DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 80N-0146]

Nailbiting and Thumbsucking Deterrent Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) nailbiting and thumbsucking deterrent drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by January 14, 1981, and reply comments by February 16, 1981.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 44-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on March 12, 1979, a report on nailbiting and thumbsucking deterrent drug products from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

Under § 330.10(a) (6) (21 CFR 330.10(a) (6)), the agency issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC nailbiting and thumbsucking deterrent drug products are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recongized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document as a formal proposal to obtain public comment before the agency reaches any decisions on the Panel's recommendations. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it. After reviewing all comments submitted in response to this proposal, FDA will issue a tentative final regulation in the **Federal Register** to establish a monograph for OTC nailbiting and thumbsucking deterrent drug products.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC nailbiting and thumbsucking deterrent drug products submitted for consideration by the Advisory Review Panel. All the submitted information will be put on public display at the Hearing Clerk's Office, Food and Drug Administration, after (November 17, 1980), except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301 (j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

Based upon the conclusions and recommendations of the Panel, FDA proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (monograph conditions), be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph, either because they would cause the drug to be not generally recognized as safe and effective or to be misbranded or because the available data are insufficient to support the inclusion of such conditions in the monograph (nonmonograph conditions), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register,** regardless of whether further testing is undertaken to justify their future use.

FDA published in the **Federal Register** of May 13, 1980 (45 FR 31422) its proposal to revise the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug regulations (21 CFR 330.10) are unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph. Accordingly, the proposed regulations delete this provision and provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (45 FR 31422).

Although it was not required to do so under *Cutler,* FDA has also decided to stop using the terms "Category I," "Category II," "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). Any OTC drug product containing a "nonmonograph condition" will be subject to regulatory action after the establishment of a final monograph. This document, however, retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, requests for data and information on all active ingredients used in OTC miscellaneous external drug products were issued in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179).

The Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety, effectiveness, and labeling of those products:

William E. Lotterhos, M.D., Chairman
Rose Dagirmanjian, Ph. D.
Vincent J. Derbes, M.D. (resigned July 1976)
George C. Cypress, M.D. (resigned November 1978)
Yelva L. Lynfield, M.D. (appointed October 1977)
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Chester L. Rossi, D.P.M.

J. Robert Hewson, M.D. (appointed September 1978)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1978. Both were nominated by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

Two nonvoting consultants, Albert A. Belmonte, Ph. D., and Jon J. Tanja, R.Ph., M.S., have provided assistance to the Panel since February 1977.

The following FDA employees assisted the Panel: John M. Davitt served as Executive Secretary until August 1977, followed by Arthur Auer until September 1978, followed by John T. McElroy, J.D., Thomas D. DeCillis, R.Ph., served as Panel Administrator until April 1976, followed by Michael D. Kennedy until January 1978, followed by John T. McElroy, J.D., Joseph Hussion, R. Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D., until March 1978, followed by Thomas J. McGinnis, R.Ph.

The Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for nailbiting and thumbsucking deterrent drug products in this document. The review of other categories of miscellaneous external drug products will be continued by the Panel, and its findings will be published periodically in future issues of the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on: June 27 and 28, August 15 and 16, 1975; May 16 and 17, 1976; September 30, December 11 and 12, 1977; January 29 and 30, September 17 and 18, October 29 and 30, 1978; January 14 and 15, and March 11 and 12, 1979.

The minutes of the Panel meetings are on public display in the Hearing Clerk's Office (HFA–305), Food and Drug Administration (address above).

No person requested an opportunity to appear before the Panel to present information on nailbiting and thumbsucking deterrent drug products.

The Panel has thoroughly reviewed the literature, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through March 12, 1979, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC nailbiting and thumbsucking deterrent drug products with respect to the following three categories:

Category I. Conditions under which OTC nailbiting and thumbsucking deterrent drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC nailbiting and thumbsucking deterrent drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

I. Submission of Data and Information

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients recognized, either through historical use or use in marketed products, as nailbiting and thumbsucking deterrent active ingredients. Three ingredients were identified as follows: denatonium benzoate, sucrose octaacetate, and isopropyl alcohol. Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC nailbiting and thumbsucking deterrent drug products.

A. Submissions

Pursuant to the above notices, the following submissions were received:

Firms and marketed products.

Commerce Drug Co. Inc., Farmingdale, NY 11735—Don't.

Mentholatum Co., Buffalo, NY 14213—Stop 'n grow.

Purepac Pharmaceutical Co., Elizabeth, NJ 07207—Nailicure, Stop zit.

In addition, the following firms made related submissions.

International Research and Development Corp., Mattawan, MI 48232—Testing for Toxicity of Denatonium Benzoate.

Parke, Davis & Co., Detroit, MI 49071—Denatonium Benzoate (December 12, 1975), Denatonium Benzoate (April 11, 1977; Additional Data), Sucrose Octaacetate.

B. Ingredients Reviewed by the Panel

Labeled ingredients contained in marketed products submitted to the Panel.

Denatonium benzoate
Isopropyl alcohol
Sucrose octaacetate

C. Classification of Ingredients

1. *Active ingredients.*

Denatonium benzoate
Sucrose octaacetate

2. *Inactive ingredient.*

Isopropyl alcohol

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All the information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions as set forth in § 330.10(a)(2), will be put on public display after November 17, 1980, in the Hearing Clerk's Office (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

A. *Nailbiting.* Fingernail biting is an extremely common habit among young and old alike. Nailbiting occurs in 43 percent of preadolescent children, 25 percent of college students, and 10 percent of adults (Ref. 1).

The nail is a horny plate on the dorsal surface of the distal end of a finger or toe and is made of hard keratin. The nail is continuously produced by the matrix, which is visible as the white, half-moon (lunula) at the base of the nail and extends back under the skin of the posterior nail fold. Nailbiting (onychophagia) usually occurs at the tip of the nail resulting in short, irregular nails. The nail is often bitten back to a point of separation from the nail bed (the tissue under the portion of the nail which appears pink), and in severe cases, the nail bed bulges beyond the nail plate. As a result of the nailbiting, fine needlelike projections are left at the edge of the nail which cause splits and mild paronychia (inflammation involving folds of tissue surrounding the nail). When nails are bitten excessively, open wounds result making this area highly susceptible to infections.

Nails are very quick to reflect local stresses such as disease, emotional stresses, drugs, and mechanical trauma. These stresses can lead to thinning, splitting, furrowing, and laddering of the nail. Nails normally grow at the rate of

0.1 millimeter (mm) daily. Nailbiting doubles this rate (Ref. 2).

The psychology of nailbiting is still uncertain. Sometimes, nailbiting is an expression of discontent, pressure, or maladjustment (Ref. 3). It is most likely to occur in a stressful situation. In most cases, nailbiting is an unconscious habit and provides an outlet for oral gratification (Ref. 4). Many different treatments have been tried to prevent nailbiting. Some of these treatments include negative practice, operant procedures, and psychotherapy; none have been very successful (Ref. 1).

One of the primary methods of treating nailbiting is to make the patient aware of the nailbiting activity. The Habit Reversal Procedure uses the awareness technique (Ref. 1). Awareness, control motivation, and activities designed to compete with the habit were emphasized in a study using the Habit Reversal Procedure. In a 1-month study involving 13 patients who were chronic nailbiters, using this procedure, the nailbiting stopped in all cases by using the Habit Reversal Procedure (Ref. 1).

Nailbiting can be a source of embarrassment. Frequently habitual nailbiters, upon recognition of their unsightly and ragged nails, try some of the nailbiting deterrent drug products that are on the OTC market in hopes of breaking the habit. These products contain bitter substances which alert the nailbiter to the activity. The two substances which have been evaluated by the Panel are denatonium benzoate and sucrose octaacetate. They are commonly used as alcohol denaturants because they impart a bitter taste, thus making the alcohol unfit to drink. Deterring nailbiting is based on this same principle. Home remedies such as pepper are used in a similar fashion to deter nailbiting (Ref. 5). Since these products are intended for topical application to deter nailbiting and/or thumbsucking, they should not be taken internally. Accordingly, these products should be labeled, "For topical use only."

Denatonium benzoate and sucrose octaacetate are used in combination or alone with vehicles such as isopropyl alcohol or pharmaceutical-grade shellac. The finished drug product is painted on the nails, thumbs, or other fingers. Additionally, appropriate warning labels should accompany any product containing flammable vehicles.

Because ingredients in the finished product may be irritating to the corneal and conjunctival areas of the eye, the product should be kept away from the eyes (Ref. 6).

B. *Thumbsucking.* In several studies the reported incidence of thumbsucking has varied from 16 to 46 percent of the child population (Refs. 7, 8, and 9).

Sucking of thumbs and other fingers is a natural act in the newborn, sometimes beginning prior to birth (Ref. 10).

Thumbsucking usually stops spontaneously at about age four (Refs. 11 and 12). Although a variety of theories have been proposed, current thinking holds that it is an empty or simple habit, a result of learned behavior, and that finger suckers are not emotionally disturbed (Ref. 10).

There are numerous reports which show an association of thumbsucking and malocclusion (Refs. 13 through 16). Persistent thumbsucking may lead to the incomplete eruption of incisors. It also affects development of muscles of the lips, thus affecting swallowing. Arch and palate formation may be adversely affected, causing deviation of the nasal septum and mouthbreathing. A crossbite or other or other occlusal abnormalities may also develop. Thus, respiration, mastication, speech, and swallowing may be affected. The consensus is that if the habit persists beyond the age of four, it may lead to clinically significant problems, and should be treated.

Among the tactics advocated for curtailment of thumbsucking are orthodontic devices such as a palatal arch or palatal crib, mechanical thumb guards, ridicule or harangue by parents, drug therapy in the form of bitter substances applied to the thumb, and combinations of the above (Ref. 17).

The consensus at this time is that the thumbsucking habit can be lessened if not eliminated without emotional disturbances or other undesirable consequences such as temper tantrums (Ref. 18).

Because persistent thumbsucking is a relatively common condition that can result in clinically significant problems, some form of therapy is warranted. However, the Panel is of the opinion that thumbsucking or nailbiting is not a significant problem in children below the age of 4 years. Labeling for these drug products should be directed to use in persons aged 4 years and over.

References

(1) Nunn, R. G., and N. H. Azrin, "Case Histories and Shorter Communications: Eliminating Nail-biting by the Habit Reversal Procedure," *Behavior Research and Therapy*, 14:65–67, 1976.

(2) Pillsbury, D. M., "A Manual of Dermatology," W. B. Saunders & Co., Philadelphia, pp. 17–21, 1971.

(3) Rook, A., D. S. Wilkinsin, and F. J. Ebling, "Textbook of Dermatology," 2d Ed., Blackwell Scientific Publications, Philadelphia, p. 1659, 1968.

(4) Sutton, R. L., Jr., "The Practitioner's Dermatology," Yorke Medical Books, New York, p. 221, 1962.

(5) OTC Volume 160020.

(6) OTC Volume 160010.

(7) Haryett, R. D., et al., "Chronic Thumb-Sucking: The Psychologic Effects and the Relative Effectiveness of Various Methods of Treatment," *American Journal of Orthodontics*, 53:569–585, 1967.

(8) Klackenberg, G., "Thumbsucking: Frequency and Etiology," *The Journal of Pediatrics*, 4:418–423, 1949.

(9) Zadik, D., N. Stern, and M. Litner, "Thumb- and Pacifier-Sucking Habits," *American Journal of Orthodontics*, 71:197–201, 1977.

(10) Fletcher, B. T., "Etiology of Fingersucking: Review of Literature," *Journal of Dentistry for Children*, July–August, pp. 293–298, 1975.

(11) Traisman, A. S., and H. S. Traisman, "Thumb- and Finger-Sucking: A Study of 2,650 Infants and Children," *The Journal of Pediatrics*, 52:566–572, 1958.

(12) Brenner, J. E., "Thumbsucking: Dental and Psychological Aspects," *New York State Dental Journal*, 40:78–80, 1974.

(13) Gardiner, J. H., and D. Orth, "A Survey of malocclusion and Some Aetiological Factors in 1,000 Sheffield Schoolchildren," *The Dental Practitioner*, 6:187–201, 1956.

(14) Johnson, L. R., "The Status of Thumb-sucking and Finger-sucking," *The Journal of the American Dental Association*, 26:1245–1254, 1939.

(15) Rhobotham, F. B., "Children's Dentistry in Relation to Orthodontia," *The Journal of the American Dental Association*, 20:865–870, 1933.

(16) Popovich, F., "The Incidence of Sucking Habits and Its Relationship to Occlusion in 3-Year-Old Children," Burlington Orthodontic Research Center, Progress Report Series No. 1, Division of Dental Research, University of Toronto, 1956.

(17) Jacobsen, A., "The Treatment of Thumbsucking, Part III," *The Journal of the International Association of Orthodontics*, 2:4–16, 1964.

(18) Ayer, W. A., and E. N. Gale, "Psychology and Thumbsucking," *The Journal of the American Dental Association*, 80:1335–1337, 1970.

III. Categorization of Data

A. Category I Conditions

These are conditions under which active ingredients used as nailbiting and thumbsucking deterrents are generally recognized as safe and effective and are not misbranded. The Panel recommends that Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

1. *Category I ingredients.* The Panel concludes that none of the submitted active ingredients are generally recognized as safe and effective and are not misbranded as OTC nailbiting and thumbsucking deterrents.

2. *Category I labeling.* The Panel recommends the following labeling for Category I nailbiting and thumbsucking deterrent active ingredients.

a. *Indications.* (1) "For use as a nailbiting deterrent in persons aged 4 years and older."

(2) "For use as a thumbsucking deterrent in persons aged 4 years and older."

(3) "For use as a nailbiting and thumbsucking deterrent in persons aged 4 years and older."

b. *Warnings.* (1) "Avoid contact with eyes."

(2) "For topical use only."

(3) *For products containing flammable vehicles.* "Keep away from flame."

c. *Directions.* (1) "Apply to the nail after washing hands and at bedtime, or as directed by a physician."

(2) "Apply to the thumb after washing hands and at bedtime, or as directed by a physician."

(3) "Apply to the nail or thumb after washing hands and at bedtime, or as directed by a physician."

B. Category II Conditions

These are conditions under which active ingredients used as nailbiting and thumbsucking deterrents are not generally recognized as safe and effective or are misbranded. The Panel recommends that the Category II conditions be eliminated from OTC nailbiting and thumbsucking drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

1. *Category II ingredients.* None.

2. *Category II labeling.* None.

C. Category III Conditions

These are conditions for which the available data are insufficient to permit final classification at this time. The Panel recommends completion of additional studies to support the movement of Category III conditions to Category I.

1. *Category III ingredients.*
Denatonium benzoate
Sucrose octaacetate

a. *Denatonium benzoate.* The Panel concludes that denatonium benzoate is safe when topically applied on children 4 years of age and over, but that there are insufficient data to show that it is effective for OTC use as a nailbiting and thumbsucking deterrent.

The chemical formula for denatonium benzoate is designated as benzyldiethyl[(2,6-xylylcarbamoyl) methyl]-ammonium benzoate (Ref. 1). It is a white, crystalline powder with an intensely bitter taste. This bitter taste has been utilized in denatured alcohol to signal that it is not intended for ingestion but rather for topical application and industrial usage. Denatonium benzoate has been added to a brand of lead paint to discourage children from biting and ingesting paint chips (Ref. 2).

(1) *Safety.* There have been limited studies to establish the safety of denatonium benzoate.

In a 2-year oral toxicity study, denatonium benzoate was administered by gavage to Charles River CD rats, in dosage levels of 1.6, 8, and 16 milligrams/kilogram (mg/kg) daily. Sixty-five male and 65 female rats were studied at each dosage level and a like number of male and female rats were in a control group. The rats were observed daily for signs of toxicity and for mortality; detailed observations were recorded weekly. Individual body weights and sex-group food consumptions were measured daily for the first 5 weeks of study and weekly thereafter. Hematological, biochemical, and urinalysis studies were conducted at 3, 6, 12, 18, and 24 months of the study. All rats received opthalmoscopic examinations during the control periods and at 3, 6, 12, 18, and 24 months of the study. The rats shows no ill effects at the maximum daily dose of 16 mg/kg of denatonium benzoate (Ref. 3). This amount would far exceed that used in various nailbiting and thumbsucking deterrent products.

The Litchfield and Wilcoxon (Ref. 4) method of calculation determined that the median lethal dose (LD_{50}) of denatonium benzoate is 820 mg/kg (95 percent confidence limits—569 to 1,179 mg/kg). The highest dose was 1,430 mg/kg, and toxic effects usually appeared within 30 minutes after administration. Deaths occurred within the first 24 hours.

In another oral toxicity study, it was found that the oral LD_{50} dose for adult male and female albino rats was 612 mg/kg with confidence levels of 558 to 671 mg/kg (Ref. 3).

Ninety neonatal albino rats, produced in the laboratory by mating the Charles River CD albino rats, were used in another study. Undifferentiated as to sex, these rats weighed from 5.7 to 9.6 grams (g). Following birth, each litter of newborn pups was allowed to remain with its respective mother throughout the course of the 14-day study. Each litter was reduced to 10 pups. The parental female and litter were maintained in plastic breeding cages containing ground corncob bedding and controlled temperature and humidity throughout the study period. The parental females had food and water available ad libitum.

Each of the neonatal rats used was administered the test compound (denatonium benzoate in distilled water) within the first 24 hours following parturition. Dosing was accomplished by means of a polyethylene catheter attached to a syringe.

The test compound was administered orally at dosage levels of 7.9, 12.5, 19.8, 31.5, 50.0, 79.4, 125, and 315 mg/kg. Ten neonates were used at each dosage levels. Volumes of 10 milliliters/kilogram (mL/kg) of body weight were administered at all dosage levels.

A control group of an additional 10 neonatal rats was administered volumes of 10 mL/kg distilled water.

The neonatal rats were observed for pharmacodynamic signs and mortality during the first 5 hours following oral intubation, again at 24 hours, and daily thereafter for a total of 14 days. Gross necropsy (cell death) examinations were conducted on animals that died during the study period.

Individual body weights were obtained just prior to compound administration and again 14 days after compound administration. After the 14-day observation period, all surviving neonatal rats were destroyed.

All 10 neonatal rats in the control group survived the 14-day observation period and appeared normal on the day of dosing, at 24 hours, and throughout the 14-day observation period.

All 10 neonatal rats in both the 7.9 and 12.5 mg/kg dosage level groups survived the 14-day observation period and appeared normal on the day of dosing, at 24 hours, and throughout the 14-day study period.

At the 19.8 mg/kg dosage level, 3 of 10 neonates were dead within 60 minutes following oral dosing. At the 31.5 mg/kg level, 7 of 10 neonates were dead within 5 hours following oral intubation. Two additional neonates at the 31.5 mg/kg dosage level group were found dead at 24 hours.

At the 50.0 mg/kg dosage level, one neonate was dead at 2 hours, five at 3 hours, one at 4 hours, and the remaining three neonates were found dead at 24 hours.

At the 79.4 mg/kg level, three neonates were dead at 2 hours, four at 3 hours, and the remaining three were dead at 4 hours.

At the 125 mg/kg level, one neonate was dead within 60 minutes, eight at 2 hours, and the remaining neonate was dead at 3 hours.

At the 315 mg/kg level, eight neonates were dead at 2 hours, and one each was dead at 3 hours and 4 hours.

Based on the results obtained, an LD_{50} for denatonium benzoate in neonatal rats was calculated to be 23 mg/kg with

confidence limits of 19 to 27 mg/kg (Ref. 5).

An irritation study was done on 90 volunteers for a 30-day period. They were instructed to paint their fingernails daily with a product containing 0.15 percent denatonium benzoate and 6 percent sucrose octaacetate. At 4-hour intervals the nails were licked to expose the mouth and tongue to the painted surface of the nail. Nails, mouth, and tongue were checked daily for any signs of irritation. No irritation or damage to the nails, mouth, or tongue was found when this product was applied to the nails and tested for 30 days (Ref. 4).

Patch tests using 5 percent solutions of denatonium benzoate were done on 6 patients, who were allergic to quaternary (four-ringed) chemical compounds. No irritation was seen (Ref. 4).

(2) *Effectiveness.* As part of the irritation study involving the 90 volunteers applying a combination of 0.15 percent denatonium benzoate and 6 percent sucrose octaacetate for 30 days, the nail growth of the 19 nail biters in the group of 90 volunteers was visually observed and graded to 1 of 4 criteria (Ref. 4). Results of the uncontrolled study are summarized in the following chart (Ref. 4):

Visual Nail Growth of 19 Nailbiters Applying a Combination of 0.15 Percent Denatonium Benzoate and 6 Percent Sucrose Octaacetate for 30 Days

Nail growth	Number	Percent
Good	12	63.1
Fair	3	15.8
Poor	1	5.3
No noticeable growth	3	15.8
	19	100.0

In an uncontrolled study for the treatment of nailbiting and thumbsucking, the effectiveness of two marketed denatonium benzoate (0.35 percent) products was tabulated. The results, taken from reply cards, indicated that 66 percent of the replies were positive and 34 percent of the replies claimed the product to be ineffective or partially effective. It was concluded by the manufacturer that this response showed the products to be effective (Ref. 6). It was noted that of the 165,000 bottles of 1 product that were sold from 1972 to 1973, only 192 requests for refunds were made. The manufacturer assumed that the rest of the consumers were pleased with the results received from the products.

One manufacturer stated that, owing to many factors, the consumer response method was a better indication of effectiveness than controlled studies (Ref. 6). Some of these factors include:

(i) That the products are cosmetically oriented and that the effect of the principal ingredient is well recognized for its intended purpose of imparting a bitter taste which will make nailbiting and thumbsucking unpleasant.

(ii) The results of the consumer studies allow for much greater statistically significant data.

(iii) The difficulty in designing a meaningful, controlled study plus the unavailability of a patient population to participate in such a study renders the consumer response method more desirable (Ref. 6).

(3) *Proposed dosage.* Adult and children 4 years of age and older: Topical dosage is the preparation containing 0.35 percent denatonium benzoate or less.

(4) *Labeling.* The Panel recommends Category I labeling for nailbiting and thumbsucking deterrent active ingredients. (See part II. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as a nailbiting or thumbsucking deterrent will be required in accordance with the guidelines set forth below for testing thumbsucking and nailbiting deterrent ingredients. (See part II. paragraph C. below—Data Required for Evaluation.)

References

(1) "Merck Index," 9th Ed., Merck & Co., Rahway, NJ, p. 378, 1976.

(2) Challop, R. S., "Evaluation of an Acerbic Paint Containing Denatonium Benzoate for the Prevention of Paint Ingestion," Draft of unpublished study is included in OTC Volume 160020.

(3) OTC Volume 160228.

(4) OTC Volume 160020.

(5) OTC Volume 160295.

(6) OTC Volume 160054.

b. *Sucrose octaacetate.*

The Panel concludes that sucrose octaacetate is safe, but there are insufficient data to establish general recognition of effectiveness for use as an OTC nailbiting and thumbsucking deterrent.

Sucrose octaacetate is used as a denaturant for alcohol (Ref. 1). It is prepared by subjecting sucrose to exhaustive acetylation by reaction with acetic anhydride in the presence of a condensing agent such as pyridine (Ref. 2). Sucrose octaacetate is a white, practically odorless powder with an intensely bitter taste. It is hygroscopic (has the ability to take on and retain water readily) and has a melting point not lower than 78° C (Ref. 1).

Sucrose octaacetate has the chemical formula, $C_{28}H_{38}O_{19}$, and a molecular weight of 678.60 (Ref. 1). It is very soluble in methanol and chloroform, soluble in alcohol and ether, and very slightly soluble in water. Sucrose octaacetate has been used as a repellent for food sources for birds (Ref. 3). It has been used as a means of determining diet selection in free-choice situations for rats (Ref. 4). Studies of these uses revealed an initial success by producing aversion to food containing the sucrose octaacetate. However, a fast recovery was made followed by actual consumption of the diet containing the sucrose octaacetate. The rate of recovery, or consumption of the sucrose octaacetate supplemental diet, appeared to be influenced by the diet alternatives presented to the animals.

A study by Warren and Pfaffman (Ref. 5) showed no known toxic properties associated with sucrose octaacetate. Because a 0.06 percent concentration renders sugar inedible, the belief is that vomiting or gastric irritation would occur long before a toxic dose could be ingested (Ref. 6).

The Panel received a submission for a product containing sucrose octaacetate for use as a nailbiting and thumbsucking deterrent (Ref. 7). Additionally, a submission was received for a product containing sucrose octaacetate plus denatonium benzoate for use as a nailbiting deterrent (Ref. 8).

(1) *Safety.* In a study done by Linegar (Ref. 9), the minimum lethal dose of sucrose octaacetate could not be determined; 25 to 45 g did not kill any of the animals. No detectable pathological lesions of the kidney, spleen, or stomach could be determined after feeding the drug in the diet to rats and administering the drug orally to rabbits over a 3-month period (Ref. 9). The Panel concludes that sucrose octaacetate is safe in concentrations up to and including 6 percent.

(2) *Effectiveness.* There are insufficient data (controlled studies) to adequately judge the effectiveness of sucrose octaacetate as a nailbiting and thumbsucking deterrent.

(3) *Proposed dosage.* Adults and children 4 years of age and older: Topical dosage is the preparation containing 6 percent sucrose octaacetate or less.

(4) *Labeling.* The Panel recommends Category I labeling for nailbiting and thumbsucking deterrent active ingredients. (See part II. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as a nailbiting or thumbsucking deterrent will be required in accordance with the guidelines set forth below for testing nailbiting and thumbsucking deterrent ingredients. (See part II. paragraph C. below—Data Required for Evaluation.)

References

(1) "The National Formulary," 14th Ed., American Pharmaceutical Association, Washington, DC, p. 838, 1975.

(2) "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1267, 1975.

(3) Rogers, J. G., "Responses of Caged Red-Winged Blackbirds to Two Types of Repellents," *Journal of Wildlife Management*, 38:418–423, 1974.

(4) Naim, M., M. R. Kare, and D. E. Ingle, "Sensory Factors Which Affect the Acceptance of Raw and Heated Defatted Soybeans by Rats," *The Journal of Nutrition*, 107:1653–1658, 1977.

(5) Warren, R. P., and C. Pfaffmann, "Early Experience and Taste Aversion," *Journal of Comparative Physiology and Psychology*, 52:263–266, 1959.

(6) Arena, J. M., "Poisoning. Toxicology-Symptoms-Treatments," 2d Ed., Charles C. Thomas, Springfield, IL, p. 165, 1974.

(7) OTC Volume 160010.

(8) OTC Volume 160020.

(9) Linegar, C. R., "Acute and Chronic Studies on Sucrose Octa Acetate by the Oral Method," *in* "Bulletin of the National Formulary Committee," 11:59–63, 1943.

2. *Category III labeling.* None.

D. Data Required for Evaluation

The Panel considers the guidelines recommended in this document for the studies required to bring a Category III ingredient into Category I to be in agreement with the present state of the art and does not intend to preclude the use of any advances or improved methodology in the future.

A double-blind study, using the vehicle as a control, in a patient population of nailbiters as well as thumbsuckers is needed.

1. *Interpretation of data.* The Panel requires investigators to develop methods for human experimentation and to design studies which are well-controlled and safe. Data produced from these studies should be statistically significant and reproducible.

2. *Effectiveness.* Evidence of drug effectiveness, based on the results of two independent investigators or laboratories, is required from a minimum of two well-controlled studies.

All data, both favorable and unfavorable, must be submitted to FDA.

3. *Completion of studies.* Because the Panel is unable to recommend the precise protocols for such investigations at this time, 2 years will be allowed to develop the methodology and conduct studies for nailbiting and thumbsucking deterrent drug products in human subjects.

E. Combination Policy

The Panel concurs with the OTC drug review regulation [21 CFR 330.10(a)(4)(iv)] which states:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel recognizes the combination of denatonium benzoate and sucrose octaacetate as a Category III combination because the perception of a bitter taste may vary from person to person and from ingredient to ingredient.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding to Part 358, new Subpart C, to read as follows:

PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart C—Nailbiting and Thumbsucking Deterrent Drug Products

Sec.

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart C—Nailbiting and Thumbsucking Deterrent Drug Products

§ 358.201 Scope.

(a) An over-the-counter nailbiting and thumbsucking deterrent drug product in a form suitable for topical application is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 358.203 Definitions.

(a) Nailbiting is the habitual biting of the fingernails.

(b) Thumbsucking is the habitual sucking of a thumb.

§ 358.210 Nailbiting and thumbsucking deterrent active ingredients [Reserved].

§ 358.250 Labeling of nailbiting and thumbsucking deterrent drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "nailbiting deterrent," "thumbsucking deterrent," or "nailbiting-thumbsucking deterrent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one of the following phrases: (1) "For use as a nailbiting deterrent in person aged 4 years and older."

(2) "For use as a thumbsucking deterrent in persons aged 4 years and older."

(3) "For use as a nailbiting and thumbsucking deterrent in persons aged 4 years and older."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For product containing any ingredient identified in 358.210.*

(i) "Avoid contact with eyes."

(ii) "For topical use only."

(2) *For products containing flammable vehicles.* "Keep away from flame."

(d) *Directions.* The labeling of the product contains one of the following directions under the heading "Directions," followed by "or as directed by a physician."

(1) "Apply to the nail after washing hands and at bedtime."

(2) "Apply to the thumb after washing hands and at bedtime."

(3) "Apply to the nail or thumb after washing hands and at bedtime."

Interested persons are invited to submit their comments in writing

(preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before January 14, 1981. Comments should be addressed to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replaying to comments may also be submitted on or before February 16, 1981. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, as amended by Executive Order 12221, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: October 6, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80–31958 Filed 10–15–80; 8:45 am]

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21 CFR Part 358

[Docket No. 80–0348]

Ingrown Toenail Relief Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) ingrown toenail relief drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by January 14, 1981, and reply comments by February 16, 1981.

ADDRESS: Written comments to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: In accordance with part 330 (21 CFR part 330), FDA received on April 21, 1980 a report on ingrown toenail relief drug products from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the agency issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC ingrown toenail relief drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel detemined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's diliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it. After reviewing all comments submitted in respose to this proposal, FDA will issue a tentative final regulation in the **Federal Register** to establish a monograph for OTC ingrown toenail relief drug products.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC ingrown toenail relief drug products submitted for consideration by the Advisory Review Panel. All the submitted information will be put on public display at the Hearing Clerk's Office, Food and Drug Administration, after November 17, 1980, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

Based upon the conclusions and recommendations of the Panel, FDA proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (monograph conditions), be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph, either because they would cause the drug to be not generally recognized as safe and effective or to be misbranded or because the available data are insufficient to support the inclusion of such conditions in the monograph (nonmonograph conditions), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register,** regardless of whether further testing is undertaken to justify their future use.

FDA published in the **Federal Register** of May 13, 1980 (45 FR 31422) its proposal to revise the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug regulations (21 CFR 330.10) are unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph. Accordingly, the proposed regulations delete this provision and provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (45 FR 31422).

Although it was not required to do so under *Cutler,* FDA has also decided to stop using the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). Any OTC drug product containing a "nonmonograph condition" will be subject to regulatory action after the establishment of a final monograph. This document, however, retains the concepts of Categories I, II, and III because that was the framework in