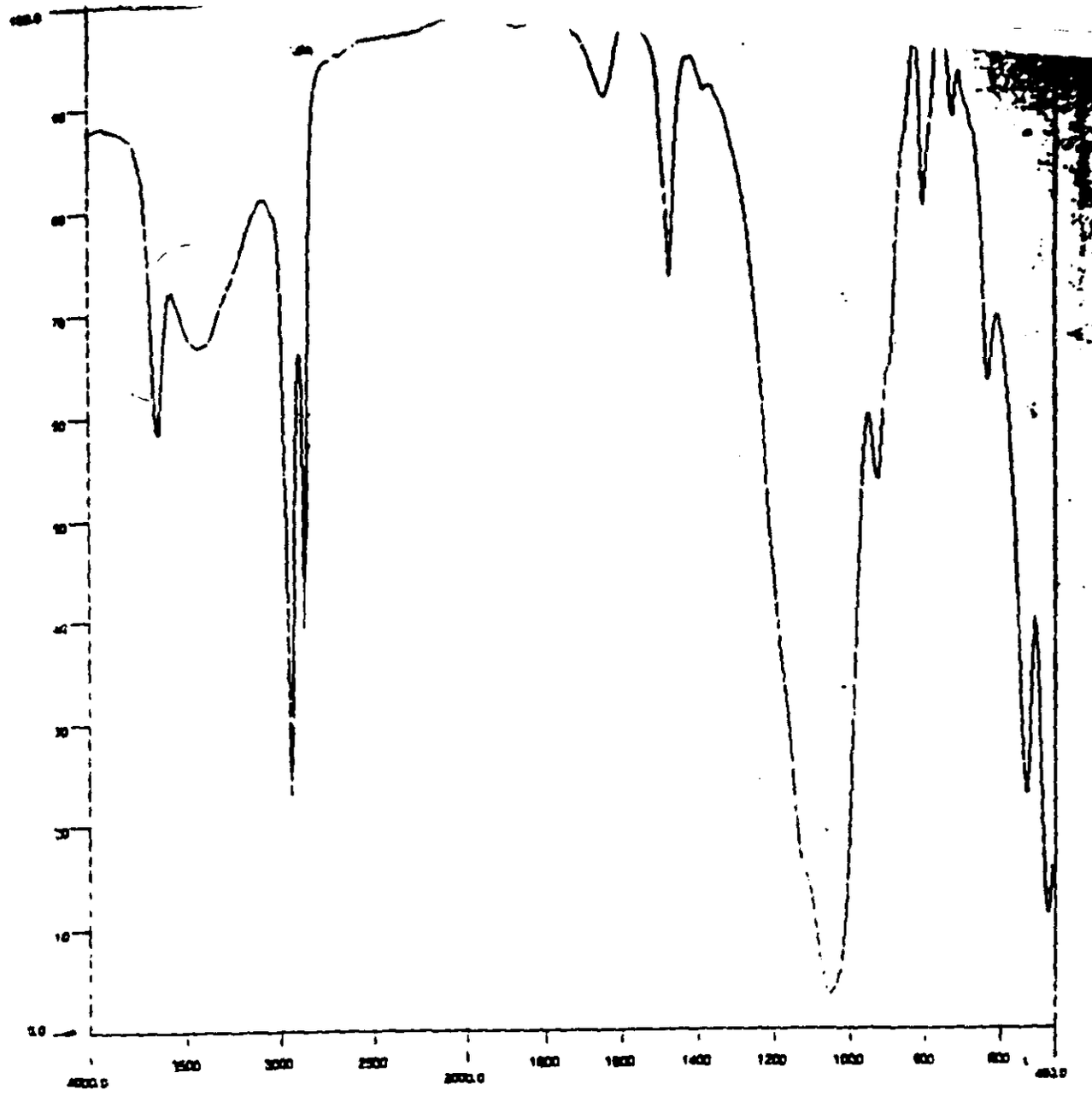


Lot #

Sample - Q1000

6/1/9

AF

PE 1700 Filename: Q1000RX.SP Date: 94/07/27 Time: 07:18:44.00

Scans: 16 Resolution: 4.00 Comment: KBR 7/27/94 NORMALIS

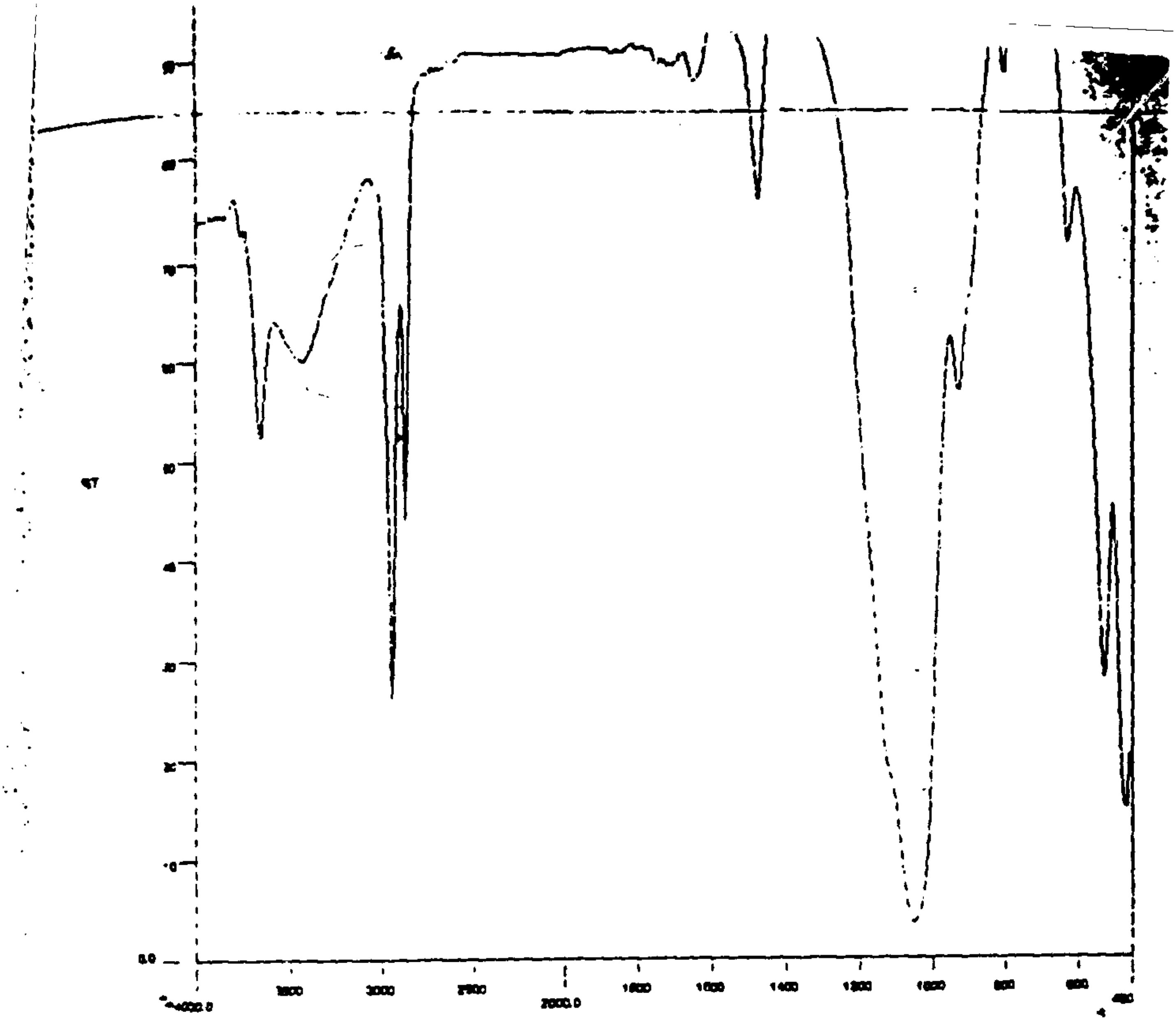
Sample: IVY BLOCK @Q1000 REPEAT KBR PELLET

Filename: Q1000RI.SP	Date: 94/07/27	Time: 07:18:44.00
Points: 3551	Ordinate: %T	Abscissa: CM-1
Start: 4000.00	End: 450.00	Interval: -1.00
Minimum: 3.343	Maximum: 98.859	Scans: 16
Data Flags: N F4 S	Operator: KIN 7/27/94 NORMALIS	

Sample: IVY BLOCK @Q1000 REPEAT KBR PELLET

Model: Perkin-Elmer 1700

Source: OPPERMAN	Detector: TGS	Beamsplitter: KBr
Resolution: 4.00 cm-1	Apodization: Normal	J. Step: 2 ea
[illegible]	[illegible]	[illegible]



Sample = Lot # Q1002

8/1
A

PE 1760 Filename: Q1002X.SP Date: 94/07/19 Time: 06:55:55.00

Scans: 16 Resolution: 4.00 Operator: KIM 7/20/94 re-norml

Sample: IVY BLOCK #Q1002 (7/94) KBR PELLET

Filename: Q1002Z.SP	Date: 94/07/19	Time: 06:55:55.00
Points: 3551	Ordinate: %T	Abscissa: CM-1
Start: 4000.00	End: 450.00	Interval: -1.00
Minimum: 3.472	Maximum: 99.872	Scans: 16
Data Flags: F4	Operator: KIM 7/20/94 re-norml	

Sample: IVY BLOCK #Q1002 (7/94) KBR PELLET

Model: Perkin-Elmer 1760

Source: OFFERMAN	Detector: TGS	Beamsplitter: KBr
Resolution: 4.00 cm-1	Apodization: Normal	J. Stop: 2 mm
Gain: 1	OPD velocity: 0.20 cm/s	Zero-crossing: 3
Spectrum Type: Real	Scan Type: Ratio	Ratioed Against:

X-Ray Fluorescence Analytical Results
Quaternium-18 Bentonite Production Run
July 1995

	Sample Designation					
Element	Q1000	Q1001	Q1002	Q1003	Q1004	Q1005
Mg	1.0 %	1.2 %	1.0%	1.2 %	1.2 %	1.2%
Al	10	10	10	10	10	10
Si	33	32	32	33	32	31
P	0.24	0.25	0.24	0.21	0.23	0.28
S	0.07	0.06	0.06	0.05	0.05	ND
Cl	0.[illegible]	0.61	0.50	0.43	0.47	0.47
K	0.09	0.06	0.05	0.04	0.04	0.04
Ca	0.80	0.65	0.63	0.60	0.72	0.70
Ti	0.10	0.12	0.12	0.11	0.13	0.11
Fe	4.6	5.0	5.5	4.7	5.3	5.4
Ni	0.03	0.03	0.02	0.02	0.02	0.03
Cu	ND	ND	ND	ND	ND	ND
Zn	0.02	0.02	0.03	0.03	0.04	0.03
Ga	ND	ND	ND	ND	ND	0.02
Sr	0.04	0.05	0.04	0.03	0.05	0.04
Y	ND	0.02	0.03	0.02	0.02	ND
Zr	0.06	0.08	0.09	0.07	0.09	0.07
Nb	ND	ND	ND	0.02	ND	ND
Ba	0.06	ND	ND	ND	ND	ND

X-Ray Fluorescence Analytical Results
Quaternium-18 Bentonite Production Run
July 1995

Sample Designation

Element	Raw Bentonite Silo	Raw Bentonite Lot# 59365
Mg	1.0 %	1.2 %
Al	10	10
Si	33	32
P	0.24	0.25
S	0.07	0.06
Cl	0.59	0.61
K	0.09	0.06
Ca	0.80	0.65
Ti	0.10	0.12
Fe	4.6	5.0
Ni	0.03	0.03
Cu	ND	ND
Zn	0.02	0.02
Ga	ND	ND
Sr	0.04	0.05
Y	ND	0.02
Zr	0.06	0.08
Nb	ND	ND
Ba	0.06	ND

Designation: E 1421 – 91

AMERICAN SOCIETY FOR TESTING AND MATERIALS
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Standard Practice for Describing and Measuring Performance of Fourier Transform Infrared (FT-IR) Spectrometers: Level Zero and Level One Tests[1]

This standard is issued under the fixed designation E 1421 ; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This practice describes two levels of tests to measure the performance of Fourier transform infrared (FT-IR) spectrometers.

2. Referenced Documents

2.1 *ASTM Standards:*

E 131 Definitions of Terms and Symbols Relating to Molecular Spectroscopy[2]

E 168 Practices for General Techniques of Infrared Quantitative Analysis[2]

E 334 Practices for General Techniques of Infrared Microanalysis[2]

E 932 Practice for Describing and Measuring Performance of Dispersive Infrared Spectrophotometers[2]

E 1252 Practice for General Techniques for Qualitative Infrared Analysis[2]

3. Terminology

3.1 For definitions of terms used in this practice, refer to Definitions E 131. All identifications of spectral regions and absorption band positions are given in wavenumbers (cm^{-1}). and spectral energy, transmittance, and absorbance are signified in equations by the letters E, T and A respectively. A subscripted number signifies a spectral position in wavenumbers (for example, A_{3082}, the absorbance at 3082 cm^{-1}).

4. Significance and Use

4.1 This practice permits an analyst to compare the general performance of an instrument on any given day with the prior performance of an instrument. This practice is not necessarily meant for comparison of different instruments with each other.

5. Test Conditions

5.1 *Operating Conditions*—In obtaining spectrophotometric data, the analyst must select the proper instrumental operating conditions in order to realize satisfactory instrument performance. Operating conditions for individual instruments are best obtained from the manufacturer's literature because of variations with instrument design. It should be noted that many FT-IR instruments are designed to w best when left o.. or in the standby mode. A record should kept to document the operating conditions selected so t they can be duplicated. Note that spectrometers are to tested only within their respective wavenumber ranges.

5.2 Instrumental characteristics can influence these m surements in several ways. Vignetting of the beam redu the transmittance value measured in nonabsorbing regi and on most instruments can change the appa wavenumber scale by a small amount, usually less than cm^{-1}. Focus changes can also change transmittance val so the sample should be positioned in approximately same location in the sample compartment each time. angle of acceptance (established by the f number) of optics between the sample and detector significantly af apparent transmittance. Heating of the sample by the b or by the higher temperatures which exist inside s spectrometers changes absorbances somewhat, and changes band ratios and locations slightly. Allow the sa to come to thermal equilibrium before measurement.

5.3 The recommended sample of matte-finish polyst used for these tests is approximately 38 μm (1.5 mils) film mounted on a card. The sample is mounted in a 2. (1 in.) circular aperture centered within the 5 cm (2. with of the card, and centered 3.8 cm (1.5 in.) from bo.om of the card. The card should be approximately cm (0.1 in.) thick, and individually and unambigu identified. Very small beam diameters can defeat the ference fringe suppression provided by the matte finis the sample.

6. Level Zero Tests

6.1 *Nature of Tests*—Routine checks of instrumen formance, these tests can be performed in a few mi They are designed to uncover malfunctions or other ch in instrument operation but not to specifically diagn quantitatively assess any malfunction. For Level Zero t resolution of four cm^{-1} and a nominal measurement t 30 s should be used. The exact measurement time, with the date, time, sample identification, number of and operator's name, should always be recorded.

6.2 *Philosophy*—The philosophy of the tests is previously stored test results as bases for comparison visual display screen or plotter to overlay the curr results with the known, good results. If the old a results agree, they are simply reported as *no change* Zero consists of three tests. Run the tests under th

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[1] This practice is under the jurisdiction of ASTM Committee E-13 on Molecular Spectroscopy and is the direct responsibility of Subcommittee E 13.03 on Infrared Spectroscopy.

Current edition approved June 15, 1991. Published August 1991.

[2] *Annual Book of ASTM Standards*, Vol 14.01.

conditions that you would normally use to run a sample (e.g. purge time, warm-up time, detector, etc.).

6.3 *Variations in Operating Procedure for Different Instruments*—Most of the existing FT-IR instruments should be able to use the tests in this procedure without modification. However, a few instruments may not be able to perform the tests exactly as they are written. In these cases, it should be possible to obtain the same final data using a slightly different procedure. The FT-IR manufacturer should be consulted for appropriate alternate procedures.

6.4 *Sample*—The recommended sample is described in 5.1. It is a matte-finish polystyrene film (approximately 38 μm thick, in a 2.5 cm aperture). The same sample should be used for all comparisons (note serial number).

6.5 *Reference Spectra*—Two spectra acquired and stored during the last *major* instrument calibration are used as references. These spectra will be identified as Reference 1 and Reference 2.

6.5.1 Reference 1 is a Fourier-transformed single-beam energy spectrum of an empty beam. (In this and all later usage, *empty beam* means that *nothing* is in the sample path except air or the purge gas normally present within the spectrometer sample compartment).

6.5.2 Reference 2 is a transmittance spectrum of the polystyrene sample.

6.6 *Reproducible Procedures*—Care should be taken that each of the following measurements is made in a consistent and reproducible manner, including sample orientation (although, different spectral measurements do not necessarily use the identical procedure). In particular, for those instruments having more than one sample beam or path in the main sample compartment, all of the test spectra always should be measured using the same path.

6.7 *Measurements*—Three test spectra will be acquired and stored. The test spectra will be identified hereafter as Spectrum 1, Spectrum 2, and Spectrum 3.

6.7.1 *Spectrum 1*—An empty-beam spectrum stored as a Fourier-transformed single-beam energy spectrum (or as an interferogram). If stored as an interferogram, it must be transformed before use in the ensuing tests.

6.7.2 *Spectrum 2*—An empty-beam spectrum taken immediately after Spectrum 1. This spectrum should be stored as either a Fourier-transformed single-beam energy spectrum or as a transmittance spectrum ratioed against Spectrum 1.

6.7.3 *Spectrum 3*—A spectrum of the polystyrene sample obtained reasonably soon after Spectrum 2. This spectrum should be stored as a transmittance spectrum ratioed against either Spectrum 1 or Spectrum 2, or as a single-beam energy spectrum. To reproducibly insert the sample, the serial number (or other identifying information) should be right side up facing the instrument detector.

7. Level Zero Test Procedures

7.1 *Energy Spectrum Test*—Overlay Spectrum 1 and Reference 1. Note any changes in energy level across the spectrum. Ratio Spectrum 1 to Reference 1. Video display resolution may limit the accuracy to which this test can be interpreted if the comparison is made on-screen. In addition, if the interferograph was saved, it may be displayed or plotted and the center burst height recorded. Use caution in interpreting this because minor changes in interferogram height only affect performance at high wavenumbers, and do not necessarily affect photometric performance.

7.1.1 *Reportage*—Report by (1) making an overlay plot of Spectrum 1 and Reference 1, (2) plotting the transmittance spectrum of Spectrum 1 ratioed against Reference 1 over the range of 95 % to 105 % *T*, and by reporting the following energy ratios:

$$R_{\text{cutoff/max}} = E_{\text{cutoff}}/E_{\text{max}}$$
$$R_{\text{noise/max}} = E_{\text{noise}}/E_{\text{max}}$$

If possible, report the ratio between the apparent energy in the wavenumber region below the instrument cutoff and the energy in the maximum-energy region of the spectrum, for example:

$$R_{\text{cutoff/max}} = E_{\sim 10}/E_{\text{max}}$$

Report the date and time of both spectra used, and the actual numbers of scans and measurement times.

7.1.2 *Interpretation*—An overall drop in the energy level in which the largest percentage of change occurs at higher wavenumbers usually indicates interferometer misalignment or a reduction in source temperature. If the instrument has been exposed to high humidity, this drop in energy level may reflect beamsplitter or window fogging. An overall drop in the energy level without wavenumber dependence suggests beam obstruction or misalignment of noninterferometer optical components. The appearance of bands or other features indicates purge gas contributions, beam obstruction by a partially transmitting object, oil or smoke deposition on mirrors or windows, or a forgotten sample in the beam. With cooled detectors, the appearance of a band around 3440 cm^{-1} indicates ice deposition on the detector surface. Nonzero energy levels below the detector cut-off (more than 0.2 % of the maximum energy level in the single beam spectrum) indicate system nonlinearities or detector saturation. On many instruments anomalous increases in the actual measurement time for a set number of scans indicate instrument problems (mis-triggering, white light misalignment, excessive purge rate, or interferometer drive problems).

7.2 *One Hundred Percent Line Test*—Ratio Spectrum 2 to Spectrum 1. Note the noise level and any variations from 100 % transmittance across the spectrum.

7.2.1 *Reportage*—Make an overlay plot of Spectra 1 and 2. Then ratio the two and plot the 100 % transmittance line. The ordinate range should be 99 % to 101 % *T*. If the noise or baseline drift exceeds these bounds, make plot from 90 % to 110 % *T* and consider performing Level One tests. Report the RMS (preferred) or peak-to-peak noise levels at over a 100 cm^{-1} range centered at 4000, 2000, 1000, and 500 cm^{-1}. If the instrument wavenumber range does not include some of these, substitute the nearest measurable frequency.

7.2.2 *Interpretation*—Excessive noise may result from misalignment or source malfunction (refer to the energy spectrum test) or from a malfunction in the detector or the electronics. Repetitive noise patterns (for example, spikes or sinusoids) sometimes indicate digital problems. Isolated noise spikes may be digital malfunctions or they can indicate electromagnetic interference. Positive or negative bands often indicate a rapid change in purge quality. Simultaneously positive and negative sharp bands in the water region may indicate instrumental problems or excessive water vap-

the spectrometer. Deviations from the 100 % level usually at the higher wavenumbers) indicate interferometer misalignment, or source instability.[3] *Refer* to Tomas Hirschfeld's chapter in "FT-IR: Application to Chemical Systems," Vol. 1, Academic Press.

8.3.3 *Polystyrene Test*—Ratio Spectrum 3 to Spectrum 2 (or 1) to produce a polystyrene transmittance spectrum. Subtract the stored polystyrene transmittance spectrum from this new polystyrene transmittance spectrum. Note any changes. Subtracting transmittance spectra from each other is not appropriate for most chemical applications, but here it is relevant to the instrument's performance, and avoids possible overrange problems associated with zero or *negative* transmittance.

8.3.3.1 *Reportage*—Plot the polystyrene transmittance spectrum over the range 0 % *T* to 100 % *T*. Plot the subtraction result over a range of −1 % to +1 % *T*.

8.3.3.2 *Interpretation*—Sharp features in the water vapor absorption regions (2 irregular groups of lines ca. 3600 cm^{-1} and ca. 1600 cm^{-1}) indicate excessive water vapor levels in the spectrometer or instrumental problems unless all such features point in the same direction. All band features pointing in the same direction indicates a change in purge level. A similar interpretation can be obtained from artifacts in carbon dioxide absorption regions (doublet near 2360 cm^{-1} and sharp spike near 667 cm^{-1}). Instrumental problems may include JacQuinot vignetting, source optics or laser misalignment, or interferometer scan problems. In the subtraction spectrum, first-derivative-like bandshapes that correspond to absorption band positions indicate these instrumental problems. Artifacts appearing only at the positions of the strongest (completely absorbing) bands may indicate phasing or other problems associated with detector non-linearity. Artifacts at both medium and strong band positions indicate analog electronic, ADC, or computer problems, or sampling jitter (Zachor-Aaronsen distortion).

8. Level One Tests

8.1 *Nature of Test*—A series of tests, which uses only the standard matte-finish polystyrene, designed to more completely test the instrument performance. The main purpose of Level One tests is to compare performance with previous results obtained on the same instrument. The tests can also be used to compare two instruments of the same model type and, with considerable caution, to roughly compare different models.

8.2 *Philosophy*—Level One tests are similar to, but more extensive than Level Zero tests. The reportage for Level One tests is designed to facilitate diagnosis instead of just indicating [illegible] such that interpretation is beyond the scope of this document.

8.3 *Sample*—The same matte-finish polystyrene sample described in 6.3 is used for measurements. In well-purged or evacuated spectrometers, the introduction of a water vapor or carbon dioxide sample (diluted with nitrogen or air to atmospheric pressure) may be necessary for some tests.

8.4 *Measurements*—In Level One, each test requires its own measurement. For comparisons involving a single instrument or model of instrument, choose any convenient measurement parameters, preferably those which reflect the operating parameters used for measurements of analytical samples. The parameters must always be the same for comparisons. On most instruments, use the stored parameter file for the original measurements as a way to get parameter consistency. If inter-instrument comparisons are attempted, several factors must be strictly adhered to before any valid comparison can be made. These factors concern the instrument lineshape function (ILS), which is the detailed way of expressing resolution. Peak positions and photometer data must be reported at the highest possible resolution. They are useful for inter-instrument comparison only to the extent that one of the instruments being compared is producing essentially undistorted (that is, Coblentz Class I) spectra.

9. Level One Test Procedures

9.1 *Energy Spectrum Test*—For an energy spectrum, obtain a single beam spectrum. The beam path in the sample compartment must be empty. Several specific indicators may be reported.

9.1.1 *Energy Ratio*—Calculate the ratio of the energy at 4000 cm^{-1} to energy at 2000 cm^{-1}. In each case, a 100 cm^{-1} wide region centered around the wavenumber position specified is used for obtaining an averaged energy value.

$$R = E_{4000}/E_{2000}$$

9.1.2 *Spectral Range*—Report wavenumber points where spectral energy reaches one-tenth of the energy level found at the energy maximum for the range.

9.1.3 *Water Vapor Level*—Report water vapor band absorbances identified below. If nominal instrument resolution is 4 cm^{-1} or poorer (for example, 8 cm^{-1}), or if digital resolution is coarser than 2 cm^{-1}, confirm that the spectrum shows clear bands at the named wavenumber positions. Nonlinear interpolation is strongly recommended for determining absorbances.

$$A_{3756} = -\log_{10}[2E_{3756}/(E_{3751} + E_{3761})]$$

$$A_{1596} = -\log_{10}[2E_{1596}/(E_{1591} + E_{1601})]$$

9.1.4 *Carbon Dioxide Level*—Report the CO_2 band absorbance identified below using low to medium resolution (8 to 4 cm^{-1}).

$$A_{2362} = -\log_{10}[2(E_{2362})/(E_{2382} + E_{2342})]$$

9.1.5 *Aliphatic Hydrocarbon Level*—Report hydrocarbon C-H stretching band intensity absorbance identified below, medium resolution (for example, 4 cm^{-1}).

$$A_{2926} = -\log_{10}[(E_{2926})/(0.3E_{2956} + 0.7E_{2853})]$$

9.1.6 *Non-Physical Energy*—Report the ratio of the energy level found below the detector/spectrometer cutoff to the energy found at the energy maximum for the range, for example:

$$R = E_{1750}/E_{2000}$$

9.1.7 *Peculiarities*—Report any other peculiarities of the single beam spectrum. Ratioing to an old reference single beam spectrum and looking for bands is a sensitive way to detect such peculiarities.

9.2 *One Hundred Percent Line Test*—Obtain two s

[3] Hirschfeld, T., *FT-IR: Application to Chemical Systems*, Academic Press, Vol 1.

the single-beam spectra and calculate their transmittance. Several specific indicators can be reported.

9.2.1 *Noise level at 250, 500, 1000, 2000, and 4000* cm^{-1}—A 100 cm^{-1} wide spectral portion centered around each position should be used for calculating the noise level in percent T units. Specify report as peak-to-peak or average root-mean-square (RMS) noise level. RMS is preferred.

9.2.2 One hundred percent line position at each wavenumber in 9.2.1. The average transmittance value determined as part of the RMS calculation in 9.2.1 over the same 100 cm^{-1} ranges can be used.

9.2.3 *Artifacts*—Report any sinusoids or spikes in the 100 % line spectrum.

9.3 *Stability Test*—Obtain successive single beam spectra at intervals over a period of time. Use a period of time which is representative of your usual stability requirements (for example, usual period of time between background spectra). Ratio all spectra to the first spectrum to obtain a set of n-1 transmittance spectra, and determine 100 % line position at 250, 500, 1000, 2000, and 4000 cm^{-1} as described in 9.2.2.

9.3.1 The RMS variation in the average transmittance is an index of system stability. Large variations at the highest wavenumbers suggest source temperature flicker or variable interferometer misalignment. Variations in transmittance in all regions are less common, and suggest detector or electronic problems, or serious optical (non-interferometer) misalignments.

9.3.2 The trend and total variation in the average transmittance indicate time-dependent instabilities, usually connected to temperature variations. Simultaneous temperature measurement will reveal the connection, often with a significant time delay between temperature change, its effect on the spectrometer, and the total variation over the period.

9.3.3 Purge variations can be observed in the transmittance spectra, and quantitatively assessed by calculating the band strengths using the same bands as used in 9.1.3 and 9.1.4, as shown in the equations below.

$$T_{3744,3} = T_{3744,3} - [(T_{3744,1} + T_{3744,5})/2]$$

$$T_{1616,3} = T_{1616,3} - [(T_{1630,2} + T_{1613,8})/2]$$

$$T_{2362} = T_{2362} - [(T_{2387} + T_{2323})/2]$$

9.3.4 Other artifacts can clearly be seen in the transmittance spectra. Ice on (cooled) detector surfaces (broad band around 3440 cm^{-1}), condensed water (very broad, 2400–3600), and hydrocarbon contaminants (structure, ca. 2937 and 2850) are examples.

9.4 *Signal Averaging Test*—Obtain a pair of subspectra, each having the same number of scans. Do this for the following number of scans: 1, 4, 16, 64, 256, 1024, 4096, 16384, etc., up to the maximum measurement time of interest. Ratio each pair and calculate the noise level at 250, 500, 1000, 2000, and 4000 cm^{-1} as described in 9.2.1. The noise level should be reduced by a factor of 2 for each successive ratioed spectrum; for example, if 1 scan gave a noise level of 1, 4 scans would give ½, 16 would give ¼, 64 would give ⅛ and so on until signal averaging fails. The ratioed noise level for each successive ratioed spectrum should be a factor of 2 lower, for example, 1, ½, ¼, ⅛, 1/16, 1/32, 1/64, 1/128, etc.

9.4.1 *Failure of Signal Averaging*—Report the number of scans and the measurement time for each of the pair used in the particular ratioed spectrum which has a noise level at least twice that predicted by the single scan pair. All spectrometers have a limit to their practical signal-averaging capability, often set by residual interference fringing by optical components or by the apodization-determined feet of the purge band absorptions.

9.4.2 Scaling problems and digital errors are uncovered by noting any drastic (usually a factor of 2) changes in energy in the single beam spectra, or abrupt appearance of spikes or sinusoids in the ratioed spectra. These problems are rare.

9.5 *Polystyrene Test*—Obtain an empty-beam single-beam spectrum followed by a spectrum of the matte-finish standard polystyrene. Ratio the polystyrene spectrum to the clear-beam spectrum to produce a polystyrene transmittance spectrum. Also convert this to the absorbance spectrum.

9.5.1 Peak positions for the following bands should be reported. Note these are bands recommended by IUPAC, and the real peak positions will be somewhat different for any particular sample of polystyrene and may be affected by the interpolation method. Report the actual peak positions and the peak center finding algorithm. A center of gravity algorithm is preferred, but a parabolic curve fit or cubic spline curve fit are also acceptable. The digital data point interval should be specified.

3082 cm^{-1}	2852 cm^{-1}	1028 cm^{-1}
3060 cm^{-1}	1945 cm^{-1}	907 cm^{-1}
3028 cm^{-1}	1601 cm^{-1}	540 cm^{-1}

9.5.2 *Resolution*—An indirect method for measuring resolution is the measurement of peak ratios of narrow/broad band pairs with similar absorbances. The component absorbances are each measured as the absolute absorbance value at the specified peak's maximum.

$$R_1 = A_{2852}/A_{2849}$$

$$R_2 = A_{1583}/A_{1154}$$

$$R_3 = (A_{2852} - A_{2849})/(A_{2849} - A_{2870})$$

$$R_4 = (A_{1601} - A_{1344})/(A_{1583} - A_{1344})$$

$$R_5 = (A_{1028} - A_{906.6})/(A_{1028} - A_{906.6})$$

9.5.3 Midrange photometry is quite sensitive to resolution. At constant resolution, the following ratios can be calculated as described in 9.5.2.

$$R_1 = (A_{2852} - A_{2849})/(A_{2852} - A_{2906})$$

$$R_2 = (A_{2849} - A_{2906})/(A_{2852} - A_{2906})$$

$$R_3 = (A_{2923} - A_{2870})/(A_{2849} - A_{2870})$$

$$R_4 = (A_{1601} - A_{1344})/(A_{1583} - A_{1344})$$

$$R_5 = (A_{1028} - A_{906.6})/(A_{1028} - A_{906.6})$$

9.5.4 The photometry of strongly absorbing bands is sometimes dominated by detector or other analog non-linearities, especially with photon detectors such as HgCdTe. This non-linearity produces a pseudo-stray light (most commonly a negative pseudo-stray light) and can easily be seen as variations in the apparent transmittance of highly absorbing bands. It also appears as nonphysical energy below the spectrometer low-wavenumber cutoff (see 9.1.6). For this test it is desirable to use a normally (Mertz or Foreman method) phase corrected spectrum, where the phase correction array has lower resolution (for example, 100 to 200 cm^{-1}) than the bands being measured or is a stored-phase

away from the empty-beam spectrum. If the instrument uses a magnitude calculation, the test can still be performed, but negative pseudostray light will be rectified to positive values. Report the transmittance at the transmittance minimum (or inverted minimum) for each of the following band positions. The highly absorbing region around each peak center can be averaged to improve the precision of this measurement.

3026 cm^{-1}	1493 cm^{-1}	756 cm^{-1}
2922 cm^{-1}	1453 cm^{-1}	697 cm^{-1}

9.6 *Photometric Jitter Test*—This test is quite similar to 9.5 polystyrene test, and uses the same sample and bands. Obtain a empty-beam single-beam spectrum followed by a series (for example, 30) of single-scan spectra of the matte-finish standard polystyrene. Ratio each polystyrene spectrum to the empty-beam spectrum to produce a series of polystyrene transmittance spectra.

9.6.1 *Peak Position Jitter*—Determine the RMS variation in the peak center wavenumber positions of each of the bands identified in 9.5.1, using the peak-center finding procedure described in that section. Peak position jitter is usually negligible, that is, it is usually dominated by photometric jitter and spectral noise.

9.6.2 Resolution jitter is generally found along with midrange photometric jitter. The absorbance spectra are calculated and the RMS variation of each of the four ratios described in 9.5.2 are reported.

9.6.3 Midrange photometric jitter is often the result of sampling inaccuracy (for example, Zachor-, Aronson distortion). Otherwise, spectral noise may be predominant. Report the RMS value of the percent T jitter in the following bands:

$\Delta T_1 = T_{3060} - T_{2960}$ $\quad \Delta T_5 = T_{1601} - T_{1584}$
$\Delta T_2 = T_{3060} - T_{2960}$ $\quad \Delta T_7 = T_{1583} - T_{1584}$
$\Delta T_3 = T_{3060} - T_{2960}$ $\quad \Delta T_8 = T_{1600} - T_{1584}$
$\Delta T_4 = T_{2922} - T_{2870}$ $\quad \Delta T_9 = T_{2850} - T_{2870}$
$\Delta T_5 = T_{2849} - T_{2870}$ $\quad \Delta T_{10} = T_{1602} - T_{1584}$

9.6.4 Strongly absorbing band jitter is usually the result sampling inaccuracy or clipping in the analog circuit Report the RMS variation of the transmittances of each the band centers identified in 9.5.4. If magnitude calculati is used, assume that band centers are at 0 % T and calcul the RMS variation from 0 % T, or else determine the tr transmittance of each of the band centers by an independe method and use these values for calculating the RI variations.

10. Keywords

10.1 spectrometers; Fourier transform infrared; FT-I Level Zero Test; Level One Test; Performance Tes

The American Society for Testing and Materials takes no position respecting the validity of any patent rights asserted in connection with any item mentioned in this standard. Users of this standard are expressly advised that determination of the validity of any such patent rights, and the risk of infringement of such rights, are entirely their own responsibility.

This standard is subject to revision at any time by the responsible technical committee and must be reviewed every five years and if not revised, either reapproved or withdrawn. Your comments are invited either for revision of this standard or for additional standards and should be addressed to ASTM Headquarters. Your comments will receive careful consideration at a meeting of the responsible technical committee, which you may attend. If you feel that your comments have not received a fair hearing you should make your views known to the ASTM Committee on Standards, 1916 Race St., Philadelphia, PA 19103.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: September 23, 1994

To: Bob Wolters, HFD-110

From: Wilson H. De Camp
Supervisory Chemist, HFD-540

Subject: USAN GG-56

I recommend that the name "quaternium-18 bentonite" be adopted as USAN. My primary reason for this is that the name already has wide recognition, and little would be served by establishing a distinct name for drug use. Furthermore, please note that, although this product has a CAS number, the alkyl groups may vary in length, and bentonite is a mineral of somewhat variable composition. Finally, the CAS number shown in the USAN application is different from that shown in CTFA.

Also, please note that, as far as I can establish, the CFR references in CTFA are incorrect. I can find no reference to quaternium-18 bentonite in 21 CFR 175.3570, and the references 21 CFR 175.300 are to bentonite compounds with benzyl dimethyl alkyl ammonium chloride. Quaternium-18 is a dimethyl dialkyl ammonium chloride.

JUL 17 1995

DIVISION OF TOPICAL DRUG PRODUCTS HFD-540
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-532 with user fees due date 9/29/95

REVIEW # 1 **DATE REVIEWED:** 1/25/95, Revised 6/27/95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	9/28/94	9/30/94	10/14/94
AMENDMENT	1/20/95	1/25/95	2/17/95

NAME & ADDRESS OF APPLICANT:

United Catalysts Inc.
1227 South 12th Street
Louisville, KY 40210
Tel 502-634-7531
Mr. Anthony A. Schultz

DRUG PRODUCT NAME

Proprietary: IVY BLOCK
Established: BENTOQUATAM (USAN - 12/28/1994); Quaternium-18 Bentonite (CTFA); Q-18B; Organoclay generic name; Tixogel VP (applicants cosmetic use ingredient).
Code Name/#: CAS# 1340-69-8 (USAN); and CAS# 68911-87-5 (Tixogel VP).
Chem.Type/Ther.Class: 1-P

PHARMACOL. CATEGORY: Barrier for the prevention of allergic contact dermatitis; Poison ivy and poison oak skin protectant.

DOSAGE FORM: Lotion
STRENGTHS: 5% bentoquatam w/w
ROUTE OF ADMINISTRATION: Topical
DISPENSED: 4 oz white HDPE bottle ___ Rx _X_ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Quaternium-18 Bentonite.
See attached structural formula adopted by USAN.

SUPPORTING DOCUMENTS:

DMF

RELATED DOCUMENTS:

IND
GLC analysis of Urushiol, *J. Pharm. Sci.*, vol. 67, No. 4, April 1978, pp. 483-485.

CONSULTS:

Trade name to CDER labelling committee (Ivy Block name for OTC product was accepted on 2/6/95).
EA consult to HFD-102 initiated on 11/10/94 is still pending.
Microbiology consult to HFD-520.

REMARKS:

IVY BLOCK Lotion assay for Q-18B Bentonite by method is problematic. Q-18 was removed from bentoquatam by

Original IND was reviewed by Dr. Wilson DeCamp. At the original IND filing stage, the assay method was under development. The proposed methods were Q-18B binding to natural urushiol (release method) and the extent to which synthesized

Urushiol is the main constituent of the irritant oil of poison ivy.

The submission fails to provide the linkages between the 3 methods in terms of their equivalency, precision, and accuracy (natural Urushiol binding, synthetic

Other missing critical items were : (a) Assay method for

(b) A specification for free Q-18. (c) Method details and validation data for free Q-18 by method

CONCLUSIONS & RECOMMENDATIONS:

The NDA is NOT APPROVABLE. The deficiencies are discussed in the following sections: Controls for the finished dosage form, Stability, and Methods validation.

I. The following information should be submitted:

II. Please submit the following information, if possible.

(c) Final printed labels should be submitted.

cc: Orig. NDA 20-532
HFD-540/Division File
HFD-007/PMaturu
HFD-540/WDeCamp
HFD-540/JHolmes
HFD-540/Huene
HFD-540/Sheevers
filename: N20532.795

P. Maturu
P.Maturu, Primary Review Chemist

10/30/95

NOT APPROVABLE

7/17/95

December 28, 1994

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

USAN (GG-56)	BENTOQUATAM
PRONUNCIATION	bĕn´ tō kwă tăm˝
THERAPEUTIC CLAIM	barrier for the prevention of allergic contact dermatitis

CHEMICAL NAMES

1) quaternium-18 bentonite

2) bis(hydrogenated tallow alkyl)dimethylammonium complex with sodium bentonite

STRUCTURAL FORMULA

See page 2

TRADEMARK	Tixogel VP
MANUFACTURER	United Catalysts, Inc.
CAS REGISTRY NUMBER	1340-69-8

NOTES: 1) The trivial name "organoclay" has been used for this substance.

2) Quaternium-18 bentonite is the CTFA name for this substance.

RF/gat

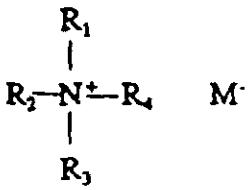
STRUCTURAL FORMULA:

Bentonite

$((Al_{4-x}Mg_x)(Si_{8-y})O_{20}(OH)_{4-f}F_f) \cdot (x+y)Na^+$

Where $10.0 \leqq x \leqq 1.10$, $0 \leqq y \leqq 1.10$, $0.55 \leqq (x+y) \leqq 1.10$, and $f \leqq 4$.

Quaternary Amine



M^- = Cl^-

R_1, R_2 = CH_3

R_3, R_4 = hydrogenated tallow

The alkyl distributions for R_3 and R_4 (hydrogenated tallow) are:

C_{14} = 2.0%,	C_{15} = 0.5%,	C_{16} = 29.0%,
C_{17} = 1.5%,	C_{18} = 66.0%,	C_{20} = 1.0%

QUATERNIUM-18 BENTONITE

DEFINITION: Quaternium-18 Bentonite is a finely divided creamy white powder resulting from cation exchange reactions between organic bases and the inorganic clay mineral montmorillonite.

TEST	SPECIFICATION	METHOD
Color	As specified by the buyer	
Odor	As specified by the buyer	
Identification	Positive: Close match to CTFA Spectrum-IR with no indication of foreign materials	CTFA G 3-1
Gel Strength of 2.0% Gel in Toluene-Methanol	160 cps minimum	CTFA C 15-2
Sulfated Ash	35.5 to 40.5%	CTFA E 5-2
Loss on Drying	3.5% maximum	CTFA E 34-1
Arsenic (as As)	3 ppm maximum	CTFA F 1-1, Parts I-A and II
Lead (as Pb)	20 ppm maximum.	CTFA J 2-1

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micro

MAY - 3 1996

Blatt
540

REVIEW TO HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF AMENDMENT

April 30, 1996

A. 1. **NDA 20-532** **APPLICANT:**

United Catalysts Inc.
P.O. Box 32370
Louisville, KY 40232 USA

2. **PRODUCT NAMES:** IVY BLOCK ™ (Bentoquatam, 5%)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:**
Topical Lotion (5 % w/w)

4. **PHARMACOLOGICAL CATEGORY:**
Protects against poison ivy and poison oak rash when applied before exposure.

B. 1. **DATE OF AMENDMENT:** February 26, 1996
OTHER COMMUNICATIONS: Phone, April 26, 1996
Facsimile, April 26, 1996

2. **RELATED DOCUMENTS:**

IND	IVY BLOCK™	United Catalysts, Inc.	Filed 27 April 1989
DMF	Master File		On File
DMF	Master File	United Catalysts, Inc.	Filed 2 Sept 1994

3. **ASSIGNED FOR REVIEW:** April 5, 1996

C. **REMARKS:** A microbiology consult was requested by the HFD-540 division to review the applicants response to FDA's letter of September 28, 1995 containing comments (# 8, 9a and 9b) relating to microbial limits.

D. **CONCLUSIONS:** This amendment to NDA 20-532 for IVY BLOCK™ is recommended for approval from the standpoint of microbiology. The applicant has made a commitment to perform Antimicrobial Preservative Effectiveness Tests on the first three production batches initially and at expiry. Please see Section E for specific comments.

5/3/96

Patricia F. Hughes, Ph.D.
Review Microbiologist

Date 5/3/96

cc Original NDA 20-532
HFD-160/Consult File
HFD-160/P F Hughes
HFD-540/Division File
HFD-540/H Blatt
Drafted by P F Hughes, 10/30/95
R/D initialed by P Cooney, 10/30/95

E. REVIEW NOTES:

Comment 8: Regarding the Microbial Limits testing performed on the drug substance, it appears that preparatory testing as described in <61> to determine if organisms will grow in the product was not performed. Please perform preparatory testing to validate the utility of the method. In addition, it is recommended that when this test is performed, a limit of 100 CFU/g be utilized.

Applicants's Response:

The USP Preparatory Testing to determine if organisms will grow in the drug substance is contracted out to A report from this lab is included in Appendix 9 (page 72). The contract lab has demonstrated that, with the exception of *Salmonella* sp., all challenge microorganisms were recoverable from two lots of quaternium-18-bentonite. Failure to recover *Salmonella* indicates that the drug substance is not likely to be contaminated with this microorganism. The total aerobic counts on Test 1 and 2 were <10 CFU/g and 180 CFU/g. Yeast and mold counts were <10 CFU/g (p. 72, Appendix 9).

Satisfactory

The USP Microbial Limits Preparatory Testing was not carried out by the formulating laboratory They used another method yielding similar results. *However, they will carry out and validate the preparatory test method and a report will be sent to the FDA when the method validation is completed.*

Satisfactory

The applicant states that there is no need to place a specification limit of 100 CFU/g on the drug substance because the finished product is highly bacteriostatic and only a small amount of drug substance is introduced into the final drug product formulation. The applicant states that even if the bulk drug substance contained 1,000 CFU/g, the drug substance after formulation could account for only 50 CFU/g in the finished IVY Block Lotion.

Satisfactory

Comment 9:

a. Before Microbial Limits testing is performed, preparatory testing, as described in USP <61> should always be performed to show that test organisms will grow in the product. Microbial Limits testing of the finished product may not be necessary if it can be shown that the finished product does not support growth. If this testing is deemed necessary, it should be performed at least initially and at the end of the expiry on each lot of product.

Applicant's Response:

Validation of the Microbial Limits Test as per USP <61> is described in Appendix 10 (pages 73-101). As reported in the original submission of Sept. 28, 1994 (volume 4, pages 953-956), the preservative effectiveness test was conducted on two lots of Ivy Block Lotion in accordance with protocols and USP <51> Antimicrobial effectiveness Test (PET). The data showed that the drug product does not support microbial growth and is antimicrobial. As a consequence of these results, the applicant proposes drop Microbial Limits testing on the finished product and to maintain the original specifications listed in the Sept. 28, 1994 submission, volume 4 page 888.

Comments; The applicant can drop the Microbial Limits Tests on the finished product.

Satisfactory

Comment 9.b. A rational is needed as to why Microbial Limits testing is performed on the stability lots, and this is not included in the tests and specifications listed for the finished product.

Applicant's Response:

Because the drug product contains alcohol and other preservatives and possesses antimicrobial properties, the Microbial Limits testing on the finished product will not be done but the testing initiated on the stability lots in progress will be continued.

Satisfactory

Comments 9.c. The product has specifications of not less than 80% of theory for both methylparaben and benzyl alcohol. Please demonstrate that the product formulated with the minimum amount of both of these ingredients will pass the USP <51> Antimicrobial Effectiveness Test (PET). If this is not done, then please show that each lot will pass the PET at both initial and end of expiry time periods.

Applicants's Response:

A report on the PET is included in Appendix 11 (pages 102-108). The drug product was formulated with methyl paraben and benzyl alcohol levels reduced to 80% of the theoretical amount and USP PET were performed. Five test microorganisms were used at concentrations of 10^5-10^6 CFU/g of product. Test samples were incubated for 7, 14, 21 and 28 days. After 7 days, the test microorganisms were decreased to <10 CFU/g of product. From these results it was concluded that the product is adequately preserved even with reduced preservative levels.

Comments: Antimicrobial preservative effectiveness tests should be performed on the first three production batches, initially and at expiry. Chemical tests will be sufficient for subsequent production batches. The applicant has made a commitment to carry out the APET on the first three production batches and the results will be incorporated into the validation reports for the batches.

Satisfactory

Consultative Review for HFD-540
Division of Topical Drug Products
Division of Anti-Infective Drug Products (HFD-520)
Microbiological Review of Manufacturing Controls

Requestor: Joanne Holmes, CSO HFD-540

Date of Request: September 31, 1994

Reason for Request: Microbiological Review of manufacturing controls

NDA #: 20-532 **MICRO REVIEW #:** 1 **REVIEW DATE:** 29-NOV-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	28 SEPT-94	29-SEPT-94	03-NOV-94
AMENDMENT	04-NOV-94	04-NOV-94	17-NOV-94

NAME & ADDRESS OF APPLICANT: UNITED CATALYSTS, INC.
1227 South 12th Street
Louisville, KY 40210

CONTACT PERSON: Anthony A. Schulz
Phone Number: (502) 634-7531
Fax Number: (502) 634-7727

DRUG PRODUCT NAME

Proprietary:	IVY-BLOCK™
Nonproprietary/USAN:	Benquatamine
Code Names/#'s:	
Chemical Type/	chemically-modified clay
Therapeutic Class:	2P

ANDA Suitability Petition/DESI/Patent Status:
US Patent No. 4,861,584--issued August 29, 1989 to Thomas W. Powell, Jr. assigned to United Catalysts, Inc., claims a metnod of using the active ingredient in this application. Expires August 29, 2006.

PHARMACOLOGICAL CATEGORY/INDICATION:
Barrier to protect skin against the allergenic oil produced by poison ivy and poison oak.

DOSAGE FORM: Lotion
STRENGTHS: 5%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: ___Rx _X_OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

NOT APPLICABLE

SUPPORTING DOCUMENTS:
DMF
DMF United Catalysts, Inc.
IND IVY BLOCK™

RELATED DOCUMENTS (if applicable): NONE

CONSULTS: NONE

REMARKS/COMMENTS: NONE

CONCLUSION & RECOMMENDATIONS:

The application is NOT APPROVABLE for microbiological manufacturing and controls under section 505 of the Act. The sponsor should be notified of the following deficiencies:

1. Regarding the Microbial Limits Testing performed on the drug substance.

   a. It appears that preparatory testing as described in USP<61> to determine if organisms will grow in the product was not performed. Preparatory testing should be performed to validate the utility of the method.

   b. The limit of <1000 cfu/g for the total count should be reestablished as <100 cfu/g, since this is the limit used for the finished product lots presented in the NDA and the count for materials that go into the finished product should not be higher than the limit for the finished product.

2. Regarding the Microbial Limits Testing performed on Purified Bentonite.

   Since the finished product has a total aerobic count of 100 cfu/g the material going into the product should not have a total aerobic count higher than 100 cfu/g.

3. Regarding the testing of the finished product.

   a. Microbial Limits testing on the finished product is not included in the tests and specifications for the finished product. Since the product is over 30% alcohol nothing is probably going to grow in it. The sponsor should have performed the preparatory testing (as described in USP<61> to show that test organisms will grow in the product. The initial results obtained with the stability lots is not surprising considering the amount of alcohol in the product. The reason why the stability lots have a limit for this test and it is not included in the specifications for the finished product should be given. Testing the finished product does not seem to be needed. If the test is to be included in the specifications for the finished product it should be performed at least initially and at the end of expiry on each lot of product.

b. Since the product has specifications of NLT 80% of theory for both methylparaben and benzyl alcohol the sponsor should demonstrate that the product formulated with the minimum amount of both of these ingredients will pass the USP <51> Antimicrobial Preservatives Effectiveness Test. If this is not done, then the sponsor must show that each lot will pass this test at both initial and end of expiry time periods.

Peter A. Dionne
Review Microbiologist

cc: Orig. NDA 20-532
HFD-540/Division File
HFD-520/Micro/Dionne
HFD-540/MO/Huene
HFD-540/Pharm/Sheevers
HFD-540/Chem/Maturu
HFD-540/CSO/Holmes

Log in 02-28-95
540

Concurrence Only:
HFD-540/Dir/JWilkin
HFD-520/SMicro/ATSheldon
RD1/31/95
2/1/95
2/1/95

REQUEST FOR WAVIER OR REDUCTION OF USERS FEES FOR NDA REVIEW

IVY-BLOCK™ (benquatamine)

NDA Number 20-532

a) This request for a waiver or reduction of users fees for NDA review is filed by:

United Catalysts, Inc.
P.O. Box 32370
Louisville, Kentucky 40232

Users Fee I.D. Number 2656

The name and telephone number of the contact person for the waiver or reduction request is:

Mr. Anthony A. Schulz
Manager Business Development
502-634-7531 or 800-468-7210

b) The fee for which a waiver or reduction is requested is:

This request is in regard to the fee for review of New Drug Application number 20-532, IVY-BLOCK (benquatamine) which is indicated for the prevention of poison ivy and poison oak rash. The application is being submitted on September 28, 1994 and includes limited clinical data.

This product is the only human drug product of the company and its affiliates, and since the product is intended for over-the-counter sale, there are no product fees or establishment fees.

c) Initial payment of users fees in the amount of _____ was made to the Food and Drug Administration on September 28, 1994, concurrent with the filing of the NDA.

d) This request is made under the provisions of 21 U.S.C. 379h(d).

e) Information and analyses showing the statutory criteria for the waiver or reduction are met:

This is an NDA of very limited size for a topical OTC drug product in which the active ingredient is a widely used cosmetic component. The submission consists principally of clinical studies and Chemistry, Manufacturing and Control information on the manufacture of the active ingredient and on the production of the drug product. Preclinical laboratory animal studies were not performed by the sponsor because the new drug substance has previously been subjected to a variety of such studies and is the subject of a CTFA monograph on its safety for topical use.

Due to its widespread application in cosmetics over a period of several decades, the active ingredient, benquatamine, (known in the cosmetics industry as "quaternium-18 bentonite") is believed by the sponsor to be generally recognized as safe for topical use in the amounts employed in the drug product when used as directed. Consequently, there are no new studies on adsorption, distribution, metabolism or excretion (ADME) because safety for topical use has been established and the drug is merely for topical application as a barrier to plant allergens. Clinical studies are also quite limited in scope because the presence or absence of a rash is readily determined without sophisticated equipment or lengthy procedures. Clinical reports are quite brief and statistical analyses readily indicate effectiveness is significant ($P \leq 0.0001$). Rather than consisting of 200 volumes as is often

the case, there are only twelve volumes in the entire archive copy of the NDA and only two volumes in the Drug Master File on the manufacture of the bulk active ingredient. Thus, although the statute states FDA "may use standard costs" (21 U.S.C. 379 h(d)) the standard costs for NDA review should not apply to NDA 20-532 because such costs exceed the anticipated present and future costs incurred by FDA in conducting the process for the review of the NDA.

Review copies of the NDA consist of:

Four volumes - Chemistry, Manufacturing, and Control
One volume-Pharmacology Section
Three volumes - Clinical Section
Three volumes - Statistical Section

This is also an NDA for an indication for which there is no approved drug or device, i.e., prevention of poison ivy and poison oak rash. Although rashes from these plants are rarely life threatening, their impact on the health of selected populations is substantial. We request the agency consider waiving the user fees for NDA review as necessary to protect the public health based, in part, on the U.S. Forest Service report by Jerry Oltman and Robert Hender ("Poison Oak/Ivy and Forestry Workers", Clinics In Dermatology, Vol. 4, No. 2, April-June 1986, pp. 213-216 -- copy attached) that the single largest lost-time injury among its foresters is poison oak and poison ivy (10% of all lost-time injuries).

The sponsor undertook development of the drug at a time (1987) when user fees were not expected and since that time developmental costs have considerably exceeded the sponsor's expectations. Because of the economics involved with a limited

market, the user fees for NDA review present a significant barrier to continued sponsorship of the drug.

25 Poison Oak/Ivy and Forestry Workers

Jerry Oltman, BS, and Robert Hensler, BA

From the United States Department of Agriculture, Forest Service Equipment Development Center, Missoula, Montana

Contact dermatitis from poison oak and poison ivy, a long-time problem of our forestry workers, accounts for more than 10% of all U.S. Department of Agriculture Forest Service lost-time injuries, and is our biggest single cause of injuries. The magnitude of the problem has prompted extensive investigation, but a solution may be near if the current field test for a new poison oak/ivy preventive proves it to be effective.

The contact dermatitis problem is greatest for Forest Service workers in California, Oregon, and Washington: states that have vast areas of national forest land, where poison oak grows in abundance. In the eastern states, poison ivy poses a similar problem for Forest Service employees in, for example, Illinois, Kentucky, West Virginia, and Mississippi. Poison sumac is less a problem because it is rarely found where our crews work. In the Rocky Mountain states, many of the national forests are located in mountainous regions where employees seldom contact toxicodendrons.

Exposure to poison oak and poison ivy is inescapable in forestry work. Conducting timber and road surveys, maintaining trails, piling brush, thinning trees, or fighting fires does not permit one to choose his or her work site. The contact dermatitis that results has always been considered a standard work hazard; but during a severe fire season, cases of contact dermatitis multiply so rapidly that the situation becomes anything but routine. At such times, exposure to poison oak in California fires may affect almost a quarter of the firefighters, forcing their removal from the fireline and causing widespread misery, lost time, and, often, incapacitation.

Firefighters are skilled, physically fit employees who are not easily replaced—especially during a critical fire. A firefighter with severe poison oak dermatitis represents an expensive loss to the Forest Service. Therefore, the Forest Service Equipment Development Center in Missoula, Montana, was asked to find a solution for the problems of contact dermatitis. This proved to be no mean task—poison oak/ivy, by its very nature, is difficult to eradicate; and medical science could not offer a satisfactory solution for the medical problem.

We believed that an improvement in identification, prevention, treatment, or desensitization might help. To evaluate the potential of each approach, we consulted a team of experts including Drs.

William L. Epstein and Vera Byers of the University of California Medical Center, who provided helpful direction. We elected not to pursue treatment as a solution because so many different treatments are already available that a breakthrough seemed less probable. Desensitizing products were available, but posed problems for users. Therefore, we chose identification and prevention as the most promising avenues to pursue.

At the beginning, we decided to focus on fire crews. Fire crews were chosen as the prototype for all work crews because the firefighter probably has more opportunity for exposure to these plants than any other worker. Firefighters are also highly motivated because they know the magnitude of the problem and have used almost every remedy without success.

Identification and prevention overlap somewhat. Identification was improved by providing a plant identification card, and by identifying those employees sensitive to poison oak/ivy, since they had the greatest need to learn good identification and avoid unnecessary contact.

Because avoidance is essentially impossible in the field, it is important to identify those who are sensitive and the level of sensitivity. To do this, Drs. Epstein and Byers recommended developing a skin patch test kit that could be administered by Forest Service employees. Results of tests of 50 prototype kits (Fig. 1), carried out at 10 locations in California, Oregon, and Montana, proved gratifying. The kits met our needs for simplicity and accuracy, identifying (Fig. 2) those mildly, moderately, or exquisitely sensitive to poison oak/ivy, without inducing sensitivity. We hope soon to complete the preliminary purchase and test phase, so that these kits can be made available to state and federal land management offices for their workers.

No effective prophylaxis was available according to our consultant, Dr. Epstein. No acceptable "barrier creams" were on the market, so we contracted with Dr. Edward E. Waali, a chemist at the University of Montana, to identify potentially usable products or materials that bond with urushiol. Using standard chromatographic techniques, he identified three very good adsorbents for urushiol: alumina, silica gel, and activated carbon. Alumina proved best, binding up to 100% of the urushiol used in Dr. Waali's testing.

Dr. Waali also tested several common fabrics for binding capacity with urushiol. Because records indicate that many poison oak/ivy injuries occur on wrists and forearms and around eyes and forehead, we

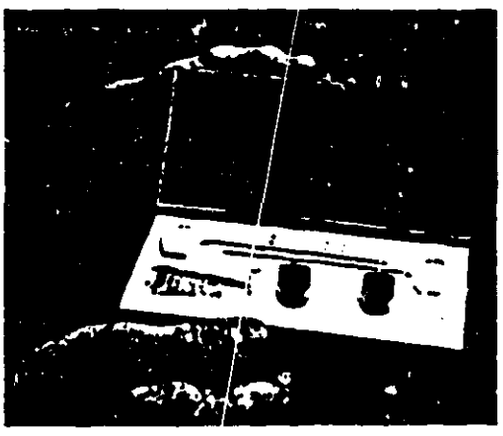


FIG. 1. Prototype skin patch-test kit used by Forest Service employees.

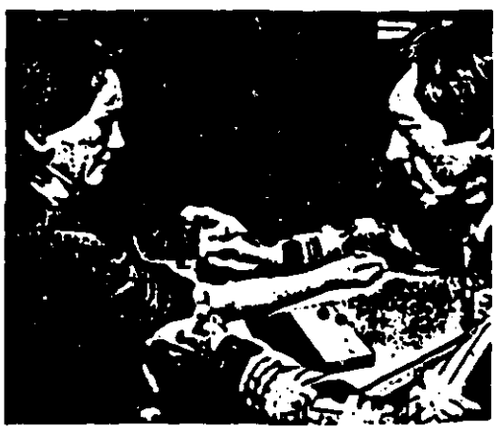


FIG. 2. Forest Service employee being tested for poison oak/ivy sensitivity.

looked for special sweatbands for wrists and forehead to protect areas not normally covered by clothing. This localization may be due to reaching while digging and grubbing, so that wrists and forearms often are exposed, and wiping sweaty brows with sleeves or gloves spreads the urushiol to the face.

Pursuing data from the first laboratory tests, we searched for cloth or paper impregnated with alumina that we could field test as sweatbands or wipes for tools, boots, and other fomites. Our search led to other aluminum compounds as well as other promising substances. We tested magnesium aluminum silicate, aluminum chlorohydrate, several bentonite clays, and several carbon filter papers.

Our high expectations for magnesium aluminum silicate were not realized. It was commercially available as a product called Les-Ivy (Marceca Inc., Harrisonburg, VA) and marketed as an astringent. The tests showed more effective compounds among the clays or even with aluminum chlorohydrate.

We decided to focus on aluminum chlorohydrate, in the form it occurs in almost all antiperspirants. We again contracted with Dr. Epstein to identify the relative prophylactic effect of this and a clay compound by skin testing known urushiol-sensitive subjects. He obtained the antiperspirant, Sure (Procter & Gamble, Cincinnati, OH), from the manufacturer as the complete product, as aluminum chlorohydrate without the base, and as only the base without the aluminum chlorohydrate. We included a very promising clay, called organoclay, an organophilic bentonite clay widely used in antiperspirants and cosmetics.

The results in ten subjects tested by Dr. Epstein showed the organoclay to be the most effective of the four products tested. At our request, United Catalysts, Inc. (Louisville, KY) had packaged the clay in spray cans for the test, enabling immediate field testing should it prove successful. With organoclay in aerosol cans, we had a product ready for field testing (Fig. 3).

To determine the effectiveness of organoclay under actual field conditions, we conducted a trial near the end of the 1985 field season. We established two criteria for volunteers: they had to have moderate or greater sensitivity and an occupation that required them to work near the plants. Most of our volunteers are located at nine national forests in Washington, Oregon, California, Illinois, and Kentucky.

Fig. 3. Organoclay in a spray can, used for field testing as a poison oak/ivy preventative.

By September 17, we had mailed out 165 cans of the organoclay, now called "Ivy-Block" by United Catalysts, to 55 volunteers. Each tester received three cans, one as a spare and two to be used in their entirety before stopping the test. They were told to spray the material on exposed skin, gloves, shirt sleeves, pant legs, boots, and tools, or almost any place that might normally come into contact with the urushiol. Testers also were told to reapply it if they were sweating heavily.

United Catalysts is ready to patent and market the product as a poison oak/ivy preventative should the product prove successful. The Forest Service stands ready to implement it, and other agencies, eg, the Bureau of Land Management and the National Park Service, also are looking at these trials.

If "Ivy-Block" is effective, it may be marketed and in use before the skin patch-test kit is implemented, even though field testing of that product was completed a full year before

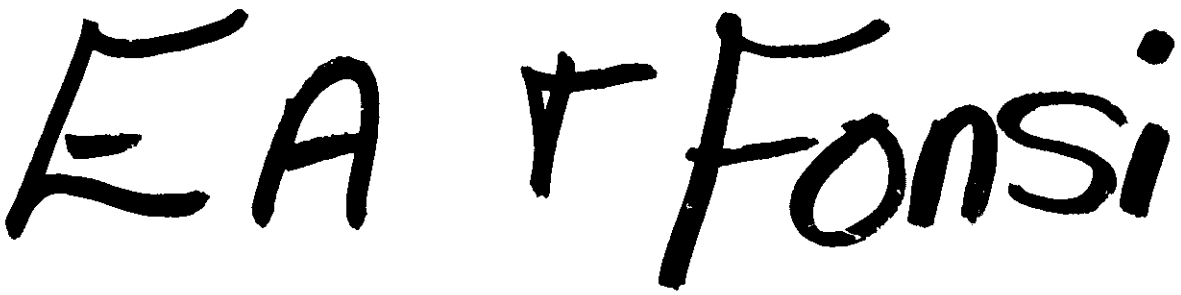
"Ivy-Block." The reason for this is that we developed the kit ourselves, so it must undergo a purchase and test phase before it becomes available.

Conclusion

Normally, most of the 121 national forests and their smaller units, ranger districts (about 620), are left to solve problems unique to their areas; but the problem with poison oak/ivy required a concerted effort.

Once the scope of the problem was realized, it was assigned to our Center and more resources were committed to solving the problem. With consultant direction from experts like Dr. Epstein, the programs for the skin patch-test kit and development of a barrier product were tailored to the needs of Forest Service field crews. It is hoped that this joint effort has brought us close to a solution of a long-standing and severe forestry problem, and one that also promises help for everyone who goes into the woods.

Address for correspondence: Jerry Oltman, USDA Forest Service, Equipment Development Center, Fort Missoula, MT 59801.



ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

IVY BLOCK LOTION (BENTOQUATAM) 5%

NDA 20-532

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-532

IVY BLOCK

(BENTOQUATAM)

LOTION, 5%

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for IVY BLOCK (Bentoquatam Lotion, 5% w/w), United Catalysts, Inc., has prepared an environmental assessment in accordance with 21 CFR 25.31a (b) (3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Bentoquatam (Quaternium-18 Bentonite or Q-18B) is a modified organo clay bentonite, chemically synthesized from a natural bentonite clay source, which is administered as a lotion for the prevention of allergic contact dermatitis from poison ivy (OTC product). Bentoquatam drug substance and Bentoquatam lotion are manufactured by United Catalysts, Inc.,

and

respectively. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Bentoquatam is a stable compound, heat stable up to 500°C and resistant to acid and base attack over a wide pH range 3-11. [redacted]

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed landfill (Louisville Outer Loop Road). At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic

regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacturers of the drug substance and drug product are expected to minimize occupational exposure and environmental releases.

The Center for Drug Evaluation and Research has concluded that Bentoquatam Lotion can be manufactured, used and disposed of without any expected adverse environmental effects.

8/22/96
DATE

James D. Vidra
PREPARED BY
James D. Vidra, Ph.D.
Review Chemist
HFD-540

8/22/96
DATE

Wilson H. DeCamp Ph.D.
DIVISION CONCURRENCE
Wilson H. DeCamp, Ph.D.
Supervisory Chemist

DATE

APPROVED
Nancy Sager
Team Leader
Center for Drug Evaluation and Research

cc: HFD-357/FONSI File (NDA 20-532)
HFD-357/Docket File
HFD-357/FOI File
Orig. NDA 20-532
HFD-540/Division File
HFD-540/CSO/Blatt
HFD-540/MO/Heuene
HFD-540/Chem/Vidra
HFD-540/ChemTmLdr/DeCamp
filename: NDA20532

The environmental assessment (EA) prepared by for the manufacture of the subject drug product (IVY-BLOCK) follows the abbreviated format provided under 21 CFR 25.31a(b)(3) for a human drug product intended for topical application. This EA is presented in the following pages.

ENVIRONMENTAL ASSESSMENT

for

Manufacturing

Bulk Quaternium-18 Bentonite

and

Ivy Block Lotion

Prepared By:

United Catalysts, Inc.
Louisville, Kentucky 40210

Environmental Assessment

Section 1. **Date:** 8/1/94

Section 2. **Name of Applicant:**
United Catalysts, Inc.

Section 3. **Address:** 1227 South 12th Street
Louisville, KY 40210

Section 4. **Description of the Proposed Action:**

This environmental assessment, prepared in abbreviated format pursuant to the provisions of 21 CFR 25.31a(b)(3), is a required portion of a proposed action to approve a new drug application is pursuing for a topically-applied dermatologic product indicated for the prevention of allergic contact dermatitis resulting from contact with various species of Toxicodendron.
intends to be the bulk drug manufacturer and will have the finished drug product, a lotion, produced by a contract manufacturer

Need for the Action:

Emphasis of the product is placed on preventing dermatitis resulting from contact with poison ivy, poison oak, and poison sumac. Plants of the Toxicodendron family, which includes poison ivy, poison oak, and poison sumac, contain an oil called Urushiol, which is the contact allergen most often responsible for plant-related dermatitis. Contact with even a minute amount of the oil through a wide variety of vectors results in a multitude of occupational and recreational injuries each year, many of which require medical treatment.

Since there does not now exist an FDA-approved preventive for these indications, sufferers have no recourse but to avoid exposure, which is an obvious burden not only to the worker who must be outdoors, but also to those who seek outdoor recreation. The proposed action will ameliorate this lack of an approved preventive.

Location of Manufacturing:

Bulk Drug Product - Q-18 B:

The bulk drug product, quaternium-18 bentonite (Q-18), will be manufactured at

environmental assessment for the manufacture of bulk drug product (Q-18 B) is provided in the following pages:

Location of Manufacturing:

Bulk Drug Product - Q-18 B:

The bulk drug product, quaternium-18 bentonite (Q-18 B), will be manufactured at The manufacturing site is an urban industrial complex located within the city of Louisville. The climatic conditions for Louisville are typical for the midwest.

Importantly, the bulk drug product will be produced at a facility which currently produces [redacted] per year for industrial use as a rheological additive.

Locations Of Product Use and Disposal:

Bulk Drug Product - Q-18 B Use and Disposal:

The bulk drug, Q-18 B, will be produced in Louisville, KY and shipped to the contract manufacturer in for compounding into the final drug product form, a lotion.

Bulk Q-18 B which is not shipped for lotion formulation will be re-classified by the applicant as non-drug material, and will be transferred to the applicant's for use as an industrial grade additive.

It is anticipated that, due to the relative lack of toxicity of the product, disposal of unusable or unused material will be through conventional and suitably controlled landfill techniques. The disposal facility which currently receives non-hazardous industrial solid wastes generated by this facility is a state-permitted municipal solid waste landfill located in rural Jefferson County, KY (Outer Loop Landfill, 2673 Outer Loop Road, Louisville, KY 40259-0498). Wastewater generated by the production of Q-18 B will also proceed to the Louisville and Jefferson County Metropolitan Sewer District in accordance with permit #8212.

Final Drug Product - Lotion:

The final drug product in lotion form is anticipated to be used throughout most of the United States due to the widespread nature of the plants of the Toxicodendren family. However, heaviest use is anticipated in those regions wherein severe problems occur, such as through the sunbelt and the western and eastern coasts.

Section 5. **Chemical Substances Identification:**

Bulk Drug - Q-18 B:

Quaternium-18 bentonite is the CTFA nomenclature for the bulk drug chemical (generically termed an organoclay) and the **Chemical Abstract Service** registration number is 68911-87-5.

This compound is a substance which has been CTFA-monographed and has been utilized in large quantities for over 30 years as a control additive in the cosmetic industry. It is a binary compound based on a substrate of purified sodium bentonite which has been surface-reacted with a quaternary amine compound (quaternium-18). Q-18 B is a relatively inert compound that is heat stable up to 500°C and resists acid and base attacks over a pH range of 3-11. (See References 1 and 2.)

The sodium bentonite substrate, a native, colloidal, hydrated aluminum silicate, is a naturally occurring mineral found in large quantities in the central northwest, especially in the state of Wyoming. The silicate-based clay is composed of three-layer sub-units consisting of two tetrahedral layers sandwiching an octahedral layer. The former layers contain silicon and oxygen in tetrahedral configuration; the latter contains aluminum and oxygen in octahedral configuration.

[redacted]

The chemical composition of the sodium bentonite is as follows:

$$((Al_{4-x}Mg_x)(Si_{8-y})O_{20}(OH)_{4-f}F_f).(x+y)\,Na+$$

Where $1.0 \leq x \leq 1.10$, $0 \leq y \leq 1.10$, $0.55 \leq (x+y) \leq 1.10$, and $f \leq 4$.

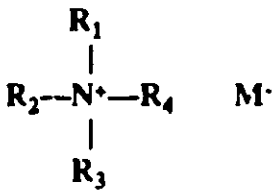
The CAS number for bentonite is 1302-78-9. (See Appendix C for MSDS.) Typical impurities found in the raw bentonite clay include shale, feldspar, quartz, and other siliceous minerals. [redacted] s. The solid impurities are subsequently isolated and also sent to the Outer Loop Landfill. [redacted]

[redacted]

Quaternium - 18:

This quaternary ammonium compound used in the manufacture of Q-18 B is chemically designated di-hydrogenated tallow, di-methyl quaternary ammonium ion, normally provided as the chloride salt. It is typically supplied in suspension form including water and a small amount of isopropanol. Typical concentration of active quaternary is 75%. (See the Appendix C for the MSDS.)

The general chemical structure of this quat is shown below:



In this formula, R1 and R2 represent methyl groups, and R3 and R4 represent hydrogenated tallow. Commercial quat of this type analyzes 2.0% C14, 0.5% C15, 29.0% C16, 1.5% C17, 66.0% C18 and 1.0% C20 alkyl radicals. The anion, M, typically is chloride.

This compound, known to the CTFA as Quaternium-18, is used in a wide variety of consumer goods including vast quantities of fabric softener products. The CAS number is 61789-80-8.

ORGANOCLAY SYNTHESIS REACTION

Bulk Drug - Q-18 B:

The reaction of the purified sodium bentonite and the quaternary amine is a classic ion-exchange reaction in which exchangeable sodium ions on the surface of the bentonite platelets exchange with the cationic amine moiety. The resultant product, quaternium-18 bentonite, is now hydrophobic and is easily isolated and dried to a fine powder. This substance becomes the bulk drug and will be compounded at another site into the lotion final-product form.

Section 6: **Introduction Of Substances Into The Environment**

Bulk Drug Product - Q-18 B:

The bulk drug product, quaternium-18 bentonite, will be manufactured at [redacted] The manufacturing site is an industrial complex located within the city of Louisville.

[redacted] Very little, if any, Q-18 B material is anticipated to be released to the environment. As described below process and plant controls effectively remove any product from air emitted into the local ambient air. Thus, the approval of the application which this environmental assessment supports will produce minimal, if any, effect on the environment.

Substances Expected To Be Emitted:

Bulk Drug Product - Q-18 B Manufacturing Emissions:

These include clay purification by-products, which are comprised of various siliceous minerals, shale, feldspar, and the like. These substances are non-hazardous and are landfilled. [redacted] The presence of residual amine in the water outflow has never been observed.

Emission Controls Exercised:

Bulk Drug Product - Q-18 B Emission Controls:

Controls exercised include dust management and baghouse recovery systems designed to prevent the expulsion of any dry, raw bentonite or dry quaternium -18 bentonite from exiting the plant proper.

[redacted]

[redacted] Appendix B provides supportive data showing that nuisance dust during Q-18 B manufacturing is well below the occupational health guidelines for employee safety over 8 hour sampling times.

[redacted] Wastewater effluents fall under the jurisdiction of the Louisville and Jefferson County Metropolitan Sewer District and the applicant's facility is currently in compliance with the regulations set forth by this agency. Production of the amount of Q-18 B envisioned by the proposed action will not result in significant additional effluents to the wastewater discharge system.

Citation And/Or Statement Of Compliance:

Local & Regional: See Appendix A

These certifications are provided by the Louisville and Jefferson County Metropolitan Sewer District and the Jefferson County Regional Air Pollution Control Board. Both organizations have certified that the applicant's facility meets current mandates.

In addition, the facility is subject to the U.S. Occupational Safety and Health Administration Act of 1970 and specifically the health and safety standards promulgated and enforced by the Occupational Safety and Health Administration, U.S. Department of Labor. The facility has implemented appropriate programs which ensure that copies of material safety data sheets are made available to employees.

A certification of compliance with environmental and occupational exposure regulations applicable to the manufacture of Q-18 B is presented in Appendix D.

Effect Of Proposed Action Upon Compliance With Current Emissions:

Bulk Drug Product - Q-18 B:

[redacted]

Sections 7-11. **Not applicable for abbreviated environmental assessment.**

Section 12. **List Of Preparers:**

Anthony A. Schulz
Manager of Business Development

Schulz holds a Bachelor's Degree in Chemistry. Concurrent with management of this project, Schulz was Manager of Technical Services for the

Section 13. **Certification:**

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the

Date: September 1, 1994

Signature: [redacted]

Title: Business Unit Manager

Section 14. **References:**

1. CTFA Dictionary information on Quaternium -18 and Quaternium-18 Bentonite.

2. CTFA "Final Report on the Safety Assessment of Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite"

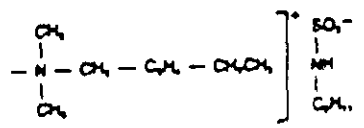
Section 14. References

CTFA Dictionary information on Quaternium-18 and Quaternium-18 Bentonite

Q

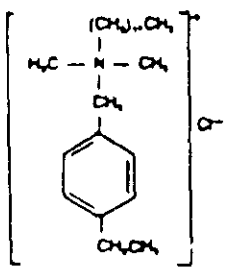
SSIN
Number: 79-78-8
ical Formula:
$H_{30}O_8$
tion: Quassin is a bitter alkaloid
ed from the wood of Quassia amara.
nefly used as a denaturant for
alcohol.
ation Sources: 27CFR212.87a, ARG,
15), FOR, TSCA
Names:
2-Dimethoxypicrasa-2,12-diene-
,11,16-trione
rasa-2,12-diene-1,11,16-trione, 2,12-
)imethoxy-
rials Containing:
-Dendra Plex (Bio-Botanica)

TERNIUM-8
umber: 977066-07-1
ition: Quaternium-8 is the quaternary
onium salt that conforms generally to
rmula:



e esents a mixture of fatty acid
als.
nation Sources: 21CFR175.105.
C
Names:
yl Dimethyl Ethylbenzyl Ammonium
Cyclohexyl Sulfamate
nyride 172 (Onyx)

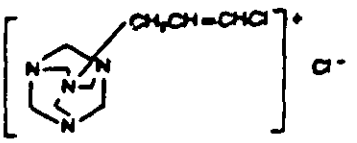
TERNIUM-14
Number: 27479-28-3
ical Formula:
$H_{42}N \cdot Cl$
ition: Quaternium-14 is the quaternary
onium salt that conforms generally to
ormula:



mation Sources: TSCA
r Names:
ene-1-ethanaminium, N-Dodecyl-N-
E N-Dimethyl-, Chloride
T Onyx)
Dodec.,- Dimethyl Ethylbenzyl Ammonium
Chloride
-Dodecyl-N-Ethyl-N,N-
Dimethylbenzenemethanaminium Chloride

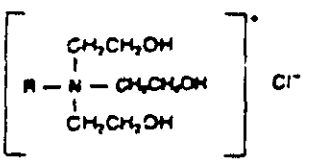
Materials Containing:
BTC 2125 (Onyx)
BTC 2125 M (Onyx)

QUATERNIUM-15
CAS Number: 4080-31-3
Empirical Formula:
$C_6H_{12}ClN_4 \cdot Cl$
Definition: Quaternium-15 is the quaternary ammonium salt that conforms to the formula:



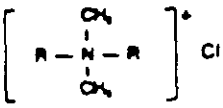
Information Sources: 21CFR175.105, 21CFR178.170, CTFA C, MI(2089), TSCA
Other Names:
N-(3-Chloroallyl)Hexaminium Chloride
Chloroallyl Methenamine Chloride
1-(3-Chloroallyl)-3,5,7-Triaza-1-Azoniaadamantane Chloride
1-(3-Chloro-2-Propenyl)-3,5,7-Triaza-1-Azoniatricyclo[3.3.1.1]Decane Chloride
Dowicil 200 (Dow)
3,5,7-Triaza-1-Azoniatricyclo[3.3.1.1]Decane, 1-(3-Chloro-2-Propenyl)-

QUATERNIUM-16
RD Number: 977068-37-3
Definition: Quaternium-16 is the quaternary ammonium salt that conforms to the formula:



where R represents tallow fatty radicals.
Information Sources: CTFA C
Other Names:
Monaquat TEA-30 (Mona)

✳ QUATERNIUM-18 ✳
CAS Number: 61789-80-8
Definition: Quaternium-18 is the quaternary ammonium salt that conforms generally to the formula:

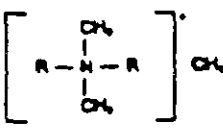


where R represents hydrogenated tallow fatty radicals.
Information Sources: TSCA
Other Names:
Adogen 442 (Sherex)
Adogen 442-100P (Sherex)
Ammonyx 2200 (Onyx)
Dimethyl Di(Hydrogenated Tallow) Ammonium Chloride
Kemamine O-9702C (Humko)
Quaternary Ammonium Compounds, Bis(Hydrogenated Tallow Alkyl)Dimethyl, Chlorides
Varisoft 100 (Sherex)
Materials Containing:
Arquad 2HT-75 (Armak)
Varisoft 775 (Sherex)
Varisoft 3262 (Sherex)

✳ QUATERNIUM-18 BENTONITE ✳
CAS Number: 68953-58-2
Definition: Quaternium-18 Bentonite is a reaction product of Bentonite (q.v.) and Quaternium-18 (q.v.).
Information Sources: 21CFR175.300, 21CFR178.3570, CTFA C, TSCA
Other Names:
Bentone 34 (NL Chemicals)
Quaternary Ammonium Compounds, Bis(Hydrogenated Tallow Alkyl)Dimethyl Chlorides, Reaction Products with Bentonite

QUATERNIUM-18 HECTORITE
RD Number: 977062-10-4
Definition: Quaternium-18 Hectorite is a reaction product of Hectorite (q.v.) and Quaternium-18 (q.v.).
Other Names:
Bentone 38 (NL Chemicals)
Quaternary Ammonium Compounds, Bis(Hydrogenated Tallow Alkyl)Dimethyl Chlorides, Reaction Products with Hectorite
Materials Containing:
Bentone Gel MIO (NL Chemicals)
Bentone Gel SS 71 (NL Chemicals)
BLUU NC-20 (Mearl)
BLUU TX-LAL-D-6 (Mearl)
BLUU Ultra TX-LCL-E-6 (Mearl)
Flamenco TX-EVF-H-6 (Mearl)
Mearmaid TX-EPM-8-6 (Mearl)

QUATERNIUM-18 METHOSULFATE
CAS Number: 61789-81-9
Definition: Quaternium-18 Methosulfate is the quaternary ammonium salt that conforms to the formula:



where R represents the hydrogenated tallow radical.
Information Sources: TSCA
Other Names:
Carsosoft V-100 (Lonza)
Quaternary Ammonium Compounds, Bis(Hydrogenated Tallow Alkyl)Dimethyl Methyl Sulfates
Materials Containing:
Carsosoft V-90 (Lonza)

QUATERNIUM-22
CAS Number: 51812-80-7
Empirical Formula:
$C_{18}H_{36}N_2O \cdot Cl$
Definition: Quaternium-22 is the quaternary ammonium salt reported to conform generally to the formula:

CTFA "Final Report on the Safety Assessment of Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite"

5

Final Report on the Safety Assessment of Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite

Quaternium-18 is a mixture of quaternary ammonium chloride salts. Quaternium-18 Hectorite and Bentonite are the reaction products of Quaternium-18 with clays. These compounds are poorly absorbed through the skin. Acute oral and percutaneous toxicity tests in animals indicate that they exhibit little or no systemic toxic effects. Subchronic oral and dermal toxicity tests on Quaternium-18 and Quaternium-18 Bentonite present no evidence of systemic toxicity.

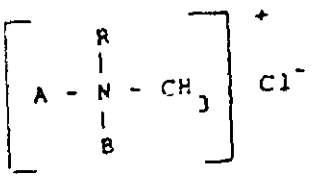
These compounds are only slightly irritating to the animal skin, and are not sensitizing agents. In ocular irritation studies all three compounds have been shown to be at most mild irritants.

Quaternium-18 has been found to be practically nonirritating and nonsensitizing to human skin. Quaternium-18 Hectorite is classified as a nonirritating, and nonsensitizing agent. It does not present adverse phototoxic or photoallergenic effects. Quaternium-18 Bentonite is not an irritating or sensitizing agent to the human skin and does not induce ocular irritation in humans.

On the basis of the available information, it is concluded that Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite are safe as cosmetic ingredients in the present practices of use and concentration.

CHEMICAL PROPERTIES

Quaternium-18: Quaternium-18 is a mixture of quaternary ammonium chloride salts conforming to the general formula:



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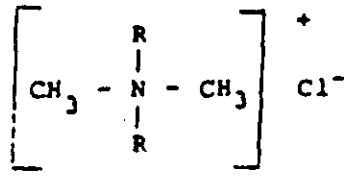
where R = hydrogenated tallow fatty radicals having a chain length distribution of C_{18}(63%), C_{16}(31%) and C_{14}(4%) and where A,B = $-CH_3$, $-CH_3$, or $-CH_3$, R or R,R. Tallow is fat derived from ovine or bovine adipose tissue that is comprised principally of fatty acid glycerides.[1]

Quaternium-18 is predominantly (90–100%) a dimethyl, ditallow quaternary nitrogen compound as shown below. From 0–5% trimethyl monotallow ammonium chloride, or monomethyl tritallow ammonium chloride may also be present.[1,2]



Quaternium-18 is produced by hydrolysis, ammonolysis, and hydrogenation of tallow. Quaternization is completed by alkylation with CH_3Cl.[2]

Quaternium-18 Clays: Quaternium-18 Hectorite and Quaternium-18 Bentonite are the ion exchange addition products of Quaternium-18 and Hectorite or Bentonite clays, respectively.[1,2] The production of these two ingredients is described in U.S. Patent No. 2,531,427.[3] The clay material is reacted with an aqueous slurry of the quaternary compound. When the adduct precipitate is washed and dried, the final product is ready.

Bentonite is a native hydrated colloidal aluminum silicate clay which has absorptive properties. It is a Smectite (Montmorillonite) mineral clay with a general formula of $Al_2O_3 \cdot 4SiO_2 \cdot H_2O$; magnesium can displace some of the constituent aluminum. Although the composition of Bentonite varies regionally, a typical analysis is as follows: SiO_2 (64.32%), Al_2O_3 (20.74%), Fe_2O_3 (3.03%), Na_2O (2.59%), MgO (2.30%), CaO (0.52%), FeO (0.46%), K_2O (0.39%), SO_3 (0.35%), TiO_2 (0.14%), and H_3PO_4 (0.01%).

Hectorite is a Smectite mineral clay with a general formula of $3\,MgO \cdot 4SiO_2 \cdot H_2O$; lithium can displace some of the constituent magnesium. While the composition of Hectorite varies according to its regional origin, a typical analysis is as follows: SiO_2 (56.30%), MgO (26.00%), F^- (3.47%), Na_2O (2.70%), CaO (2.50%), Li_2O (1.51%), CO_2 (1.30 percent), Al_2O_3 (0.1%), and FeO (0.05%).[1,2,4]

Physical Properties

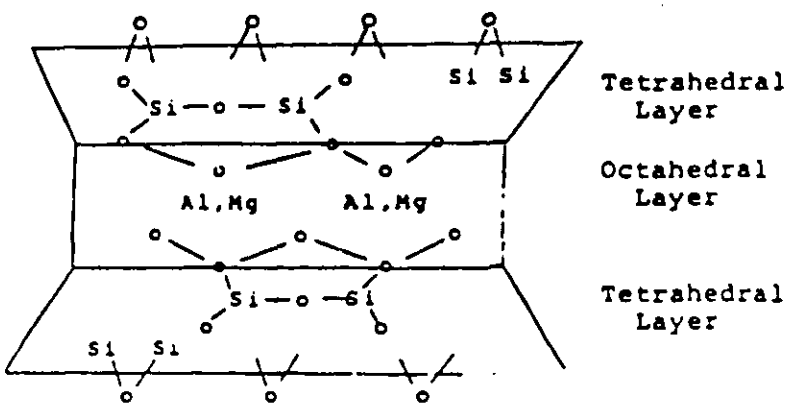
Quaternium-18: As a result of its polar nature, Quaternium-18 exhibits hydrophilic properties. A paste-like substance, it is soluble in both water and isopropyl alcohol.[2]

Quaternium-18 Clays: Quaternium-18 Hectorite and Bentonite are relatively inert organo-clay compounds that are heat stable up to 500°C and resist base or acid attacks over a pH range of 3–11. When added to other compounds, they tend to render them more stable. Both are hydrophobic agents but can stabilize emulsions by inhibiting oil-water phase separation. These ingredients have a gel-like consistency that display thixotropic properties. When the gel is

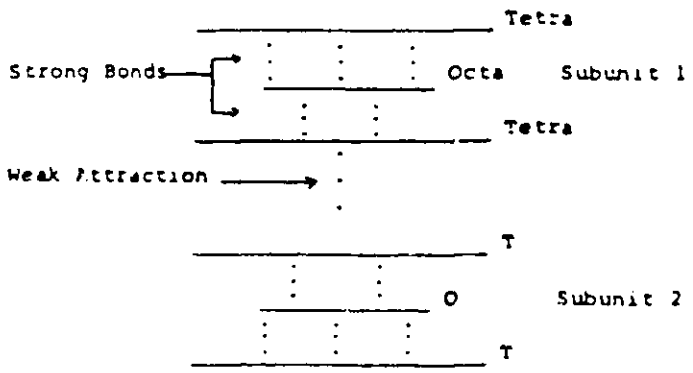
disturbed, it tends to become more fluid, which adds aesthetic value to certain cosmetic products.[5,6]

The Quaternium-18 clays are expansible in water, methanol, ethanol, isopropanol, sorbitol, glycerine and acetone.[4]

Hectorite and Bentonite Clays: Silicate clays are composed of three-layer subunits. Each trilaminar subunit consists of two tetrahedral layers sandwiching an octahedral layer. The former layers contain silicon and oxygen in tetrahedral configuration; the latter contains aluminum (Bentonite) or magnesium (Hectorite) and oxygen in octahedral configuration. Oxygen molecules located along the faces of the octahedral subunit are shared with the tetrahedral subunits. Thus, intralayer binding within a given subunit is covalent and strong.



Oxygen molecules also project from the free surfaces of the tetrahedral layers. Interlayer attraction between subunits is by Van der Waals forces and is relatively weak. The individual subunits are free to slide over one another so as to give the clay a slick texture.



Hectorite and Bentonite are swelling clay minerals in which the interlayer spacing between adjacent subunits is in dynamic equilibrium with the amount of available moisture. Since the interlamellar forces are weak, water molecules can readily permeate the interlayer spaces. Dry clay has a spacing between subunits of 9.5 Å. At 50% relative humidity, the spacing is 12.5–15 Å; at 100% saturation, it reaches 18 Å. Many water-miscible organic compounds (methanol, ethanol,

isopropanol, sorbitol, glycerine and acetone) can also expand these clays in the same way.

The combination of weak interlayer forces and the percent hydration with such other factors as the presence of interlaminar cations gives these clays their gel-like nature. Changes in hydration or electrolyte composition of the cosmetic medium being used or the application of shearing stresses can cause the gel to become more fluid (thixotropy). Removal of such perturbations promotes regelation of the formulation.[8]

Reactivity

Quaternium-18 Hectorite and Bentonite are inert, chemically stable materials. They are both pH and heat stable under the normal conditions of cosmetic use.[5,6]

Analytical Methods

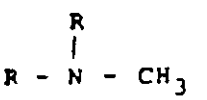
Four techniques are described for the determination of quaternary ammonium chloride salts.[2]

1. *Free sodium chloride content.* The sample is ashed and titrated with $AgNO_3$ (0.1 N).
2. *Quaternary chlorides.* The sample is dissolved in isopropanol and titrated with $AgNO_3$ (0.1 N) in the presence of dichlorofluorescein (0.1% w/v of isopropanol) indicator.
3. *Free amine value.* The sample is melted (if solid) and dissolved in isopropanol to which brompherol blue (0.2% w/v of isopropanol) indicator has been added. The solution is then titrated with isopropanol-HCl (0.1 N).
4. *Acid value–percent amine hydrohalide.* The sample is melted (if solid) and dissolved in isopropanol to which phenolphthalein indicator has been added. The solution is then titrated with isopropanol-KOH (0.1 N).

Impurities

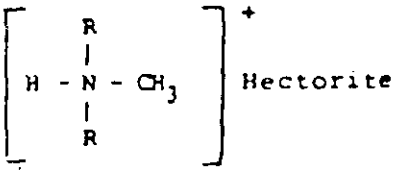
Three groups of impurities are associated with Quaternium-18 Hectorite and Bentonite. These are listed below in descending order of predominance (concentrations not reported).[2]

1. Methyl, ditallow amine



where R is as before.

2. Methyl, ditallow ammonium Hectorite



3. Sodium chloride, NaCl

No reference has been found pertaining to the use of preservatives or antioxidants with these compounds.

PURPOSE AND FREQUENCY OF USE IN COSMETICS

In a variety of cosmetic products, the Quaternium-18 compounds are employed to maintain suspensions during application (that is, to ensure uniform dispensing of the active ingredients) and to inhibit compaction or settling. They are added to lotions and creams for both thermal and physical emulsion stabilization (that is, to inhibit phase separation). The thixotrophic properties of these ingredients add aesthetic value to lipsticks and makeups.[7]

Table 1 presents categories and concentrations of use of the Quaterniums.[8] The cosmetic product formulation computer printout which is made available by the Food and Drug Administration (FDA) is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations (1979). Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the true, effective concentration found in the finished product; the effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Quaternium-18 has been reported to be used in 20 products (concentration range of 0.1–10%); it is employed in hair conditioners and rinses and in nail polish and enamels. Quaternium-18 Bentonite is used (concentration range of 0.1–10%) in eight personal cleanliness and lipstick products. Quaternium-18 Hectorite is used (concentration range of 0.1–10%) in over 140 eyeshadows and mascaras, face powders, blushers and rouges, lipsticks, nail polish and enamels, and various gels, creams, and lotions. These products, along with the approximate Quaternium concentration used in each of them, are listed in Table 1.[8]

Quaternium-based formulations can come into contact with the face (makeups, rouge, blushers, powders); the eyelids (mascara, eyeshadows); the lips (lipsticks); the hair (conditioners, rinses); the nails (polish, enamels); the entire skin (gels, creams, lotions); and the hands (when the product is applied to other areas of the body) (Table 1).

The frequency with which Quaternium-containing products are applied may vary from occasionally (hair conditioners and rinses) to daily (eyeshadow, mascara, lipsticks). The duration of application can range from seconds (hair conditioners and rinses) to all day (creams, lotions, mascara, powder, lipstick); these products may remain in contact with the body for extended periods of time (nail polishes and enamels), and occasional or daily use may extend over many years (Table 1).

TABLE 1. Product Formulation Data.[a]

Ingredient/ Cosmetic product type	Concentration (%)	No. of product formulations
Quaternium-18 Hectorite		
Eyeshadow	>5-10	3
	>1-5	9
	>0.1-1	5
Mascara	>1-5	9
	≤0.1	3
Other makeup preparations	>1-5	1
Blushers (all types)	>5-10	1
	>0.1-1	4
Face powders	>0.1-1	1
Foundations	>0.1-1	1
Lipstick	>1-5	7
	>0.1-1	1
Makeup bases	>1-5	1
	>0.1-1	1
Rouges	>1-5	5
	≤0.1	1
Other makeup preparations	>5-10	1
	>1-5	1
Nail polish and enamel	>1-5	26
	>0.1-1	55
	≤0.1	1
Other personal cleanliness products	0.1-1	4
Suntan gels, creams, and lotions	>5-10	1
Quaternium-18		
Hair conditioners	>5-10	1
	>1-5	4
Rinses (noncoloring)	>0.1-1	4
Nail polish and enamel	>0.1-1	11
Quaternium-18 Bentonite		
Lipstick	>5-10	1
Other personal cleanliness products	>0.1-1	7

[a]Data from Ref. 8.

BIOLOGICAL PROPERTIES

General Effects

Dimethyl, dioctadecyl ammonium chloride (DDAC), has been evaluated in an in vivo percutaneous absorption study. Ten mg of the ^{14}C-radiolabeled (30 μCi) compound was applied in an open patch test to a 5 × 8 cm area on the dorsal surface of each of four rabbits. All excreta (urine, feces, expired CO_2) were collected for 72 hours. Approximately 89% of the delivered radioactivity was recovered: 88% (skin test site); 0.29% (cage wash); 0.27% (CO_2); 0.20% (other skin); 0.16% (feces); and 0.15% (urine). These data indicate that DDAC does not appreciably penetrate the skin.[19]

The same investigator who conducted the study just described confirmed his

results in an in vitro study which used skin from the abdomen of human infants; DDAC did not penetrate this material.[9]

The FDA has proposed that Bentonite clay be granted GRAS status as a direct food ingredient. Upon oral administration, very little (if any) Bentonite clay is absorbed. As much as 3% in the diet of experimental animals had no negative effects.[10]

Animal Toxicology

Acute Studies

Oral toxicity

Acute oral toxicity studies have been conducted on all three Quaternium compounds and on a variety of cosmetic formulations in which they appear.

Quaternium-18: A 5% aqueous dispersion of this ingredient was administered to male rats by intragastric intubation. Six rats each received 5 g/kg of the dispersion and four received 10 g/kg. No deaths occurred in either group. The LD50 of the dispersion was estimated to be in excess of 10 g/kg. The estimated LD50 of Quaternium-18 is somewhat greater than 0.5 g/kg, since the dispersion contained only a 5% concentration of this ingredient.[11]

In another study, a 4% aqueous dispersion was given orally in doses of 5, 10, and 20 ml/kg to groups of six rats. None of the rats died during the 14-day observation period that followed dosing. The LD50 was reported as greater than 20 ml/kg of the 4% dispersion, which allows the LD50 of the ingredient to be calculated as greater than 0.8 g/kg.[12]

A 75% aqueous suspension administered orally to rats at two dose levels (doses or number of rats were not specified) was described as having an LD50 of 7000 mg/kg. This reflects an oral LD50 of the ingredient of 5250 mg/kg.[13]

Doses varying from 1 g/kg to 10 g/kg of a 70% solution of Quaternium-18 in isopropanol were given orally to 98 rats. The doses below 5 g/kg were further diluted with isopropanol. The resultant LD50 was 6.35 g/kg. (This LD50 included the effect of the isopropanol, which was not tested separately).[14]

Quaternium-18 Hectorite: In an acute oral toxicity study, five groups of five rats each were given a 50% (w/v) aqueous suspension by gavage; the doses ranged from 1.25–20 g/kg. No deaths occurred during the 14-day observation period. The oral LD50 of the suspension is greater than 20 g/kg or greater than 10 g/kg of the ingredient.[15]

Products that include relatively small amounts of the ingredient were tested for oral toxicity. When an eyeshadow formulation containing 10 percent Quaternium-18 Hectorite was evaluated in rats, the product's LD50 was calculated to be greater than 5 g/kg.[16] Three personal cleanliness formulations were each given to 10 rats in 1 g/kg oral doses; for each formulation tested, the LD50's were greater than 1 g/kg.[17]

When a fingertip powder blusher (10% Quaternium-18 Hectorite) was administered orally to 10 rats via stomach intubation at a single dose of 25 g/kg, no mortalities resulted. The LD50 of the product was reported as greater than 25 g/kg.[18]

Quaternium-18 Bentonite: This ingredient was given orally, as a suspension in cottonseed oil in doses of 8 g/kg, to twenty rats. No deaths occurred in two weeks following dosing. The suspension was difficult to manipulate, so no higher doses were given. Available data indicate that the LD50 is greater than 8 g/kg.[14]

Skin irritation

Quaternium-18: An aqueous dispersion containing 5% of this ingredient was applied to one intact and one abraded area of the skin of each of six rabbits. To each area, 0.5 ml was applied and covered by a gauze patch which was removed after 24 hours; then the remaining dispersion was washed off. At 24 and 72 hours after application, the reaction was graded; no irritation was found.[111]

Tested with a similar procedure, a 4% aqueous dispersion gave comparable results.[112]

A more concentrated (75%) sample of the ingredient was tested according to the Draize method. The Primary Irritation Index (PII) was calculated to be 1.92 out of a possible maximum of 8. Examination of the scores showed that erythema had increased at the 72-hour observation period, indicating that there had been a delayed irritant reaction.[113]

Another commercial 75% aqueous dispersion of Quaternium-18 was studied at concentrations of 2%, 5% and 10%. The actual concentrations of the ingredient were 1.5, 3.7, and 7.5%. Patches containing 0.05 g of the suspensions were applied to the skin of rabbits and allowed to remain there for 21 days, after which the patches were removed and the irritation at the sites graded. The dispersion was determined to be a mild irritant at the concentrations used.[112] This same product was also tested at 10 percent to determine its ability to irritate mucosa; 0.2 ml of the commercial product was applied to the penile mucosa of rabbits. Grading of the irritation gave a score of 0.43 out of a possible maximum of 4, showing this product had a mild ability to irritate mucosa.[112]

Quaternium-18 Hectorite: A Federal Hazardous Substance Act skin irritation test was conducted with this compound, using a dose of 0.5 g of a 50% suspension in water on each of six rabbits. When it came in contact with intact or abraded skin, this material did not produce any irritation.[114]

Quaternium-18 Bentonite: The undiluted ingredient was applied in quantities of 0.5 g to both intact and abraded rabbit skin. After contact was maintained for six hours per day for five consecutive days, there were 10 days of rest and then five more days of exposure. No reaction was found, and the test material was considered to be inert.[114]

Skin sensitization

Quaternium-18 Bentonite: The ability of this ingredient to produce allergic reaction on the skin of guinea pigs was studied by intracutaneous injection. Twelve guinea pigs were given an initial injection of 0.05 ml of the test sample (0.1% in physiological saline). Then, three additional injections of 0.1 ml were made each week for the next three weeks, after which there was a two-week rest period. At the end of this time, challenge doses of 0.05 ml were injected. Increased reaction to the challenge dose over the induction dose would have indicated a sensitization. However, the challenge doses gave less reaction than the induction dose, indicating no sensitization.[116]

Eye irritation

Quaternium-18 One-tenth of a milliliter of a 5% aqueous dispersion of this ingredient was instilled in one eye, the other remaining untreated as a control; six rabbits were used. Cornea, iris and conjunctiva were all found free of irritation during the 72-hour observation period.[111]

A 4% dispersion of the ingredient was tested by the same procedure. No cor-

neal or iridial irritation occurred, but some conjunctival irritation, which disappeared with time, was reported.[113]

A product containing a 75% suspension of the ingredient was also tested in the rabbit eye. The product was diluted to 10% (making the test material a 7.5% dispersion), and 0.1 ml of this was placed in the conjunctival sac. Readings were made at 24 and 48 hours after instillation. The eye irritation score was reported to be 11.7 out of a possible 110, making the 7.5% dispersion a minimal irritant.[113]

Quaternium-18 Hectorite: A rabbit eye irritation test was performed according to the Draize method with 0.1 ml of a 50% aqueous suspension; no irritation was produced.[115]

Quaternium-18 Bentonite: Instillation of 0.1 ml of a 10% suspension in physiological saline was made into one eye of each of 10 rabbits. Twenty-four hours after instillation, the "test eyes" were completely negative for irritation.[114]

Acute inhalation toxicity

Quaternium-18 Hectorite: An inhalation toxicity study evaluated a one-hour exposure of 10 rats to a mist containing the ingredient. Quaternium-18 Hectorite was mixed with isopropyl myristate to facilitate spraying (concentration not stated). One hundred forty-three grams of the mixture were atomized in the one-hour period; the nominal concentration was calculated to be 202 mg/l. In the 14 days following exposure, no toxic manifestations were noted and no deaths occurred.[115]

Subchronic Studies

Oral toxicity

Quaternium-18: This material was fed at varying concentrations to guinea pigs for 12 days. Uniform doses of 10 ml/kg were administered daily to two animals at each concentration. The lowest dose level that produced signs of toxicity appeared to be 1 g/kg/day.[113] Quaternium-18 was also fed to dogs and rats at subacute dietary levels of 2800 ppm for 90 days. No abnormalities were found in food consumption, body weight, reaction, mortality, or urinalysis, or in hematologic, blood chemistry, gross pathologic, or histopathologic studies.[113]

Quaternium-18 Bentonite: Groups of 12 weanling rats were fed diets containing 1%, 5%, or 25% of the ingredient for 12 weeks. Two similar groups were fed the basic diet and served as controls. The gain in weight per unit of diet consumed was practically the same for groups consuming up to 5%, while a reduction of food efficiency occurred in the 25% group. At the end of 12 weeks, hematology, organ weights, gross pathology, and micropathology were essentially the same in all groups, and there was no indication that any subchronic oral toxicity was produced by the ingredient.[114]

Dermal toxicity

Quaternium-18 Hectorite: Aqueous suspensions containing 50%, 25%, 12.5%, or 0.0% of this ingredient in quantities of 4 g/kg were applied to the exposed skin of rabbits three times a day, five days per week for three weeks. Each application, spread over at least 20% of the body surface, was allowed to remain on the skin for two hours, after which the remaining material was washed off, the skin dried, and the next dose applied. Six rabbits were used for each concentration, three with intact skin and three with the skin abraded. During the study,

general health, appetite, and activity did not differ among the groups. Weight gain, hematological elements, and gross and micropathology were similar in all groups. Some animals, including controls, had inflammatory lesions in the heart, brain, liver, kidney, and lung. These were attributed not to the test materials, but to protozoan infection, which was reported to be common in rabbits obtained from commercial suppliers. The local effects on the skin consisted of mild drying and scaling of the upper layers in the early days of the study. Continued exposure did not produce involvement of the deeper layers.[119]

Quaternium-18 Bentonite: Ten rabbits were depilated (15 x 18 cm) on their dorsa and exposed under occlusion to 0.5 g of Quaternium-18 Bentonite for six hours per day for 90 days. Ten control animals were also used. Exposure sites were scored for irritation according to the Draize criteria at the end of such exposure and at the beginning of the next. Hematological and gross pathological findings were normal for both groups. Micropathology revealed minor liver and kidney abnormalities in both experimental and control groups; chronic protozoan infection was implicated. No evidence of local or systemic toxicity of Quaternium-18 Bentonite was found.[120]

Clinical Assessment of Safety

Skin Irritation and Sensitization

Quaternium-18

This ingredient was investigated for its skin irritating and sensitizing characteristics on 25 men and 25 women (Caucasian) varying in age from 18 to 35. The repeated insult, occluded patch test was employed. Patches (1.5 in^2) were saturated with sample (7.5%, unspecified diluent) and applied for 24 hours to the volar aspect of the arm; 24 hours elapsed between each scoring and application, which totalled 15 per person. Ten days after the last induction exposure, a 24-hour challenge application of sample was made to each subject. The results and accompanying analysis can be found in Table 2. Six out of the 50 subjects reacted 13 times to the 750 induction exposures. Only two of the 13 reactions were level-2 reactions. Two of the 50 subjects reacted to the challenge exposure; there were no other reactors. The mean primary skin irritation index (PSI) for all test subjects was calculated to be 0.26 out of a maximum of 8. The

TABLE 2. Repeated Insult and Skin Sensitization Human Studies–Quaternium-18[a]

		No. of subjects	No. of applications	Intensity of reactions				
				4	3	2	1	0
Primary Skin Irritation	Male	25	375	0	0	2	7	366
	Female	25	375	0	0	0	2	373
	Total	50	750	0	0	2	9	739
Skin Sensitization	Male	25	25	0	0	1	0	24
	Female	25	25	0	0	1	0	24
	Total	50	50	0	0	2	0	48

[a]Data from Ref. 13

mean skin sensitization (SS) index (calculated in the same manner as the PSI) for the 50 subjects was 0.08 out of a maximum of 8. The number of subjects tested for potential sensitization to Quaternium-18 is suboptimal. Although the number of subjects used in the testing program is suboptimal, the ingredient was classified by the investigator as "practically nonirritating and nonsensitizing to the skin."[13]

Quaternium-18 Hectorite

Pure Ingredient: This compound was evaluated for primary irritancy, "fatiguing" ability (potential cumulative effects of repeated application), and/or skin sensitizing capacity. The study included 50 humans exposed 15 times each to undiluted sample under occluded patch (3 × 3 cm) and once each to a challenge application. No visible skin changes were reported in any subject. According to the author, Quaternium-18 Hectorite may be considered nonirritating, "nonfatiguing," and nonsensitizing to the skin.[18]

Ingredient in Cosmetic Formulations: An eye shadow (10% Quaternium-18 Hectorite) was tested for skin reaction on 50 women. The undiluted product was applied to the intended area of use twice daily for 30 days. Each woman was examined five times (Weeks 0, 1, 2, 3, and 4) by a dermatologist; no evidence of skin irritation or sensitization was found.[18] Three other formulations containing Quaternium-18 Hectorite (1.0–5.0%) were tested for skin irritation and sensitization. Twelve panelists were exposed to sample (0.5 g of undiluted product) under semiocclusive patch conditions for 23 hours per day for three weeks. The products were evaluated as being slightly irritating.[18] When these same three products were applied (0.5 g) three times per week for three weeks to 175 subjects under occlusive patch conditions for 24 hours, they were found to be nonsensitizing.[18] A fingertip powder blusher (10% Quaternium-18 Hectorite) was evaluated for primary irritation and sensitization and for phototoxicity and photocontact allergenicity. A population of 209 human subjects was exposed to the product under occlusive patch test conditions (modified Draize–Shelanski–Jordan Test). No indication of skin irritation or sensitization was found.[18]

Twenty-five male and female panelists were exposed to the fingertip powder blusher (10% Quaternium-18 Hectorite) in a photopatch test. Two $\mu l/cm^2$ of sample were applied to two different skin sites which were then covered with standard patches for 24 hours. At patch removal, one treated site and a new third site were exposed for 30 seconds to light originating from a Krohmeyer hot-quartz spot-lamp and filtered through window-glass. The irradiated sites were scored immediately for irritation. The entire protocol was repeated four additional times. Challenge applications to previously untreated sites were made 12 days after the last induction exposure; one untreated and two treated sites were used. Twenty-four hours after challenge, one treated site and one untreated site were irradiated as before. The sites were examined and scored at 24 and 48 hours. No reactions were noted; the product was reported to exhibit no evidence of phototoxicity or photoallergy.[13]

Quaternium-18 Bentonite

The repeated insult patch test was employed to test two eyebrow color preparations (4.1 or 4.0% active ingredient) on 50 human subjects. No evidence of skin irritation, "fatiguing," or sensitization was found for either product.[14] A clinical test of Quaternium-18 Bentonite at a concentration greater than 4.1 per

cent would have been desirable, since one cosmetic formulation contains > 5–10% of the ingredient.

Eye Irritation: Quaternium-18 Hectorite has been screened for its capacity to cause ocular irritation in the human. Two preparations were used: undiluted, finely divided powder (20 g of powder dissolved in 100 ml of physiological saline) and 20 g of powder suspended in 100 ml of corn oil. The undiluted powder (2 mg) was applied directly in the conjunctival sac of one eye in each of 10 subjects. Panelists were asked to describe any adverse symptoms they experienced immediately following instillation of the sample and the eyes were examined immediately and after 1 and 24 hours. All subjects reported a "sand-like" feeling in the treated eye, but without stinging or pain. The two diluted compounds were tested simultaneously, one sample per eye of each of ten panelists. Upon instillation, both eyes were held shut for one minute; the subjects were then asked to open their eyes and describe any abnormal ocular sensations. No one reported feeling pain in either eye, though (like the undiluted powder) the saline-dissolved sample gave a "sand-like" feeling to the eye. All treated eyes were examined (in an unspecified manner) at 0, 1, and 24 hours. No obvious damage to the eye was observed.[113]

SUMMARY

Quaternium-18 is a mixture of quaternary ammonium chloride salts. Quaternium-18 Hectorite and Bentonite are the reaction products of Quaternium-18 and Hectorite or Bentonite clays, respectively. All three ingredients are used in cosmetic formulations at concentrations ranging from 0.1% to 10%. Cosmetics containing these compounds may come into contact with all body surfaces and may be used on a daily basis over extended periods of time.

Quaternium-18 Hectorite and Bentonite are chemically, physically, and biologically inert. Quaternium compounds are poorly absorbed through the skin. Acute oral and percutaneous toxicity tests in animals indicate that all three compounds exhibit little or no systemic toxic effects. Quaternium-18 Hectorite was also found to be nontoxic in an acute inhalation study. Subchronic oral and dermal toxicity tests on Quaternium-18 and Quaternium-18 Bentonite presented no evidence of systemic toxicity. No chronic studies have been reported.

All three Quaternium compounds under review here can be considered to cause at most only slight irritation to the animal skin. None has been reported to be skin sensitizing agents. In ocular irritation studies in rabbits, all three compounds have been shown to be at most mild irritants.

Clinical studies have determined that Quaternium-18 is practically nonirritating and nonsensitizing to the skin. Quaternium-18 Hectorite can be classified as a nonirritating, "nonfatiguing," and nonsensitizing agent; it does not present any adverse phototoxic or photoallergenic effects. Quaternium-18 Bentonite is not an irritating, "fatiguing," or sensitizing agent to the human skin. Quaternium-18 Hectorite exhibits no ocular irritation in humans.

There is no reported information concerning any of the Quaternium-18 compounds with respect to absorption, metabolism, storage, excretion, teratology, mutagenesis, or carcinogenesis.

CONCLUSION

On the basis of the available information presented in this report, the Expert Panel concludes that Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite are safe as cosmetic ingredients in the present practices of use and concentration.

REFERENCES

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21. CTFA. (1980) Submission of data by CTFA. Unpublished safety data on Photopatch Test Protocol.*

*Available upon request, Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Ave., N.W., Washington, DC 20005

Section 15. **Appendices:**

A. Certificates of Compliance:

1. Jefferson County Department of Planning and Environmental Management, Air Pollution Control Board
2. Louisville and Jefferson County Metropolitan Sewer District

B. Reports of Nuisance Dust Sampling - United Catalysts, Inc.
Supportive data showing that nuisance dust at the Q-18 B manufacturing site is well below government guidelines. Standard air sampling techniques were utilized to provide 8 hour total data.

C. Material Safety Data Sheets
1. Tetrasodium pyrophosphate
2. Dimethyl dihydrogenated tallow ammonium chloride (Quaternium-18)
3. sodium bentonite
4. 20 deg. (31.5%) hydrochloric acid
5. Quaternium-18 Bentonite

D. General Compliance Statement

Section 15. Appendices

Certificates of Compliance

JEFFERSON COUNTY, KENTUCKY
DEPARTMENT OF PLANNING AND ENVIRONMENTAL MANAGEMENT
AIR POLLUTION CONTROL DISTRICT

DAVID L. ARMSTRONG
County Judge/Executive

ADRIAN P. FREUNT
Department Director

BILLY J. SEXTON, P
District Director

December 3, 1993

Mr. Tony Schulz
United Catalysts, Inc.
P.O. Box 32370
Louisville, Kentucky 40232

RE: AIR POLLUTION COMPLIANCE STATUS

Dear Mr. Schulz:

This letter is to advise you that United Catalysts Rheological Division "Tixogel" is presently in compliance with Jefferson County's Air Pollution Regulations and that no violations are being investigated at this time.

Sincerely,

Billy J. Sexton

Billy J. Sexton, P.E.
Director

c: Larry Maze

BJS/kbw

03:LETTER93:kbw

850 Barret Avenue
LOUISVILLE, KENTUCKY 40204
(502) 574-6000 • FAX (502) 574-5306

An Equal Opportunity Employer

Metropolitan Sewer District
Louisville, Kentucky 40201-2301
Mail To: P.O. Box 740011
Louisville, Kentucky 40201

1126

MSD

December 2, 1993

Mr. Tony Schulz
United Catalyst West Plant
P.O. Box 32370
Louisville, KY 40212

RE: Compliance Status

Dear Mr. Schulz:

The United Catalyst West Plant facility is currently in compliance with the conditions set forth in their Significant Industrial Wastewater Discharge Permit #8212. This permit includes the wastewater from the Tixogel production and process areas.

If you have any questions concerning this matter, please contact me at (502) 540-6955.

Respectfully,

Gregory D. Ratliff
Pretreatment Coordinator

cc: IWIS
permit file

gdr

An equal opportunity employer M F H V
Printed on Recycled Material

Material Safety Data Sheets

Pages 36-51
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United Catalysts Inc.

Rheologicals Group

P O Box 32370
Louisville KY 40232 USA
Telephone 502-634-7500
Telex 204190 204239
Fax 502-634-7720

MATERIAL SAFETY DATA SHEET

As explanation of the terms used herein may be found in OSHA 29 CFR 1910.1200, available from OSHA regional or area offices. (Essentially similar to U.S. Department of Labor Form OSHA 20)

Emergency Telephone No.
(502) 634-7500

Information Telephone No.
(800) 468-7210

Date of Preparation
March 5, 1992

HMIS & NFPA

HEALTH	1
FLAMMABILITY	0
REACTIVITY	0

SECTION I - PRODUCT IDENTIFICATION

PRODUCT NUMBER 36521000	CAS NO. 68911-87-5
PRODUCT NAME Tixogel VP	
PRODUCT CLASS Organoclay	

SECTION II - HAZARDOUS INGREDIENTS

INGREDIENT	OCCUPATIONAL EXPOSURE LIMITS OSHA/PEL(TWA)	ACGIH/TLV(TWA)	VAPOR PRESSURE
Crystalline Quartz (Respirable) CAS No. 14808-60-7	0.1 mg/m^3	0.1 mg/m^3	N/A
Crystalline Cristobalite (Respirable) CAS No. 14464-46-1	0.05 mg/m^3	0.05 mg/m^3	N/A

Total Silica, Crystalline: May contain greater than 0.1% wt.

SECTION III - PHYSICAL DATA

BOILING RANGE	N/A	VAPOR DENSITY	N/A
EVAPORATION RATE	N/A	% VOLATILE WEIGHT	<2.5%
		WT/GAL	14.99 lbs/U.S. Gal

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

FLAMMABILITY CLASSIFICATION: OSHA N/A DOT N/A
FLASH POINT: N/A LEL: *0.07 oz/ft^3
EXTINGUISHING MEDIA:
XX FOAM "ALCOHOL" FOAM CO_2 XX DRY CHEMICAL XX WATER FOG
UNUSUAL FIRE AND EXPLOSION HAZARDS: *Tixogel VP does not normally present a fire or explosion hazard, but dust concentrations greater than 0.07 oz/ft^3 may ignite at 510°C or when exposed to a spark or other ignition source.
SPECIAL FIREFIGHTING PROCEDURES: Normal precautions for flammable dusts should be followed.

SECTION V - HEALTH HAZARD DATA

EFFECTS OF OVEREXPOSURE: See Warning.
MEDICAL CONDITIONS PRONE TO AGGRAVATION BY EXPOSURE: Continued exposure of dust to skin and/or mucous membranes may cause drying of exposed areas. Avoid chronic inhalation of dust.
PRIMARY ROUTE(S) OF ENTRY: DERMAL XX INHALATION INGESTION
EMERGENCY AND FIRST AID PROCEDURES: No special procedures.

SECTION VI - REACTIVITY DATA

STABILITY: UNSTABLE XX STABLE
HAZARDOUS POLYMERIZATION: MAY OCCUR XX WILL NOT OCCUR
HAZARDOUS DECOMPOSITION PRODUCTS: CO, and oxides of nitrogen (possible combustion products)
CONDITIONS TO AVOID: Avoid exposure of dust aerosol to spark or open flame.
INCOMPATIBILITY (MATERIALS TO AVOID): None

SECTION VII - SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Spilled powder may be collected by shoveling or sweeping provided respirator and eye protection are worn. Care should be exercised to prevent high dust concentrations in the air.
WASTE DISPOSAL: Solid waste disposal. Not suitable for incineration, chemical, or biological degradation.

United Catalysts Inc.
Rheologicals Group
P O Box 32370
Louisville KY 40232 USA
Telephone 502-634-7500
Telex 204190 204239
Fax 502-634-7720

SECTION VIII - SAFE HANDLING AND USE INFORMATION

RESPIRATORY PROTECTION: Dust mask required.
VENTILATION: Adequate dust collection system should be used to avoid formation of dust aerosol.
PROTECTIVE GLOVES: Recommended.
EYE PROTECTION: Goggles or safety glasses.
OTHER PROTECTIVE EQUIPMENT: None
HYGIENIC PRACTICES: Avoid breathing dust.

SECTION IX - SPECIAL PRECAUTIONS

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORING: Precautions for finely divided, flammable dust should be followed. Avoid high dust concentrations. Use adequate dust collection equipment. Insure all equipment is properly grounded to prevent static discharge. Keep dust away from open flame, heat, sparks, electrical equipment.
OTHER PRECAUTIONS: None

* * * WARNING:

This clay product may contain a small amount of crystalline silica which may cause delayed respiratory disease if inhaled over a prolonged period of time. Avoid breathing dust. Use NIOSH/MSHA approved respirators where TLV for crystalline silica may be exceeded. IARC monographs on the evaluation of the Carcinogenic Risk of Chemicals to Humans (volume 42, 1987) concludes that there is "limited evidence" of the carcinogenicity of crystalline silica to humans. IARC classification 2A.

Crystalline Silica: Subject to reporting under SARA III?.....NO
Listed as a carcinogen by the NTP?.....NO
Listed as a carcinogen by OSHA?.....NO

DISCLAIMER OF WARRANTY: The information presented herein is believed to be accurate. It is based, however, on the research of others as well as ourselves and, therefore, we do not guarantee its accuracy. Furthermore, the products discussed are sold WITHOUT WARRANTY EITHER EXPRESSED OR IMPLIED, INCLUDING THE WARRANTY OF MERCHANTABILITY AND FITNESS FOR USE OF THE MATERIALS and upon further condition that the purchaser shall make its own test to determine the suitability of such products for its particular purposes. The purchaser assumes all risk of use of handling whether or not in accordance with any statements made herein. Our liability, if any, for any action arising out of the material supplied shall be limited to replacement of the material. Statements made concerning possible or suggested uses of the products described herein are not intended to be recommendations for the use of such products in infringement of any patent and the user assumes all liability as to the use of such products relative to patent infringement.

General Compliance Statement

United Catalysts Inc.

Rheologicals and
Performance Minerals
Group

P O Box 32370
Louisville, KY 40232 USA
Telephone 502-634-7500
Telex 204190 204239
Fax 502-634-7727

GENERAL COMPLIANCE STATEMENT

United Catalysts Inc., Rheological Group states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of bulk drug substance Q-18 B at its facilities in Louisville, Kentucky, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of bulk drug substance Q-18 B.

Date: March 31, 1994

Signature: Chas D Mauch

Title: Business Unit Manager, Rheology

Location of Manufacturing:

Final Drug Product - Lotion:

The final drug product, in the form of a lotion, will be produced at
environmental assessment for manufacture of the final drug product is provided in the following pages.

ENVIRONMENTAL ASSESSMENT
FOR:

IVY BLOCK LOTION (QUATERNIUM-18 BENTONITE)

I. is located approximately two miles from the center of the City of San Antonio in a light manufacturing/industrial area at has been at this location since 1953 and has conscientiously observed all environmental considerations for this type of manufacturing facility.

Is bordered on the North and East perimeters by an Interstate Highway (I.H. 37) and by the San Antonio River on the West. An elementary school is located approximately two blocks West of the facility on Josephine St. A major City Park (Brackenridge Park) occupies the approximately 600 acres immediately North and Northwest of the manufacturing facility and is the location of a municipal golf course, driving range, city zoo and other recreational facilities.

.s registered with the EPA and the local Emergency Planning Commission regarding the storage of chemicals located at this site. location is listed as: Latitude 20°, 26 minutes, 45 seconds; Longitude 98°, 28 minutes, 43 seconds.

II. Due to proper controls which are utilized in the receipt, storage and use of these substances, probable impact on the environments will be minimal. Controls exercised in the handling of these substances are as follows:

A. Covered loading dock for receipt of substances.

B. Environmentally controlled and covered warehouse storage areas.

C. Localized dust collection units for the sampling, weighing and dispersion of all the ingredients.

D. Handling of the ingredients is conducted in appropriately controlled manufacturing areas.

E. Preparation of batch is conducted in environmentally controlled and GMP controlled areas.

Waste generated from the production of Ivy Block (Quaternium-18 Bentonite) will be disposed of in accordance with Local, State and Federal requirements. . utilizes the resources of licensed, bonded and certified waste disposal firms for both hazardous and non-hazardous disposal. Non-hazardous waste are handled by Garbage Gobbler, Inc. which hauls the material to the City of San Antonio's Nelson Gardens Landfill or BFI's Tessman Road Landfill. Hazardous waste shipments are handled by

It is anticipated that preparation of the Ivy Block (Quaternium-18 Bentonite) will have no significant impact on any existing waste streams.

		WASTE STREAM
A.	Losses during weighing	
	Residual active ingredient (Quaternium -18 Bentonite) in container < 100 gm	Landfill
	Residual inactive ingredients:	
	Methylparaben < 10 mg	Landfill
	Diisopropyl Adipate < 100 gm	Landfill
	Benzyl Alcohol < 10 mg	Landfill
	SD Alcohol 40-2 (Ethyl Alcohol)< 1 Kg	Evaporation
B.	Losses during processing (compounding):	
	Evaporation of Ethyl Alcohol < 13 kilograms	Evaporation and discharge to POTW *
	Washing of alcohol phase utensils	Evaporation and discharge to POTW *

*Publicly Owned Treatment Works

C. Residual product in tank and hoses after transfer to holding vessel - approximately 5 kilograms:

	AMOUNT OF WASTE	WASTE STREAM
QUATERNIUM -18 BENTONITE	0.250 Kg.	Landfill
DIISOPROPYL ADIPATE	1.000 Kg.	Landfill
BENZYL ALCOHOL	0.010 Kg.	Landfill
ETHYL ALCOHOL	1.250 Kg.	Landfill
METHYLPARABEN	0.005 Kg.	Landfill

D. Filling operation - filler setup losses - approximately 10 kilograms:

	AMOUNT OF WASTE	WASTE STREAM
QUATERNIUM -18 BENTONITE	0.500 Kg.	Landfill
DIISOPROPYL ADIPATE	2.000 Kg.	Landfill
BENZYL ALCOHOL	0.020 Kg.	Landfill
ETHYL ALCOHOL	2.500 Kg.	Landfill
METHYLPARABEN	0.010 Kg.	Landfill

E. Residual product in holding tank and hoses after packaging - approximately 5 kilograms:

	AMOUNT OF WASTE	WASTE STREAM
QUATERIUN-18 BENTONITE	0.250 Kg.	Landfill
DIISOPROPYL ADIPATE	1.000 Kg.	Landfill
BENZYL ALCOHOL	0.010 Kg.	Landfill
ETHYL ALCOHOL	1.250 Kg.	Landfill
METHYLPARABEN	0.005 Kg.	Landfill

F. Product scrap during typical packaging run - approximately 25 kilograms:

	AMOUNT OF WASTE	WASTE STREAM
QUATERNIUM-18 BENTONITE	1.250 Kg.	Landfill
DIISOPROPYL ADIPATE	5.000 Kg.	Landfill
BENZYL ALCOHOL	0.050 Kg.	Landfill
ETHYL ALCOHOL	6.250 Kg.	Landfill
METHYLPARABEN	0.025 Kg.	Landfill

III. In order to reduce the amount of environmental releases in active and excipients, the following end process controls are utilized:

A. Raw material containers are emptied as thoroughly as possible to reduce residual substances by use of flexible scrapping utensils and/or rinsing, when appropriate, and bags are emptied as completely as possible under appropriate dust control.

B. Phases of mixtures of ingredients are rinsed to remove as much of the residual substances as possible.

C. Mixing devices and tanks are scrapped down with flexible hoses to minimize residual substances and/or product.

D. Volatile substances, example - ethyl alcohol, are kept in covered containers as much as possible during weighing and processing steps to minimize evaporation.

E. Quantity of product used to purge the filler is optimized i.e.,minimal amount required to completely flush all filler parts prior to filling of containers.

F. Fill weights, torques, label placement, placement of lot code and expiry dates are all well controlled according to established SOPs to minimize product scrap associated with the filling operation.

IV.

A. Waste water permit number PM-0035 - Attachment I - The San Antonio Water System, Wastewater Quality Division is responsible for assuring San Antonio complies with EPA and State requirements for waster water discharge, stormwater runoff and other applicable functions. They conduct quarterly, random waste water sampling to monitor plant discharge as well as conduct semi-annual inspections of the facility for compliance. In order to continue to discharge into the waste water system, the agency also requires self-monitoring, semi-annual tests to assure fluid meets requirements. This permit does not have a fixed expiration date but is continually monitored for compliance. Permit information is reviewed and updated by city personnel on a semi-annual basis. The current permit was issued in 1992.

B. Texas Natural Resource Conservation Commission - Attachment II - This agency is responsible for enforcing EPA regulation, both State and Federal, regarding the generation storage and disposition of both non-hazardous and hazardous waste. Under the regulation of this authority, generates, stores and disposes of various categories of liquid and solid waste, manifests shipments when required and submits annual summary reports on waste generated. currently is registered as a small quantity generator and meets all the provisions for this category of generator. This permit does not expire as long as the conduct of generator does not significantly change. When waste water streams are added or modified, the authority issues a revised permit to cover those activities. The current permit was issued in 1993.

C. EPA and RCRA ID Number TXD980627244 - This particular identification number is issued in conjunction with the Texas Natural Resource Conservation Commission and is used in all pertinent State and Federal reporting activities regarding various generation storage and the disposition of both hazardous and non-hazardous waste. This number is issued by the TNRCC authority and continues under that number until a change in ownership or location or some other significant reason.

D. Air Quality - Attachment III - This permit is issued by the City of San Antonio, San Antonio Metropolitan Health District. This agency is charged with maintaining air quality standards in the city limits of San Antonio. The permit is issued for a period of one year. The current permit is for the period October 26, 1993, to September 30, 1994.

E. Safety - Operating procedures are safely established to minimize exposure to chemicals. Health and environmental monitoring is performed as required. manufacturing employees participate in group and individual health and safety training programs. Training regarding the proper operation of both the manufacturing equipment and material handling equipment is conducted. Monthly reviews of employee safety records are conducted and reported in a formalized report. Routine blood profile monitoring is conducted for manufacturing, technical and other personnel who might come in contact with products manufactured at the facility. Annual blood profiles are compared to baselines previously established by qualified medical personnel.

Appropriate particulate monitoring of environmental air is conducted by in-house personnel for evaluation of bioburden and by a contract industrial hygienist for determination of airborne exposure levels. Additionally, determination of decibel ratings of different pieces of manufacturing equipment are made to identify any potential areas where any hearing protection is required.

Employees routinely receive documented training in the safe and proper handling of all chemicals used in the department and have Material Safety Data Sheets available for timely reference. Prior to manufacturing of Ivy Block (Quaternium - 18 Bentonite), compounders review the safety precautions outlined in the section provided in the Compounding Module. Personal safety protection equipment available includes surgical latex gloves when handling chemical components of the drug product; safety glasses/goggles worn during the entire manufacturing process; personal respirators when handling chemicals which are prone to generation of dust and/or exposure to organic vapors. Tyvek disposal coveralls, shoe covering and head protection are also available when required.

is currently operating in compliance with all applicable emission requirements (including operational) at Local, State and Federal levels and the additional production of Ivy Block (Quaternium - 18 Bentonite) will not have any appreciable affect on our ability to continue to comply with environmental emission/discharge requirements. Attached is a General Compliance Statement which attests to that fact (Attachment IV).

F. Emergency Response Plan - In the event of a minor release, the Emergency Response Team is activated, and the area evacuated. Plant personnel who are trained in emergency response will re-enter the area wearing proper protective clothing and respiratory protection to take remedial action. Emergency equipment immediately available includes: hazmat carts, spill control kits, personal protection equipment, respirators, rescue and escape air and first aid supplies.

In the event of a serious release or an escalation of an existing situation, the external emergency plan will take effect with plant evacuation and mobilization of the Regional Hazmat Team, Fire Department and Hospital/Emergency Services.

All material generated during a clean-up will be treated as hazardous and dealt with per Federal, State and Local regulations.

The Material Safety Data Sheet for finished Ivy Block is provided as Attachment V.

Prepared by Terrance Clifford 4-19-94
Terrance Clifford
Manufacturing Manager

Approved by Michael J. Bordovsky 4-19-94
Michael J. Bordovsky
Vice President
Manufacturing Operations

Pages 66-77
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APPENDIX A

SELF-MONITORING REPORT FORM

Date _____ Permit No. _____

I. GENERAL INFORMATION

This standard reporting form may be used for alternately submitting the BMR, 90-Day Compliance, Semi-Annual and Monthly Self-Monitoring Reports.

1. Company Name _____

2. Address of Facility _____

   City _____ State _____ Zip Code _____

3. Authorized Representative _____

4. ____ Baseline Monitoring Report ____ 90-Day Compliance Report (check one)
   ____ Semi-Annual Report ____ Monthly Monitoring Report

II. SAMPLE COLLECTION INFORMATION

1. Monitoring Point # (as referenced in permit) _____

2. Sampling Date(s): _____ Sample Start Time: _____ End Time: _____

3. Person/Organization Performing Sampling: _____

4. Sample Type: (check one)
   _____ Grab _____ Time Proportional _____ Flow Proportional

   Sample Interval _____mL
   Sample Size _____
   Number of Samples Collected _____mL
   Total Sample Volume Collected _____

*Where applicable, include charts, graphs and field notes.

III. FLOW MEASUREMENT INFORMATION

1. Primary Measuring Device
   a. Description of Device
      (e.g., flume, weir, half-round pipe, etc.): _____

   b. Size of device: _____ and Maximum Discharge Rate (gpm): _____

2. Flow Measuring Equipment (circle appropriate letter)
   a. Automated
      Name of Manufacturer _____ Model Number _____
      Description of Equipment Used _____
      _____

   b. Manual
      Description of Mehod Used (e.g., stick reading, depth gauge reading, etc.) _____

APPENDIX A

SELF-MONITORING REPORT FORM

Date _____ Permit No. _____

IV. SAMPLE ANALYSIS INFORMATION

1. *Laboratory Performing Analysis _____ Laboratory Receipt Date_____

Parameter	Conc./ Results	Permit Limit (Daily)	Permit Limit (Monthly Avg.)	Test Method#	Test Method Source	Analysis Date
FOG						
Cd						
Cr						
Cu						
Pb						
Mn						
Ni						
Ag						
Zn						
CN (T)						
As						
Ba						
B						
Se						
Hg						
*pH						
*Temp (F)						
TTO						
Other						

*NOTES:

1. ATTACH LABORATORY ANALYSIS
2. All values shall be expressed in mg/L except for pH and Temperature.
3. If the above results indicate non-compliance, include a written statement explaining the cause of the non-compliance and the corrective actions to be taken.

APPENDIX A (cont.)

SELF-MONITORING REPORT FORM

Permit No. _____

V. CHAIN OF CUSTODY

DATE/TIME	SAMPLE RELINQUISHED BY/RECEIVED BY	COMMENTS
_____	_____/_____	_____
_____	_____/_____	_____
_____	_____/_____	_____
_____	_____/_____	_____

VI. CERTIFICATION

I certify that the Pretreatment Standards are/are not (circle one) being met and that the above information was obtained from samples taken at the specified monitoring point and are representative of daily operations:

_____ _____

Signature of Authorized Representative Date

_____ _____

Certified Professional Date

VII. TOXIC ORGANIC MANAGEMENT PLAN CERTIFICATION (if applicable)

Based on my inquiry of the person or persons directly responsible for managing compliance with the pretreatment standard for total toxic organics (TTO), I certify that to the best of my knowledge and belief, no dumping of concentrated toxic organics into the wastewater has occurred since filing of the last semi-annual compliance report. I further certify that this facility is implementing the solvent management plan submitted to the Control Authority.

_____ _____

Signature of Authorized Representative Date

APPENDIX B

COMPLIANCE SCHEDULE PROGRESS REPORT*

COMPANY NAME: _____

ADDRESS: _____

DATE DUE: _____ AUTHORIZED REPRESENTATIVE: _____

1. Increment of Progress description: _____

_____

_____

2. Scheduled completion date for above Increment of Progress: _____

3. Is Increment of Progress completed on schedule? Yes No

4. If not on schedule, indicate anticipated completion date: _____

5. State reason for delay, if applicable: _____

_____

_____

_____

6. What action has been initiated to return project to original schedule?

_____

_____

_____

_____

7. What is the probability of meeting the next scheduled completion date?

_____

_____

_____

*Report is to be submitted no later than 14 days after the indicated increment of progress on the compliance schedule.

APPENDIX C

ACCIDENTAL DISCHARGE REPORT FORM

PERMIT NO. _____

COMPANY NAME _____
FACILITY ADDRESS _____
MAILING ADDRESS _____
_____
TELEPHONE NUMBER _____
AUTHORIZED REPRESENTATIVE (name) _____
(title) _____
_____

In accordance with element II(B)(9) of my wastewater discharge permit, I am submitting an Accidental Discharge Report for the incident that occurred as described herein.

Sincerely,

_____ _____
Authorized Representative Date

Commencement of Discharge:

Estimated Time _____

Date _____

Discovery of Discharge:

Estimated Time _____

Date _____

Material(s) Discharged: _____ Estimated Quantity Discharged: _____
_____ _____
_____ _____

A detailed description of the various circumstances and responses connected with the incident is provided as follows (on separate pages):

1) Cause(s) of the Accidental Discharge
2) Description of Initial Notification and Response
3) Description of Steps Instituted or Planned to Prevent Recurrence of This Discharge and Other Types of Accidental Discharges

APPENDIX D

SAN ANTONIO WATER SYSTEM

WASTEWATER QUALITY DIVISION
HAZARDOUS WASTE NOTIFICATION

This form may be used in fulfilling the reporting requirements of 40 CFR 403.12(p).

Date _____

1. Company Name _____

2. Address of Facility _____

3. Phone Number _____

4. Facility's Authorized Representative _____

_____

*HAZARDOUS WASTE INFORMATION

Name of Waste _____

EPA Hazardous Waste Number _____

Process Generating the Waste _____

Type of Discharge: Batch/Continuous/Other (circle one)

Frequency of Discharge _____

If more than 100 kilograms of any hazardous waste per calendar month is discharged to the sewer, please include the following items of information for each hazardous waste.

Hazardous Constituent Information:

Name of Constituent	Mass in Wastestream	Concentration in Wastestream	Mass Expected in next 12 months

I hereby certify that the facility, for which this notification has been made, has a program in place to reduce the volume and toxicity of the wastes generated (and described in this notification) to the fullest extent possible.

_____
Facility's Authorized Representative

*Use additional paper when necessary

Pages 84-89
Deleted

United Catalysts Inc
P O Box 32370
Louisville KY 40232 USA
Telephone 502-634-7500
Business Office 502-634-7727 (Fa
Technical Center 502-634-7720 (F

MATERIAL SAFETY DATA SHEET
IVY BLOCK LOTION

SECTION I PRODUCT IDENTIFICATION

Trade Name: IVY BLOCK LOTION

Chemical Family: CHEMICAL MIXTURE

SECTION II HAZARDOUS INGREDIENTS

Hazardous Components in the Mixture

COMPONENT	CAS No.	%	OSHA/PEL	ACGIH/TLV
Ethyl Alcohol	64-17-5	25.0	1000 ppm	1000 ppm
Quartz	14808-60-7	0.3	0.1mg/m^3 (respirable)	0.1mg/m^3
Cristobalite	14464-46-1	0.7	0.5mg/m^3 (respirable)	0.05mg/m^3

SECTION III PHYSICAL DATA

Appearance: Off White Viscous Liquid

Odor: Faint/Alcoholic

Melting Point: Not Applicable

Solubility in Water: 90% Soluble

Specific Gravity: 1.0 @ 76°F (25°C)

Percent Volatile by Weight at 1000°F: 91.7%

Created: 09-23-94

United Catalysts Inc
P O Box 32370
Louisville, KY 40232 USA
Telephone 502-634-7500
Business Office 502-634-7727 (Fax
Technical Center 502-634-7720 (Fa

MATERIAL SAFETY DATA SHEET
IVY BLOCK LOTION

SECTION IV FIRE EXPLOSION DATA

Flash Point:
>200°F (93°C) ASTM D93-90 (Pensky Martens closed cup)

Fire and Explosion Hazard:
Flammable: Fire is possible at elevated temperatures or when mixture is contacted by an ignition sources.

Firefighting Media:
Dry chemical, water spray, or foam.

Firefighting:
Use dry chemical, foam or CO_2; water may be ineffective, but should be utilized to keep fire exposed containers cool.
(Note - Individuals should perform only those fire-fighting procedures for which they have been properly trained.)

SECTION V HEALTH HAZARD DATA

Health hazards may arise from ingestion, and/or contact with the skin and/or eyes.

First Aid (Ingestion):
May cause nausea, vomiting and diarrhea. If ingestion occurs contact a physician or poison control center immediately.

First Aid (Eyes):
Wash eyes immediately and carefully for 15 to 20 minutes with running water, lifting upper and lower eyelids occasionally. Get prompt medical attention.

First Aid (Skin): Get medical attention if irritation or inflammation develops.

United Catalysis Inc
P O Box 32370
Louisville KY 40232 USA
Telephone 502-634-7500
Business Office 502-634-7727
Technical Center 502-634-7720

SECTION VI REACTIVITY DATA

Reactivity:
Material is stable under normal temperatures and pressures in sealed containers.
Hazardous polymerization will not occur.

SECTION VII SPILL OR LEAK PROCEDURES

Environmental Precautions:
Avoid uncontrolled release of this material. Where spills are possible, a comprehensive spill response plan should be developed and implemented.

Spill or Leak Procedures:
Notify safety personnel of spills or leaks. Clean-up personnel need appropriate personal protection. Eye protection is required. Contain spilled material. Transfer to secure containers. Where necessary, use absorbent materials. Place in appropriate containers for disposal.

Disposal:
All recovered material should be packaged and properly labeled. Consult applicable local, state, and federal regulations to select proper method of disposal.

SECTION VIII SPECIAL PROTECTION INFORMATION

Ventilation:
Provide general and/or local exhaust ventilation to keep exposures below the TLV.

Protective Clothing:
Wear protective clothing, including long sleeves and gloves, to minimize chronic exposure during manufacturing.

Eye Protection:
Chemical splash goggles designed in compliance with OSHA regulations are recommended. Consult your safety equipment supplier.

United Catalysts Inc
P O Box 32370
Louisville KY 40232 USA
Telephone 502-634-7500
Business Office 502-634-7727 (Fax
Technical Center 502-634-7720 (F

MATERIAL SAFETY DATA SHEET
IVY BLOCK LOTION

SECTION IX REGULATORY INFORMATION

This product contains substances which appear on lists of the indicated act or agency.

X American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values for Chemical Substances in the Work Environment

X California Proposition 65

X International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans Volumes 1-42.

X NTP Annual Report on Carcinogens

X Occupational Safety and Health Administration (OSHA) 29 CFR 1910

X Superfund Amendments and Reauthorization Act of 1986 (SARA) Title III Section 313 40 CFR 372

X Toxic Substances Control Act (TSCA) 40 CFR 700

SECTION X BIBLIOGRAPHY

Clinical Toxicology of Commercial Products, Fifth Edition, Gosselin, Smith, Hodge, Williams and Wilkins, Baltimore, 1984.

Dangerous Properties of Industrial Materials, Sax, N. Irving, ed., Van Nostrand Reinhold Company, New York, 6th Edition, 1984.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs, Volumes 1-42, Lyon: World Health Organization, International Agency for Research on Cancer, 1987.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Silica and Some Silicates, Volume 42, Lyon, World Health Organization, International Agency for Research on Cancer, 1987.

Patty's Industrial Hygiene and Toxicology, Clayton, G.D., Clayton, F.E., eds., John Wiley and Sons, New York, 3rd Edition, Volume 2, A-C, 1981.

MSDS's from Suppliers of Raw Materials.

United Catalysts Inc
P O Box 32370
Louisville KY 40232 USA
Telephone 502-634-7500
Business Office 502 634-7727
Technical Center 502-634-7720

MATERIAL SAFETY DATA SHEET
IVY BLOCK LOTIC

SECTION XI

The information presented herein is believed to be accurate but is not warranted. Recipients are advised to confirm in advance that the information is current and applicable to meet their circumstances.

Doc. 10

FDA ADDENDUM

Updated permit information was provided to CDER in a separate communication.

memos

MEMO OF TELECON

DATE: February 26, 1996

TO: David Buddrus, M.D.
7414 Craigshire
Dallas, Texas 75231
(214)340-7546

FROM: Ralph Harkins, Ph.D., Div. Director, Biometrics Div. IV
Phyllis Huene, M.D., Medical Officer, HFD-540
Rosemary Cook, M.B.A., Supervisory Project Manager, HFD-540
Harold Blatt, D.D.S., Project Manager, HFD-540

SUBJECT: Phase 4 protocol

NDA NUMBER: NDA 20-532

DRUG: Ivy Block (bentoquatam 5%)

INDICATION: Poison ivy, oak, and sumac protectant

SPONSOR: United Catalysts, Inc.

P.O. Box 32370
Louisville, Kentucky 40232
Telephone (502)634-7500

Introductions were made. Dr. Harkins made the following comments on the phase 4 protocol:

1. Our purpose is to refine the proposed label and verify the statements in the label. Dr. Harkins raised the issue of randomization after he and Dr. Buddrus agreed to a stratified, probably 4-8 block randomization plan. Dr. Buddrus and staff will assess prior history of ivy susceptibility as a stratifying variable.

2. Sponsor has to state the randomization plan in the study design, and use past history of poison ivy as a stratifying variable. Dr. Buddrus stated that application of the material would be done daily, under supervision, and the bottle would be left behind when the children go back outside. The primary interest is how well the product protects against ivy rash (not skin tolerance to repeated applications which is a primary safety tolerance variable). Dr. Harkins stated that there is a need for randomization as follows:

   If susceptible, randomized to Arm A or Arm B in blocks of 4 to 8 subjects.
   If not susceptible, randomized to Arm A or Arm B in blocks of 4-8 subjects.

HFD-540 wants it stated up front that the sponsor is going to stratify on the basis of

susceptibility.

3. Sponsor may want to consider hiring more experienced health officials to get the data required. There appears to be a need for an additional on site person to ensure obtaining complete records. Dr. Buddrus said they would have a clinical person there to keep track of the records. However, more than 20 subjects in any session may be too many.

4. Children should be treated only on days when there is potential exposure to poison ivy. Dr. Huene and Dr. Harkins said that five days of applications and poison ivy exposure are adequate.

   Dr. Buddrus said that he would like to keep a record of the children during a two week period at camp, and for a five day period after returning home from camp. Dr. Harkins felt that this additional followup period would be most desirable.

5. Final protocol should contain a detailed statistical analysis.

6. The randomization plan should be stated in the beginning and firmly adhered to.

7. The sponsor stated that they did send in a complete response letter to the N/A letter and they will send in another letter as a supplement to account for the statements made in today's telecon. Dr. Harkins requested a copy of this protocol. Rosemary Cook stated that modification of the protocol should be sent in as a clinical amendment to their IND and as General Correspondence to their NDA.

The telecon ended cordially.

NDA 20-532
DIV FILES
HFD-540/Huene
HFD-540/Harkins
HFD-540/Blatt

nda20532.tel

MINUTES OF A TELEPHONE CONFERENCE
United Catalysts & FDA/CDER
NDA 20-532 (IVY BLOCK -- Bentoquatam)
January 29, 1996
2:30-3:00 p.m.

Representing United Catalysts:

Thomas K. Shotwell, Ph.D., Regulatory Consultant
David Buddrus, M.D., Medical Directions

Representing FDA/CDER

Linda Katz, M.D., Deputy Director
Ralph Harkins, Ph.D., Acting Division Director, ODE-IV
Phyllis A. Huene, M.D., Medical Officer
Joanne Holmes, Project Manager

Dr. Shotwell opened the teleconference by thanking the FDA personnel for arranging the conference and introduced himself and Dr. Buddrus. The FDA representatives also introduced themselves.

Dr. Buddrus reviewed what United Catalysts had done in 1992 in connection with study 7-92. He noted that the Phase III plan was reviewed with Dr. Alpert's group from anti-infectives at the end of the Phase II meeting, United Catalysts and Dr. Alpert agreed that a field trial with a manageable protocol to provide control of the exposure to poison ivy and poison oak was impractical, especially since there was no placebo that would be credible. It was therefore agreed that United Catalysts would perform the 1/92 and 2/92 studies for efficacy purposes, and, then conduct 7/92 as a field trial to look at practical experience (not efficacy) with the product under typical use conditions.

Dr. Huene and Dr. Harkins advised that the Center would like to have data to compare children and adults who are treated and naturally exposed with similar subjects who are not treated to provide a better perspective of how well IVY BLOCK works and whether the product may cause any skin irritation in the real world with children, campers, and people who have occupational exposure.

Dr. Harkins noted that United Catalysts should have about 100 subjects in each arm of the study and can randomize subjects using IVY BLOCK and those using no treatment in a non-blinded trial.

Dr. Harkins expressed the opinion that United Catalysts will be able to perform the study this year because the product should be on the market in time for this season. Dr. Huene advised that the Center could commit to work expeditiously with United Catalysts to develop a protocol and would need agreement from United Catalysts to expeditiously perform the study. Dr. Shotwell advised that United Catalysts is presently working on the manufacturing chemistry questions raised by the chemistry reviewer in the September 28, 1995 letter. He noted that the sponsor hopes to complete an amendment within about three weeks that would allow NDA approval quickly.

Harkins felt the Phase IV trial could be done this June or July with girl scouts, boy scouts, and other youngsters going to summer camp and it was agreed that approval of the NDA would be needed early this year if the study is to be performed during the 1996 season.

Dr. Buddrus expressed concern that arranging a Phase IV clinical trial to be initiated by June or July of this year would be very difficult, especially in view of the current unapproved status of the IVY BLOCK NDA. However, he agreed to move ahead as quickly as possible and Dr. Harkins and Dr. Huene agreed to be available on short notice to answer questions about developing the protocol. It was agreed that specific site designations and naming of investigators will not be needed at the time of initial protocol submission with the amendment to the NDA. The protocol will provide the basic design of the study and major revisions to the design should not be made after agreement is reached with the Center. The basic purpose of the study will be to compare how many people develop irritations without treatment and how many develop irritations with treatment.

Dr. Harkins noted that the Center is concerned that some people may apply IVY BLOCK very liberally and thereby get the lotion underneath their clothing where it might conceivably lead to irritations.

Agreement was reached that the subjects are to be instructed to use IVY BLOCK according to the label (normal usage); however, it can be expected that some subjects will apply the product more generously than others.

Dr. Huene and Dr. Harkins noted that boy scouts, girl scouts, campers, road crews, foresters and the like could be used and that the age groups would therefore be scattered.

Dr. Harkins requested that the background check on the subjects include questions on whether the subject is prone to getting poison ivy or oak although it was agreed that children will often not know. She indicated that the study need not be balanced with regard to sensitivity to urushiol and certainly no intentional exposure to urushiol is expected. Efficacy should be based on whether the subjects got poison ivy/poison oak or not, including measurements of either mild, moderate or severe, using a clinical scale.

Dr. Shotwell inquired about the applicability of the user fee schedule and Dr. Katz advised that the study report should be sent to the Center as a fulfillment of a commitment regarding a Phase IV study, not as a supplement or amendment to the NDA and that no user fee would be required.

Dr. Shotwell agreed that the draft protocol for the Phase IV study would be provided with the next submission to the NDA and a copy will also be sent to the IND. Dr. Harkins advised that the study would have to be IRB approved and performed as soon as feasible, either this summer or next summer.

At the close of the meeting Dr. Shotwell thanked the FDA personnel for their assistance and agreed to send minutes to Ms. Holmes and to the NDA.

Minutes prepared by:

Thomas K. Shotwell, Ph.D.

/rs/common\173\nda\confcall.doc
96

RECORD OF A TELEPHONE CONVERSATION

DATE: February 15, 1995

TO: Dr. Tom Shatwell, Ph.D.
Regulatory Consultant
Shatwell and Carr
1-800-929-3003

FROM: Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT: Conveying Microbiology deficiencies; responding to Dr. Shatwell's question

NDA NUMBER: NDA 20-532

DRUG: IVY-Block (quaternium-18 bentonite), 5%

SPONSOR: United Catalysts, Inc.

Dr. Shatwell was informed by Ms. Holmes that while the division does not send copies of reviews to sponsors, the list of recommendations in the review could be sent by telefacsimile. The following list of deficiencies was taken from pages 3 and 4 of the Microbiologist's review dated February 1, 1995.

In a subsequent conversation, Dr. Shatwell acknowledged receipt of the telefacsimile.

Dr. Shatwell inquired as to how the responses should be submitted in order to respond to the requests made by the reviewing Medical Officer. He was informed by Ms. Holmes that he should submit them in writing to the NDA.

The conversation ended amicably.

cc:
Orig NDA 20-532
HFD-540
HFD-540/CHEM/Maturu
HFD-520/MICRO/Dionne
HFD-540/PHARM SUPV/Alam
HFD-713/BIOSTAT SUPV/Harkins
HFD-426/BIOPHARM/Ajayi
HFD-540/MO/Huene
HFD-540/DIV DIR/Wilkin

HFD-540/PROJ MGT SUPV/Cook

[redacted]

12/8/95

RECORD OF A TELEPHONE CONVERSATION

DATE: February 1, 1995

TO: Dr. Robert Carpenter
Statistician
Shatwell and Carr
1-800-929-3003
(214) 243-3567 fax

FROM: Ms. Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT. Request for information

NDA NUMBER: NDA 20-532

DRUG: IVY-Block (quaternium-18 bentonite), 5%

SPONSOR: United Catalysts, Inc.

Ms. Holmes requested information on the cumulative irritancy and sensitization studies on behalf of the reviewing Medical Offficer. The attached information was sent to him by telefacsimile.

The conversation ended amicably.

cc:
Orig NDA 20-532
HFD-540
HFD-540/CHEM/Maturu
HFD-520/MICRO/Dionne
HFD-540/PHARM/Sheevers
HFD-713/BIOSTAT SUPV/Harkins
HFD-426/BIOPHARM/Ajayi
HFD-540/MO/Huene
HFD-540/DIV DIR/Wilkin
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes JH 5/25/95

February 1, 1995

Dr. Carpenter:

This is the information requested by the reviewing Medical Officer for NDA 20-532, IVY-Block.

1. Please submit the test reaction scores for the cumulative irritancy study and the sensitization study.

2. The synopsis for the sensitization study says that the induction period was two weeks and the report says that it was three weeks. Please clarify this.

3. Please provide the reasons for the discontinuation for the 14 subjects who did not complete the study.

If the information requested for #3 is not readily apparent to be the sensitization study, please call me and I will verify the study with the clinician. She is not available today.

The information can be submitted as a single submission, although if #1 will take some time, you may wish to submit your responses to #2 and #3 first.

Thank you.

Joanne Holmes

Co. Corres

ORIGINAL

EnviroDerm
PHARMACEUTICALS, INC

August 13, 1996

NEW CORRESPONDENCE

Jonathan K. Wilkin, M.D.
Food and Drug Administration
Central Documents Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Reference: NDA 20-532 Ivy Block™
Commitment to "1-800" Telephone Number Labeling Requirement

Dear Dr. Wilkin:

Please accept this communication as a commitment to include the "1-800" telephone number on the back panel label of the Ivy Block 4 (four) ounce bottle. It is our understanding that we will be allowed to limit the hours during which this number is staffed.

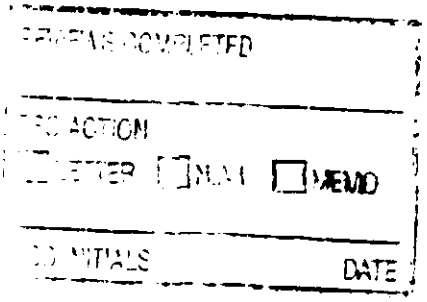
Thank you for your attention to this application.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz
Director of Scientific Affairs

/jrs



[illegible] THIRD STREET [illegible] LOUISVILLE KY 40203
[illegible] 502 634 7720 FAX 502 634 7727

EnviroDerm
PHARMACEUTICALS, INC.

August 2, 1996

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Attn: Document Control Room
Food and Drug Administration, CDER, ODEIV
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-532 IVY BLOCK™ (Bentoquatam 5%)
Commitment regarding antimicrobial preservative effectiveness testing, draft product labeling, and Phase IV requests.

Dear Dr. Wilkin:

Please accept this letter as a formal commitment and agreement to the following items, as requested via Dr. Hal Blatt's fax of August 1, 1996.

We commit to (1), conduct a clinical study on the irritation potential and effectiveness of the drug product under actual field use conditions, and (2) to perform an antimicrobial preservative effectiveness test on the first three batches of Ivy Block Lotion manufactured after approval of the NDA. This testing will be done at the time of manufacture and at the expiry date. Reports of results will be incorporated into the validation reports for these three batches.

We also are in agreement with the Draft Ivy Block labeling as indicated on the attached copy of Dr. Blatt's fax of August 1, 1996. However, if you are in agreement, we would like to have the option of not including the 800 phone number on the bottom of the back panel.

Should there be any additional requests, please don't hesitate to contact Dr. Shotwell or me directly. We very much appreciate your attention to this application.

Sincerely,

Anthony A. Schulz

Anthony A. Schulz
Director of Scientific Affairs

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

ORIGINAL

EnviroDerm
PHARMACEUTICALS, INC

NEW CORRESPONDENCE

July 24, 1996

Johnathan K. Wilkin, M.D.
Director
Division of Topical Drug Products (HFD-540)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-532 IVY BLOCK
Safety Information Update

Dear Dr. Wilkin:

Pursuant to the request of Dr. Hal Blatt, we are hereby stating that we have no new or additional safety information regarding the product covered under NDA 20-532. Should additional information be required please contact me directly.

Sincerely,

Anthony A. Schulz

Anthony A. Schulz
Director of Scientific Affairs
EnviroDerm Pharmaceuticals, Inc

AAS/jr
FDAwilkn

REVIEWS COMPLETED
CDD ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO
CDD INITIALS DATE

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

United Catalysts Inc.
P.O. Box 32370
Louisville, KY 40232 USA
Telephone 502-634-7500
Business Office 502-634-7727 (Fax)
Technical Center 502-634-7720 (Fax)

SU

January 23, 1995

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products (HFD-540)
Document Control Room: 12-B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-532 (IVY BLOCK™)

Dear Dr. Wilkin:

Please accept this letter as certification that the integrated summary of safety included herewith includes all the safety data for IVY BLOCK™ of which United Catalysts, Inc., is aware, both domestically and foreign.

Please note the enclosed integrated summary of safety replaces that found in volume 9, pages 2515-22 of the original submission dated September 28, 1994.

Sincerely,

Anthony A. Schulz

Anthony A. Schulz
Manager, Business Development

United Catalysts, Inc.

AAS/ts

Enclosures

REC'D
JAN 26 1995
HFD-520

Record of Telephone Conversation/Meeting

Date: April 26, 1996

NDA Number: 20-532 Amendment

Telecon/Meeting Initiated By: Patricia F. Hughes, Ph.D.

Product Name: IVY BLOCK ™ (Bentoquatam, 5%)

Firm: United Catalysts Inc.

Firm Representative(s): Mr. Anthony A. Schulz

Telephone Number: (502) 634-7531

I contacted by telephone Mr. Anthony A. Schulz, Director of Scientific Affairs, with respect to obtaining a commitment to conduct APET for the first three production batches. The applicant agreed and the commitment was sent in writing to Dr. Wilkin. A copy of the commitment sent by Facsimile is attached.

4/37/96

Patricia F. Hughes, Ph.D.
Office of New Drug Chemistry
HFD-805

5/3/96

EnviroDerm
PHARMACEUTICALS, INC.

April 26, 1996

F A C S I M I L E

Attention: Dr. Patricia Hughes
Fax Number: 301-443-9281

Ref: NDA 20-532 Ivy Block (Bentoquatam, 5%)
Commitment regarding antimicrobial preservative effectiveness testing

Dear Dr. Hughes:

Pursuant to our phone discussion of April 25, please find attached to this fax a copy of an official communication to Dr. Wilkin regarding our commitment to performing the antimicrobial preservative effectiveness test.

Thank you for your efforts during the review, and if you have any further comments or questions, please don't hesitate to contact me directly at 501-634-7531.

Sincerely,

Anthony A. Schulz

Anthony A. Schulz
Director of Scientific Affairs
EnviroDerm Pharmaceuticals, Inc.

AAS/jr

Phughes

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634.7700 FAX 502 634.7727

EnviroDerm
PHARMACEUTICALS INC

April 26, 1996

NEW CORRESPONDENCE

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
ATTN: Document Control Room
Food and Drug Administration, CDER, ODEIV
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-532 IVY BLOCK™ (Bentoquatam, 5%)
Commitment regarding antimicrobial preservative effectiveness testing

Dear Dr. Wilkin:

Please accept this letter as a commitment from EnviroDerm Pharmaceuticals. Inc. that the antimicrobial preservative effectiveness test will be performed on the first three (3) batches of IvyBlock™ lotion manufactured after approval of the NDA. The testing will be done at the time of manufacture and again at the expiry date. Reports of the results of this testing will be incorporated into the validation reports for these three batches.

Thank you for your attention. Prompt handling of the approval of this NDA is urgent in order for EnviroDerm to be able to perform the planned Phase IV clinical study in this season. We appreciate your efforts to finalize the approval as the earliest possible date. Should additional information be needed at this time please contact me.

Thank you for your assistance.

Sincerely,

Anthony A. Schulz

Anthony A. Schulz
Director of Scientific Affairs

AAS/jr

NDA20532

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO
CSO INITIALS

RECEIVED
APR 29 1996

029 SOUTH FOURTH ROAD STREET, SUITE A LOUISVILLE, KY 40203
PHONE 502 634 7700 FAX 502 634 7701

EnviroDerm
PHARMACEUTICALS, INC

August 26, 1996

Dr. Hal Blatt , Project Manager
Chemical Section
Division of Dermatologic and Opthalmologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

Reference. NDA 20-532 Ivy Block™
Response to Label Change Requests and Commitment to Phase 4 Requests
in Fax dated August 26, 1996

Dear Dr. Blatt

Pursuant to our phone discussion of this morning and the receipt of your fax, we respectfully voice great concern over the suggested last minute labeling changes. The removal of the phrase
is very disturbing because we feel strongly that these claims are substantiated by clinical results. The suggested language is misleading in that it does not accurately reflect the high degree of efficacy afforded by the product. Multicenter Phase III results indicated that 68% of all patch-tested subjects developed no rash whatsoever on the protected site and the remaining subjects who did develop rashes had significantly reduced reactions on the protected site ($p = < .0001$).

The deletion of the claim ' and its replacement with
is unwarranted. Importantly, the Phase IV Field/Use study will afford the Agency an opportunity to review the label claim within about a year

It is our desire, however, that the preceding expression of our strong concern over the labeling issue not jeopardize prompt Agency approval of this NDA. If there exists the possibility of allowing the previously agreed-to label copy to stand at this time, then that would be most welcomed. However, with respect to our desire to not adversely affect the approval process, we agree to the draft label as shown on the attachment, which you provided to us earlier today.

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

With respect to the other items requested by you in our discussion today, we also formally agree to the following Phase IV items:

1. The field/use study will include females, as well as males.
2. The field/use study will include male and female subjects over the age of 65, if possible.

Thank you again for your efforts in addressing this review.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz
Director of Scientific Affairs

EnviroDerm
PHARMACEUTICALS, INC

August 21, 1996

Jonathan K. Wilkin, MD
Food and Drug Administration
Central Documents Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Reference: NDA 20-532 Ivy Block™
Twenty-four Month Stability Data for Lots HFCO and HFCO-1

Dear Dr. Wilkin:

Please find enclosed twenty-four (24) month stability data for lots HFCO and HFCO-1 of Ivy Block lotion. We respectfully submit these data in support of our request for an initial 24 month expiry period. We feel that the full two year period is critical due to the seasonal nature of the product.

Should there be any questions regarding the stability report, please don't hesitate to contact me directly.

Thank you very much for your efforts in reviewing our application.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz

Anthony A. Schulz
Director of Scientific Affairs

/jrs

Enclosures

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

Ivy Block Lotion
Lot HFCO
24 Month Stability Results Summary

Assay	Specification	24 Month Result	Pass/Fail
Benzyl Alcohol	80-120%	98.0	Pass
Description	Pass	Pass	Pass
Methylparaben	80-120%	97.0	Pass
Package Integrity	Pass	Pass	Pass
Quaternium-18 Bentonite Assay	90-110%	96.0% avg.	Pass
Weight Loss	Report	1.66g	-
pH	Report	7.3	-

Ivy Block Lotion
Lot HFCO-1
24 Month Stability Results Summary

Assay	Specification	24 Month Result	Pass/Fail
Benzyl Alcohol	80-120%	99.0	Pass
Description	Pass	Pass	Pass
Methylparaben	80-120%	96.5	Pass
Package Integrity	Pass	Pass	Pass
Quaternium-18 Bentonite Assay	90-110%	93.5% avg.	Pass
Weight Loss	Report	1.53g	-
pH	Report	7.3	-

EnviroDerm
PHARMACEUTICALS, INC.

August 21, 1996

Jonathan K. Wilkin, MD
Food and Drug Administration
Central Documents Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Reference: NDA 20-532 Ivy Block™
Commitment to Phase 4 Requests in Fax dated August 21, 1996

Dear Dr. Wilkin:

Please accept this communication as a commitment to perform the following Phase 4 items relating to the Clinical/Field Study:

1. To submit the final Phase 4 Protocol within six (6) months, and
2. To not enroll subjects until after the FDA has approved the protocol

Thank you for your attention to this application.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz
Director of Scientific Affairs

/jrs

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

EnviroDerm
PHARMACEUTICALS, INC

August 16, 1996

Jonathan K. Wilkin, M.D.
Food and Drug Administration
Central Documents Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Reference: NDA 20-532 Ivy Block™
Commitment to Phase 4 Requests in Fax dated August 16, 1996

Dear Dr. Wilkin:

Please accept this communication as a commitment to perform the following Phase 4 items:

To submit the complete results of studies determining the solubility of free Q-18 in the chloroform and aqueous layers within the Assay Method plus similar studies when is added.

Thank you for your attention to this application.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz
Director of Scientific Affairs

/jrs

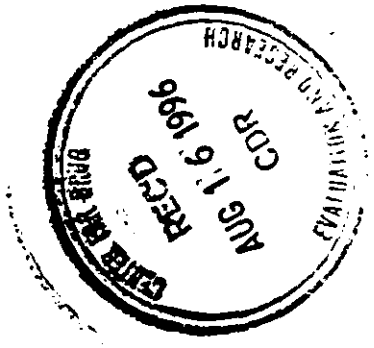
929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502.634.7700 FAX 502.634.7727

EnviroDerm
PHARMACEUTICALS, INC

August 15, 1996

BC
NDA ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Food and Drug Administration
Central Documents Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852



Reference: NDA 20-532 Ivy Block™
Dr. DeCamp's fax of August 9, 1996
Regarding Environmental Assessment Issues

Dear Dr. Wilkin:

Pursuant to the referenced fax from Dr. DeCamp, please find enclosed information addressing the Environment Assessment issues as follows:

Section 1 - This section includes the Wastewater Permit from the February 26 submission.

Section 2 - This section includes a letter of exemption from indicating that the San Antonio Metropolitan Health District has exempted from the requirement to have an air pollution license. Importantly, the City of San Antonio does not issue a formal document indicating the exemption.

Section 3 - This section includes a releasable Environmental Assessment and as such this document can be released under FOI. Confidential and proprietary information has been deleted from this releasable document.

Section 4 - This section includes an appendix which lists the nature of the deleted information referenced by page number. Note that the page numbers referenced are those present in the original submission.

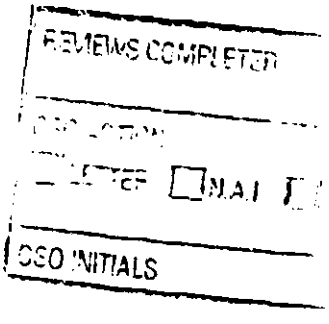
Thank you for your attention to this application.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz
Director of Scientific Affairs

Enclosures



929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

ORIGINAL

EnviroDerm
PHARMACEUTICALS INC

August 14, 1996

NEW CORRESPONDENCE

Jonathan K. Wilkin, M.D.
Food and Drug Administration
Central Documents Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

NEW CORRESPONDENCE

Reference: NDA 20-532 Ivy Block™
Commitment to Phase 4 Requests in Fax dated August 13, 1996

Dear Dr. Wilkin:

Please accept this communication as a commitment to perform the following Phase 4 items:

1. To update stability data on the existing lot # HFCO/4 oz. container.
2. To place two (2) additional manufactured lots of Ivy Block in 4 oz. bottles on long-term stability.
3. To write an acceptable stability protocol as described in the Center's Stability Guidelines.

Thank you for your attention to this application.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz

Anthony A. Schulz
Director of Scientific Affairs

/jrs

REVIEWS COMPLETED
CSO ACTION
LETTER N.A.I MEMO
CDR INITIALS DATE

CENTER FOR DRUGS
REC'D
AUG 16 1996
CDR
EVALUATION AND RESEARCH

CENTER FOR DRUGS
REC'D
AUG 16 1996
HFD
EVALUATION AND RESEARCH

REVIEWS COMPLETED
CSO ACTION
LETTER N.A.I MEMO
CDR INITIALS DATE

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

ORIGINAL

EnviroDerm
PHARMACEUTICALS, INC

August 13, 1996

NEW CORRESPONDENCE

Jonathan K. Wilkin, M.D.
Food and Drug Administration
Central Documents Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Reference: NDA 20-532 Ivy Block™
Commitment to "1-800" Telephone Number Labeling Requirement

Dear Dr. Wilkin:

Please accept this communication as a commitment to include the "1-800" telephone number on the back panel label of the Ivy Block 4 (four) ounce bottle. It is our understanding that we will be allowed to limit the hours during which this number is staffed.

Thank you for your attention to this application.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz
Director of Scientific Affairs

/jrs

FORMS COMPLETED

FDA ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

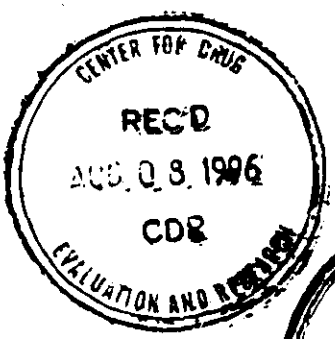
929 [illegible] STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

ORIGINAL

NEW CORRESP

NC

EnviroDerm
PHARMACEUTICALS, INC



August 7, 1996

Jonathan K. Wilkin, M.D.
Food and Drug Administration
Central Documents Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Reference: NDA 20-532 Ivy Block™
Supplemental Information as Requested by Drs. DeCamp and Vidra
via Fax of August 5, 1996

Dear Dr. Wilkin:

Please accept this document as a revised methods validation volume as requested by Drs. DeCamp and Vidra in their fax of August 5, 1996. Note that the additional information has been included in the form of an Appendix to the Method Validation section. Original source document pagination has been preserved, for the Appendix pages have been re-paginated sequentially as indicated on the bottom right of each page.

The entirety of the original volume 5 has been included to aid insertion into the primary NDA document.

Also, again pursuant to Drs. DeCamp's and Vidra's request, two additional desk copies of the revised volume have been forwarded to Dr. Vidra's office.

Thank you for your attention to this application.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

Anthony A. Schulz
Director of Scientific Affairs

Enclosures

/jrs

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 1700 FAX 502 634 1727

ORIGINAL

EnviroDerm
PHARMACEUTICALS, INC

August 2, 1996

NEW CORRESPONDENCE

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Attn: Document Control Room
Food and Drug Administration, CDER, ODEIV
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-532 IVY BLOCK™ (Bentoquatam 5%)
Commitment regarding antimicrobial preservative effectiveness testing, draft product labeling, and Phase IV requests.

Dear Dr. Wilkin:

Please accept this letter as a formal commitment and agreement to the following items, as requested via Dr. Hal Blatt's fax of August 1, 1996.

We commit to (1), conduct a clinical study on the irritation potential and effectiveness of the drug product under actual field use conditions, and (2) to perform an antimicrobial preservative effectiveness test on the first three batches of Ivy Block Lotion manufactured after approval of the NDA. This testing will be done at the time of manufacture and at the expiry date. Reports of results will be incorporated into the validation reports for these three batches.

We also are in agreement with the Draft Ivy Block labeling as indicated on the attached copy of Dr. Blatt's fax of August 1, 1996. However, if you are in agreement, we would like to have the option of not including the 800 phone number on the bottom of the back panel.

Should there be any additional requests, please don't hesitate to contact Dr. Shotwell or me directly. We very much appreciate your attention to this application.

Sincerely,

Anthony A. Schulz

Anthony A. Schulz
Director of Scientific Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

EnviroDerm
PHARMACEUTICALS, INC

April 17, 1995

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
ATTN: Document Control Room
Food and Drug Administration, CDER, ODEIV
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-532 (IVY BLOCK™)
Phase IV Study Commitment

Dear Dr. Wilkin:

Pursuant to your letter of September 28, 1995 and the telephone conference of February 26, 1996 between Dr. David Buddrus of EnviroDerm and Drs. P. Huene, R. Harkins and Mr. Hal Blatt we are enclosing herewith a draft protocol for the planned Phase IV clinical study to be conducted as promptly as is feasible after NDA approval. Finalization of the protocol is not feasible until the NDA has been approved and we can reach definitive agreements with the managers of the Boy Scouts of America on the details of subjects and sites. When finalized, the full protocol will be submitted to the NDA and to the IND.

EnviroDerm Pharmaceuticals, Inc., hereby commits to sponsor the study described in the enclosed draft protocol in a timely way as soon as is feasible after NDA approval.

Time is of the essence. As you may be aware, there is about a 90-day lead time for manufacture of finished drug product to be used in the Phase IV study and this puts us into a July 1996 start date if the NDA approval issues immediately. Please contact me or Dr. Shotwell (800-929-3003) if any questions or concerns arise.

Sincerely,

Anthony A. Schulz

Anthony A. Schulz
Manager, Business Development
EnviroDerm Pharmaceuticals, Inc.

AAS/ts

Enclosure

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

AN EVALUATION OF IVY-BLOCK USAGE FOR PROTECTION AGAINST POISON IVY RASH IN A SUMMER CAMPING PROGRAM.

Objective / Purpose: This is a Phase-IV post-approval study of the poison ivy / oak preventive effects of IVY-BLOCK Lotion, conducted to examine lotion benefits and topical effects in a population of young males attending summer camps conducted by the Boy Scouts of America in poison ivy prevalent locations.

Background: The study population will consist primarily of Boy Scouts attending summer camp for two consecutive weeks plus an additional group of adult scout "counselors" working in supervisory roles at the camp site. Subjects with previous history of poison ivy rash and those without prior poison ivy rash occurrence will be randomly assigned so that balanced "poison ivy experience" exists in a treatment and a no-treatment group. Subjects in the treatment group will apply IVY-BLOCK lotion each morning before starting daily activities which might involve exposure to poison ivy. Subjects in the no-treatment group will be involved in activities with similar poison ivy exposure but will not have IVY-BLOCK applied.

Data will be collected and analysed to compare occurrence of poison ivy rash in the two groups, as a further measure of effectiveness of IVY-BLOCK Lotion. Additional data dealing with skin tolerance of repeated applications of IVY-BLOCK lotion, under conditions where perspiration is a common and frequent occurrence, will be analysed for the treated group.

Analysis of data from this investigation could result in findings that will allow modification of copy on the current IVY-BLOCK product label.

Study Design: This will be an open-label study comparing the occurrence of allergic contact dermatitis due to poison ivy exposure in subjects randomly assigned to equal size preventive or no-preventive control groups. Past history of poison ivy occurrence will be used to balance the two study groups as to poison ivy susceptibility or non-susceptibility.

Study Population: Volunteer juvenile members and adult "counselors" attending regular sessions of summer camping programs conducted by the Boy Scouts of America will participate in this study. Subjects will be recruited by written notice of study availability given to Scouts considering summer camping at the Scout Troop level.

Study Site / Personnel: Boy Scout camps will be selected that have permanent locations and at least one structure identified as a health building, where campers customarily report

IVY-BLOCK PHASE IV PROTOCOL (cont.)

for handling of health problems during their camp stay. Some camps will have occasional visits from nurses or physicians, but none have full time on site medical people. All camps have one or more trained and experienced "health personnel" that do remain at the camp site at all times. Arrangements will be made for one or more of these health personnel to be made responsible for IVY-BLOCK application and study conduct on a day to day basis. Assigned health person will witness daily lotion applications to Scout campers at health center. Paid clerical help will be sought, to assist in subject enrollment and study record keeping.

Study Investigator: A physician, qualified by experience in conduct of controlled clinical studies plus evaluating poison ivy / oak rashes and their treatment, will be the principal investigator.

Inclusion / Exclusion Factors: Will be the same for those assigned to treatment or control groups.

1. Only scouts or counselors attending summer camp for two successive weeks will be eligible for participation.

2. Subjects will provide Informed Consent before participation. Adults will consent personally and juveniles will provide consent by parents or qualified guardians. Consent must not be contingent on subject being assigned to treatment or control group.

3. To qualify for entry into the study, subjects must be free of chronic or disabling medical problems based on history.

4. To qualify at time of study intiation, subjects must be free of skin diseases, especially active poison ivy / oak type of allergic contact dermatitis. Principal investigator will specify diseases that contraindicate enrollment in study.

5. Subjects must be able and willing to make daily application of IVY-BLOCK Lotion according to direction, if assigned to a treatment group.

6. Subjects must be willing to report any newly developed skin problem while in the study and willing to have such lesions viewed by health personnel, regardless of grouping.

Subject Numbers: At least 100 (one hundred) subjects will complete the full study protocol in both treated and control groups, for a total study of not less than 200 subjects, nor more than 300. Subjects discontinuing study early in either group will be replaced in kind during a subsequent session.

IVY-BLOCK PHASE IV PROTOCOL (cont.)

Study Duration: Planned duration of each subjects' participation is approximately two weeks, with IVY-BLOCK Lotion applications in the treatment group and control observations for the no treatment group on five successive days in which poison ivy exposure is likely to occur.

For subjects departing camp immediately following a treatment or control observation day, telephone follow up will provide data about poison ivy type rashes that might have appeared in the three days immediately following departure from camp.

Study Measurements: Refers to types of data that will be collected on Case Report Forms (CRF) assigned to each subject. Since the main objective of this study is measuring the efficacy of IVY-BLOCK as a preventive for allergic contact dermatitis due to poison ivy in susceptible subjects, data emphasis will be on occurrence of poison ivy rashes after subjects are admitted to the study.

1. CRFs will seek objective data comparing occurrence of verified poison ivy rash in the treated and non-treated groups of subjects. CRFs will provide descriptors for recording subjective symptoms accompanying rash, as described by the subject. Additionally, a description of rash site and a score for severity of the rash will be made by health personnel. Site of rash will also be related to its occurrence on treated or untreated skin areas in subjects in the treatment group.

2. Additional data collected concerning non-poison ivy type skin problems observed in the treated and non-treated populations will serve to substantiate currently approved label directions for use of IVY-BLOCK Lotion.

3. Data will be collected about ease of removal of lotion by subjects' usual skin cleansing procedures.

4. Subsequent to appearance of "poison ivy", daily notations will be made as to progression of the skin lesions, including type of treatment if required.

5. Occurrence and course of skin lesions other than "poison ivy" and other than those related to lotion application referred to above will be noted on a daily basis. Health attendants will record any subjective symptoms and describe lesions and their body locations. (Note: IVY-BLOCK lotion will not be applied over existing skin eruptions, including poison ivy rashes.)

IVY-BLOCK PHASE IV PROTOCOL (cont.)

6. Record will also be made of non-dermatologic illnesses that affect subjects during study period. Notation will be made of intercurrent illness that prevents subject from those activities that would involve exposure to poison plants, and days on which he was confined.

Statistical Methods

Development of final statistical methods for data generated by this study must await development of CRFs suited to the actual study conditions at the camp site. Definitive arrangement with local scout administrators will play a major role in defining final study conditions. Statistical Methods will be submitted in a final protocol after discussions with Principal Investigator, sponsor and appropriate FDA persons.

Study Methods and Procedures: Can only be discussed in principle at this point. A protocol with fine tuned details is only possible after planning sessions with the Boy Scout officials familiar with the camps involved and those persons actually involved in conducting the study.

1. Subjects interested in study participation will be recruited with a pre-camp enlistment program. After reporting to camp, with Informed Consent from a responsible parent or guardian and a completed Medical History concerning known susceptibility to poison ivy rash, each volunteer subject will submit to an initial health inspection by assigned camp health personnel. If there are no exclusionary conditions, subject will be given a subject number in his assigned group.

2. Subjects will be assigned to a treatment or no treatment control group after they are finally qualified, according to a pre-determined randomisation schedule that balances both treatment / no treatment and susceptibility / non-susceptibility to poison ivy (based on Medical History).

3. A specified number of treatment and control subjects will participate in any two week camping period. It is not considered probable that an experienced health official can administer and provide study needs to more than 20 total subjects in any two week camp session. If size of camp population is such that there are multiple health facilities in that camp, it may be possible to run concurrent 20 subject studies, especially if clerical help is provided.

4. Each study subject will report to the health facility before engaging in each day's activity for a detemination of possible exposure to poison ivy that day.

N 000 (AS)

EnviroDerm
PHARMACEUTICALS, INC

March 1, 1996

Attention: Document Control (HFD-540)
Room 12-B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref:

New Drug Application: #20-532 (IvyBlock)

SUBJECT: Transfer of Ownership

Effective March 1, 1996 EnviroDerm Pharmaceuticals, Inc. accepts sponsorship of the New Drug Application (unapproved) and investigational New Drug Application noted on the enclosed list previously sponsored by United Catalysts Inc.

EnviroDerm Pharmaceuticals, Inc. is a wholly owned subsidiary of United Catalysts Inc. and was formed for the purpose of sponsoring and marketing this new drug and other products.

There will be no change of manufacturing sites. Applications requiring changes will be submitted as supplemental applications. New labeling reflecting change in sponsor was submitted under separate cover. EnviroDerm has complete copies of the applications as amended, including records required, correspondence, data, etc. and is hereby committing to comply with any and all agreements, commitments, and conditions made by United Catalysts Inc., and contained in the applications.

In addition, a signed Form FDA 356H is enclosed reflecting change in sponsorship.

Should further information be required or if you have any questions, please contact Mr. Anthony A. Schulz at 502-634-7700.

Sincerely,

EnviroDerm Pharmaceuticals, Inc.

David W. Schropfer
President

Judith M. Riley, Notary

My Commission Expires
January 29, 2000

Enclosures

929 SOUTH THIRD STREET LOUISVILLE KY 40203
PHONE 502 634 7700 FAX 502 634 7727

NEW CORRESP

N C

EnviroDerm
PHARMACEUTICALS, INC.

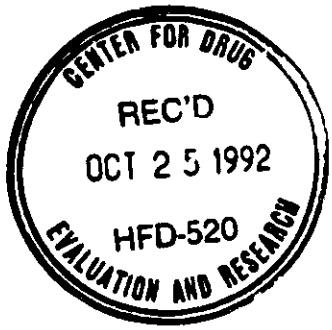
October 23, 1995

Dr. Jonathan Wilkin, M.D.
Director
Division of Topical Drug Products (HFD-540)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-532 - FDA letter Sept. 28, 1995
DMF
Request for Meeting

Dear Dr. Wilkin:

In accordance with a phone conference between Ms. Joanne Holmes and Dr. Thomas K. Shotwell, we request a meeting between FDA and United Catalysts. The purpose of the meeting is to discuss FDA responses to the original new drug application and bulk drug master file for our product IVY BLOCK LOTION. The following is our proposed agenda, listing of questions to be discussed (by discipline), tentative attendees, and tentative dates when our personnel are available for a meeting.



AGENDA

I. Introduction of participants
II. Brief overview of United Catalysts and history of project
III. United Catalysts goals for the meeting
IV. Discussion of questions/comments noted below
V. Summary

QUESTIONS/COMMENTS
Regarding NDA 20-532 AND DMF

1. Microbiology
   A. Antimicrobial preservative effectiveness tests (APE) were performed on two lots of finished drug product showing the number of colony forming units (cfu) decreased by fire to six logs against all organisms tested, therefore, why do you need to also perform the microbial limit test?
   B. Specification of 100 vs 1000 cfu for the bulk drug substance.
   C. Microbial testing on the stability lots but not as a specification for finished product.

929 South Third, Louisville, KY 40203 . Phone: 502-634-7700 Fax: 502-634-7727

EnviroDerm
PHARMACEUTICALS, INC.

II. Chemistry
- A. Discussion regarding the manufacture, characterization and analysis of the reference standard.
- B. X-ray Diffraction Analysis of Q-18-B
- C. Discussion on why equivalency testing of the three distinct bentoquatam assay methods is not necessary.
- D. Discussion regarding free Q-18.
- E. Discussion on methodology to assay bentoquatam in finished drug product.

III. Discussion regarding Phase 4 irritation/effectiveness study.

PERSONNEL ATTENDING

I. Mr. Anthony A. Schulz - Manager, Business Development, United Catalysts, Inc. P. O. Box 32370, Louisville, Ky. 40232
II. David Buddrus, M.D. Medical Directions, 7414 Craigshire, Dallas, TX 75231
III. Mr. Paul Carr,P.E/., R.A.C., Chemical Engineer - Shotwell & Carr, Inc. 3003 LBJ Freeway, Ste. 100, Dallas, TX 75234

TENTATIVE DATES

We are currently available November 15, 16, & 17, and November 20, 21 1995. Please let us know, as soon as possible, dates which will be satisfactory to your personnel and the location for the meeting.

Thank you very much for your assistance and your staff these past few months while our product was under review and for assisting us in arranging this meeting. We believe this meeting is very important to the understanding by FDA's personnel, of the unusual nature of bentoquatam and in allowing United Catalysts to prepare a comprehensive response to permit NDA approval.

Sincerely yours,

Anthony A. Schulz
Manager Business Development

AAS/jr

cc: Ms. Joanne Holmes