MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Administrative Proceedings Staff
Hearing Clerk's Office (HFA-305)

DATE: OCT 3 1980

FROM : Director
Division of OTC Drug Evaluation (HFD-510)

SUBJECT: Public Administrative File for Anorectal Drug Products for Over-the-Counter Human Use Docket No. 80N-0050

In a notice published in the FEDERAL REGISTER on September 26, 1980 the administrative record for anorectal drug products for over-the-counter human use was reopened to allow for consideration of recommendations on camphor-containing drug products that have been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

Under cover of this memorandum, we are forwarding the volume comprising the Public Administrative File for this statement of the Advisory Review Panel on OTC Miscellaneous External Drug Products concerning OTC drug products containing camphor. This volume is to be placed on public display under docket number 80N-0050.

If there are any questions, the contact person on my staff is Michael Benson at extension 31430.

William E. Gilbertson, Pharm. D.

Attachment

80N-0050

BKG2

Administrative File

Statement of the Advisory Review Panel on OTC Miscellaneous External Drug Products Concerning OTC Drug Products Containing Camphor To the Administrative Record of

Anorectal Drug Products for Over-the-Counter Human Use

Docket No. 80N-0050

Contents

receive on this working draft with the copy available for inspection at the above address.

Copies of the working draft are available and may be obtained by interested individuals or organizations by writing to the Commissioner of Social Security, Department of Health and Human Services, P.O. Box 1585, Baltimore, Maryland 21203.

We wish to point out that this is a working draft. Neither SSA nor the Department of Health and Human Services has approved these draft regulations.

FOR FURTHER INFORMATION CONTACT: Armand Esposito, Room 4234, West High Rise Building, 6401 Security Boulevard, Baltimore, Maryland 21235, (301) 594–7455.

Dated: September 12, 1980.

William J. Driver,

Commissioner of Social Security.

[FR Doc. 80–29903 Filed 9–25–80; 8:45 am]

BILLING CODE 4110–07–M

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20 CFR Parts 404 and 416

Disability Insurance and Supplemental Security Income Determinations of Disability

AGENCY: Social Security Administration, HHS.

ACTION: Notice of decision to develop regulations.

SUMMARY: The Social Security Administration plans to recommend to the Secretary proposed regulations establishing standards of performance and administrative requirements and procedures for States making disability determinations for the Secretary under titles II and XVI of the Social Security Act. These new regulations for administering the disability program are being developed to implement a provision of Pub. L. 96–265 (the "Social Security Disability Amendments of 1980") which amends section 221 of the Social Security Act.

The disability determination function is now carried out by the States and the Federal Government under negotiated agreements between the Social Security Administration and designated State agencies. The law provides that, effective June 1, 1981, disability determinations will be made by the State agencies in compliance with regulations containing performance standards and other administrative requirements and procedures relating to the disability determination function. States will have the option of turning the function over to the Federal Government if they do not wish to make disability determinations.

The proposed regulations will specify the responsibilities of the Secretary and the States in administering the disability program. They will prescribe State agency performance standards for accuracy and processing time in making disability determinations, and provide the administrative requirements and procedures the Social Security Administration and the State agencies will follow in carrying out the disability determination function. Provisions will be included specifying how the Secretary or a State may terminate the State's performance of this function.

The primary purpose of these regulations is to improve the quality and timeliness of disability determinations and to insure nationally uniform standards and procedures. At the same time, every effort will be made to preserve the Federal-State relationship and to allow States to perform their function with maximum management flexibility and a minimum of regulation.

The proposed administrative regulations will require revisions to parts 404 and 416 of Title 20 CFR. The Department has classified the proposed regulations as policy significant.

FOR FURTHER INFORMATION CONTACT: David B. Smith, Social Security Administration, Office of Disability Programs, Room 3–A–12, Operations Building, 6401 Security Boulevard, Baltimore, Maryland 21235, Telephone 301–594–7108.

Dated: September 4, 1980.

Approved.

William J. Driver,

Commissioner of Social Security.

[FR Doc. 80–29844 Filed 9–25–80; 8:45 am]

BILLING CODE 4110–07–M

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N–0227]

Camphorated Oil and Camphor-Containing Drug Products for Over-the-Counter Human Use; Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) proposes that drug products labeled as "camphorated oil" or "camphor liniment" and drug products containing camphor in excess of 11 percent be classified in Category II as not generally recognized as safe and effective and as misbranded. This document, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products and the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, is part of the ongoing review of OTC drug products conducted by the FDA. The agency, having reviewed the Panels' reports, has determined that any drug product labeled as "camphorated oil" or "camphor liniment" or any drug product containing camphor in excess of 11 percent is misbranded and is a new drug for which an approved new drug application is required for marketing. The agency has also decided that action to remove camphorated oil drug products and any drug product containing camphor in excess of 11 percent from the market should be implemented expeditiously and not await the full procedural review that has been established for OTC drug products.

DATE: Comments by November 25, 1980.

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 March 7, 1980, a report of 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 drugs are generally recognized as safe and effective and not misbranded (i.e., Category I); (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding (i.e., Category II); (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify such conditions under either (1) or (2) above (i.e., Category III); and (4) the conclusions and recommendations of the Panel. Because the Panel's recommendations on camphorated oil contain no Category I or Category III conditions, FDA is issuing a notice, containing the Panel's recommendations, which proposes

Category II classification for camphorated oil.

The Panel's report has been prepared independently of FDA, and represents the best scientific judgment of the Panel members. Because the Panel strongly recommended that FDA act swiftly to remove camphorated oil from the market, the agency has reviewed the Panel's report at this time. The Panel concluded, and FDA concurs, that camphorated oil is not generally recognized as safe for OTC use because of the large number of harmful accidental ingestions of camphorated oil, often mistaken for castor oil, cod liver oil, mineral oil, olive oil, cough medicine, or other products. Moreover, because the risk of poisoning in infants and young children upon accidental ingestion greatly outweighs any questionable benefits to be derived from the medicinal use of this drug, the agency has determined that marketing of any camphorated oil drug products should cease.

Historically, camphorated oil has been a recognized synonym for camphor liniment. Camphor liniment, which was officially recognized in the National Formulary (NF), was deleted from the official compendia with publication of NF XIII (September 1, 1970). "Camphorated oil" or "camphor liniment," or any similar name such as "camphor oil" or "camphorated liniment," as previously recognized in the official NF and as presently formulated, is a solution of 20 percent camphor in cottonseed oil. Although no longer recognized in an official compendia, the product continues to be marketed under both names.

The agency has determined that any drug product labeled as "camphorated oil" or "camphor liniment," or any similar name such as "camphor oil" or "camphorated liniment," represents a potential health hazard because of the possibility of accidental ingestion and subsequent toxic effects.

The agency, therefore, is proposing that any drug product containing camphor which is labeled as "camphorated oil" or "camphor liniment," or any similar name such as "camphor oil" or "camphorated liniment," and which is offered for any use in interstate commerce after the effective date of this regulation is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and is a new drug within the meaning of section 201(p) of the act for which an approved new drug application under section 505 of the act (21 U.S.C. 355) and Part 314 of the regulations (21 CFR Part 314) is required for marketing. In the absence of an approved new drug application such products in interstate commerce after the effective date of this regulation will be subject to regulatory action.

Although the Miscellaneous External Panel's report was concerned only with camphorated oil drug products, the Panel noted that the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (hereinafter referred to as the Topical Analgesic Panel) discussed the safety of camphor in its report on external analgesic drug products published in the Federal Register on December 4, 1979 (44 FR 69768). That Panel concluded that camphor as an ingredient was safe and effective for use in OTC drug products as a topical analgesic, anesthetic, and antipruritic in a concentration of 0.1 to 3.0 percent and as a topical counterirritant in a 3- to 11-percent concentration.

The agency has reviewed the Topical Analgesic Panel's recommendations concerning camphor. Because of the potential toxicity problems which the Miscellaneous External Panel has identified, the agency has determined at this time that no product containing camphor in excess of 11 percent can be generally recognized as safe for OTC use. Moreover, because of the risk of poisoning in infants and young children upon accidental ingestion, the agency has determined that marketing of any drug product containing camphor in excess of 11 percent should cease. The agency, therefore, is also proposing that any drug product containing camphor in excess of 11 percent offered for any use in interstate commerce after the effective date of the final regulation is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and is a new drug within the meaning of section 201(p) of the act for which an approved new drug application under section 505 of the act (21 U.S.C. 355) and Part 314 of the regulations (21 CFR Part 314) is required for marketing. In the absence of an approved new drug application such products in interstate commerce after the effective date of this regulation will be subject to regulatory action.

The agency advises that the Topical Analgesic Panel's recommendations on drug products other than those either containing camphor and labeled as "camphorated oil" or "camphor liniment," or any similar name such as "camphor oil" or "camphorated liniment," or containing camphor in excess of 11 percent are not affected by this proposed rule. The recommendations of the Topical Analgesic Panel on camphor and the safety and effectiveness of products containing camphor in concentrations less than 11 percent will be addressed in the rulemaking proceeding for external analgesic drug products.

Elsewhere in this issue of the Federal Register, the agency has published a notice reopening the administrative record for OTC external analgesic drug products to consider the Miscellaneous External Panel's recommendation. Two other OTC advisory review panels—the Advisory Review Panel on OTC Hemorrhoidal Drug Products and the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products—also reviewed the safety and effectiveness of camphor. Elsewhere in this issue of the Federal Register, the agency has published notices reopening the administrative record for OTC anorectal drug products and for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products to consider the Miscellaneous External Panel's recommendation.

By the action proposed in this document, the agency does not wish to give the impression that it has made a final determination that 11 percent is the upper safe limit for camphor-containing products for OTC use. This determination will be made at a later date in a future issue of the Federal Register.

The agency has determined that action to remove all camphorated oil drug products and all drug products containing camphor in excess of 11 percent from the market should be implemented expeditiously. Accordingly, the agency advises that it will not follow the full OTC rulemaking procedure set forth in § 330.10 (21 CFR 330.10). FDA will not publish a tentative final order, but will publish a final order soon after the receipt and consideration of comments on this proposal. It is the agency's intention that the final order will become effective upon publication in the Federal Register. Interested persons have until November 25, 1980 to submit comments on this proposal.

Upon the effective date of the regulation, because of the risk associated with use of camphorated oil drug products and drug products containing camphor in excess of 11 percent, the agency will request firms to recall to the retail level all drug products containing camphor which purport to be or are represented as camphorated oil or camphor liniment and all drug products containing camphor in excess of 11 percent. In the interim manufacturers are requested voluntarily to discontinue marketing of these products. Any

facturer wishing to ascertain her its product purports to be or is ented as camphorated oil or phor liniment should submit the uct's formulation and labeling to the sion of Drug Labeling Compliance, d and Drug Administration, 5600 ers Lane, Rockville, MD 20857.

he products affected by the proposed ion pose an unwarranted risk of rm, in the agency's judgment, because me or all of the following factors are und in these products: a high oncentration of a potentially toxic gredient; little or no data to show that he ingredient at these concentration evels has any benefit or any benefit commensurate with the risk; a name or appearance that confusingly suggests a product intended for ingestion; and a number of reported incidents of accidental ingestion and harm. Thus, it is particularly important to take action with respect to products with high concentrations of camphor because in these products the ingestion of even a small quantity of the drug poses a serious risk.

A proposed review of the safety, effectiveness, and labeling of all OTC gs by independent advisory review s was announced in the Federal ter 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, a request for data and information on all active ingredients used in OTC miscellaneous external drug products was issued in the Federal Register of November 16, 1973 (38 FR 31697). In the Federal Register of August 27, 1975 (40 FR 38179), a further notice supplemented the initial notice with a detailed list of ingredients. However, camphorated oil was not specifically included in either notice.

The Commissioner 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 the ingredients in 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 977)
y E. Morton, Sc. D.
rianne 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., nominated by 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 1970. 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, but 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 camphorated oil 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 in future issues of the Federal Register as the Panel completes its deliberations on each category of drugs.

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic of this document were held on January 14 and 15, February 27 and 28, 1977; October 29 and 30, 1978; January 27 and 28, and March 7, 1980.

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

No submissions were made for camphorated oil. However, camphorated oil came to the attention of the Panel By Mr. Carmine Varano, a New Jersey pharmacist, who reported a number of accidental ingestions of camphorated oil to FDA. In many of these cases, consumers had mistaken camphorated oil for castor oil or code liver oil (Ref. 1).

At the Panel's request, Mr. Varano appeared before the Panel at its January 28, 1980 meeting to provide information and to express his views on camphorated oil. (See *Safety* below.) No other person requested an opportunity to appear before the Panel on this subject; however, the American Pharmaceutical Association filed a written statement on camphorated oil with the Panel recommending that the Panel classify camphorated oil as Category II for both safety and effectiveness (Ref. 2). The Panel has thoroughly reviewed the literature and considered all pertinent data and information through March 7, 1980 in arriving at its conclusions and recommendations on camphorated oil.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered camphorated oil with respect to the following three categories:

Category I. Conditions under which camphorated oil is generally recognized as safe and effective and is not misbranded.

Category II. Conditions under which camphorated oil is not generally recognized as safe and effective or is misbranded.

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

The Panel concludes that camphorated oil is not safe (Category II) for any OTC external use.

Camphorated Oil

Camphorated oil, also known as camphor liniment, is a simple solution of 20 percent camphor in cottonseed oil. It was officially recognized in the first edition of "The United States Pharmacopeia," published in 1820. It has been used mainly in the past as a counterirritant, rubefacient, and liniment for treating sprains, bruises, rheumatism, and other inflammatory conditions. Historically, camphorated oil has been the official synonym for camphor liniment when camphor liniment was recognized in the official NF. It remained the officially recognized synonym in NF XI (October 1, 1960), but was deleted as the officially recognized synonym in NF XII (September 1, 1965). Ultimately, camphor liniment was deleted from the official compendia with publication of NF XIII (September 1, 1970). Although no longer recognized in an official compendia, the product continues to be marketed under both names and has fallen into disuse to some degree in recent years.

(1) *Safety.* In its report on external analgesic drug products, which was published in the Federal Register of December 4, 1979 (44 FR 69768), the Topical Analgesic Panel discussed the safety of camphor. That Panel stated that cases of systemic poisoning from topical application of camphor have not been reported. In his presentation to the Miscellaneous External Panel on January 28, 1980, Mr. Varano pointed out that three cases have been reported in the medical literature (Ref. 1). In one case, camphorated oil was applied continually for about 80 hours to the chest of a 2-year-old child. The resulting diagnosis was camphor poisoning (Ref. 3). In another case, a 15-month-old boy became progressively ataxic and had some brief generalized major motor seizures after he crawled through spirits of camphor (a 10-percent solution of camphor in alcohol) spilled by a sibling. No further seizures occurred until 1 year later when the child was exposed to a camphorated vaporizer preparation containing about 5 percent camphor. Concurrent with this inhalant exposure, the child had a brief major motor seizure. The authors concluded that the occurrence of seizures with only two camphor exposures, a year apart, indicates a specific sensitivity to this agent (Ref. 4). The third case was a near-fatal incident in a 6-week-old infant after an ointment containing camphor, menthol, and thymol had been rubbed on the chest (Ref. 5).

The Topical Analgesic Panel noted in its report that the estimated minimal lethal dose of camphor in humans is 2 grams (g) (for a 150 lb. man) when ingested orally and that one adult survived ingestion of 15 g camphor. The Panel calculates that the minimal lethal dose is thus 30 milligrams/kilograms (mg/kg) body weight. However, ingesting 0.7 to 1.0 g camphorated oil proved fatal to a child (Ref. 6).

The Panel noted that accidental poisoning has occurred from ingestion of camphorated oil when it has been administered erroneously for castor oil and that cases continue to be reported. In information Mr. Varano submitted to the FDA (Ref. 1), which he obtained from Regine Aronow, M.D., Director, Children's Hospital Poison Center, Detroit, MI, Mr. Varano presented data on hospital admissions at Children's Hospital due to ingestion of camphorated oil. Between 1975 and the first 6 months of 1979, there were 26 hospital admissions involving ingestion of camphorated oil. Of these 26, 16 were due to accidental ingestion, 5 were due to ingestion of camphorated oil mistaken for castor oil, 1 was due to an ingestion of camphorated oil mistaken for cod liver oil, and 4 were due to ingestion of camphorated oil mistaken for cough medicine. Mr. Varano also presented information which he received from the Provincial Drug and Poison Information Center of Vancouver, BC, concerning an ingestion of camphorated oil by a 2-year-old child which proved fatal (Ref. 1).

Jacobziner and Raybin (Ref. 7) reported a case in which an 18-month-old girl ingested camphorated oil, had a convulsion soon thereafter, and was hospitalized several hours later. At the hospital, the patient had generalized convulsions, right facial twitchings, and twitchings of the right leg. The infant soon became comatose and died 4 hours after admission to the hospital. Death was attributed to respiratory failure.

Phelan (Ref. 8) reported a case of a 3-year-old girl who ingested an estimated 0.7 g of camphor (of a product containing about 5 percent camphor) and had a convulsion soon thereafter. An electroencephalogram 18 hours after the seizure showed some abnormalities. A repeat electroencephalogram 15 days after discharge from the hospital was unchanged from the earlier one. An electroencephalogram 3 months later was normal.

The American Academy of Pediatrics Committee on Drugs (Ref. 9) has presented a progressive symptomatology of severe camphor intoxication. The onset of symptoms of camphorated oil poisoning may occur within 5 to 15 minutes after ingestion, although they may be delayed up to several hours if food is present in the stomach to interfere with absorption. Nausea and vomiting are usually the first symptoms to appear, followed by a feeling of warmth, headache, vertigo, mental confusion, restlessness, delirium, and hallucinations. Increased muscular excitability, tremors and jerky movements, and convulsions followed by central nervous system depression and coma may occur. In cases of severe poisoning, death occurs from respiratory failure or from status epilepticus. If death does not occur, mental retardation can be an aftereffect (Ref. 10). If the patient lives, recovery is usually complete within 48 hours (Ref. 11); however, a 19-month-old infant died 5 days after the ingestion of 1 teaspoonful of camphorated oil (Ref. 5).

Camphor is readily absorbed through mucous membranes, subcutaneous tissue, and the gastrointestinal tract. In small doses, camphor combines with glucuronic acid and is excreted via the kidneys (Ref 12). This mechanism accounts for its unusually high toxicity in fetuses and newborn infants because neither has developed the process of glucuronidation and, therefore, cannot detoxify camphor (Ref. 13) Camphor has been shown to pass through the placenta and has been implicated in the deaths of newborn infants (Ref. 14). In one case a newborn infant died 30 minutes after delivery when the mother had ingested compahorated oil 36 hours before giving birth. Camphor was detected in maternal blood 15 minutes after ingestion, gastric lavage was performed, and camphor was not found 8 hours later. At delievery, 36 hours after ingestion, camphor was found in amniotic fluid, umbilical cord blood, and fetal blood, as well as in the liver, brain, and kidney of the infant. Cause of death was failure to initiate respiration (Ref. 15). In a second case (Ref. 16) a healthy baby was delivered 20 hours after ingestion of camphorated oil. While high levels of camphor were measured in maternal blood 24 hours after ingestion and the amniotic fluid had a distinct odor of camphor, only very low levels were found in the infant's blood. In both cases (Ref. 9) the mothers mistakingly took camphorated oil, believing it to be castor oil, to induce labor.

The treatment of camphorated oil poisoning is by no means simple. Most toxicology texts recommend symptomatic and supportive treatment. Treatment is complicated by the fact that camphorated oil is highly soluble in lipid deposits. Lipid hemodialysis (Ref. 11) and resin hemoperfusion (Ref. 17) have been proven to be effective treatments, but the value of these procedures is constrained by their limited availability.

Reports of camphor poisonings have appeared in the literature for decades, with a large number of the cases involving the accidental ingestion of camphorated oil, often mistaken for such items as castor oil, cod liver oil, mineral oil, olive oil, and cough medicine (Refs. 6, 9, 14, 18, 19, 20, 21, 22, and 23). The Panel concludes that camphorated oil is the worst offender of all camphor preparations that are accidentally ingested because it is mistaken for a variety of other OTC products. The Panel further concludes that camphorated oil is unsafe because of the large number of accidental ingestions by children and the potential toxicity in infants and young children including death (Refs. 1, 6, 7, 19, 20, and 22). Statistics compiled by the National Clearinghouse for Poison Control Centers record 706 ingestions of camphorated oil, 421 occurring in children less than 5 years of age, from 1974 to 1978 (Ref. 18). The risk of poisoning in infants and young children,

as evidenced by the numerous reports in the literature and by the National [redacted]inghouse for Poison Control [redacted]ers, is a major factor in the Panel's assessment that camphorated oil is not safe for OTC use. Additionally, in reviewing toxicity in mice, rats, and rabbits, it appears that human beings may be 50 to 100 times more susceptible to camphor poisoning than the usual laboratory animals. The Panel strongly recommends that the FDA act swiftly to remove camphorated oil from the market.

(2) *Effectiveness.* The Topical Analgesic Panel, in its report published in the Federal Register of December 4, 1979 (44 FR 69768), discussed the mechanism of action of camphor as a counterirritant and stated that it was unable to find any acceptable reasons for the continued employment of camphor alone as a topical counterirritant at the concentration (20 percent) present in camphorated oil. In a statement on camphorated oil presented to the Miscellaneous External Panel on September 27, 1978, the American Pharmaceutical Association (Ref. 2) stated:

> Considering the length of its existence [redacted]horated oil was officially recognized in [redacted]st edition of the U.S.P., published in [redacted], and its widespread use, it is surprising that a search of the literature failed to yield a single reference concerning the efficacy of camphorated oil.

The Panel was not able to locate, nor is it aware of any significant body of data demonstrating, the effectiveness of camphorated oil when used as a counterirritant.

(3) *Evaluation.* The Panel believes the hazards (i.e., the dangers of poisoning) associated with the use of camphorated oil far outweigh any questionable benefits to be derived from the medicinal use of this product. The Panel has serious concerns about the potential for poisonings resulting from the accidental ingestion of camphorated oil, often mistaken for other proprietary medications; therefore, the Panel places camphorated oil in Category II for safety.

References

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(2) American Pharmaceutical Association presentation on Camphorated Oil contained in OTC Volume 160291.

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(8) Phelan, W. J., III, "Camphor Poisoning: Over-the-Counter Dangers," *Pediatrics*, 57:428–431, 1976.

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(16) Weiss, J., and P. Catalano, "Camphorated Oil Intoxication During Pregnancy," *Pediatics*, 52:713, 1973.

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(18) Poison Control Statistics, Food and Drug Administration, 1974–1978.

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(21) Haft, H. H., "Camphor Liniment Poisoning," *Journal of the American Medical Association*, 84:1571, 1925.

(22) Barker, F., "A Case of Poisoning by Camphorated Oil," *The British Medical Journal*, 1:921, 1910.

(23) Bellman, M. H., "Camphor Poisoning in Children," *British Medical Journal*, 2:177, 1973.

All references are on display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

The agency has determined that under 21 CFR 25:24(d)(9) (proposed in the Federal Register of December 11, 1979; 44 FR 71742) that this proposal is of a type that does not individually or cumulatively have a significant effect 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 in Part 310 by adding new § 310.526, to read as follows:

§ 310.526 Camphorated oil and camphor-containing drug products.

(a) Historically, comphorated oil (also known as camphor liniment), a solution of 20 percent camphor in cottonseed oil, has been marketed as an over-the-counter (OTC) drug product for various uses, primarily as a counterirritant or liniment. A large number of accidental ingestions of camphorted oil, often mistaken for castor oil, cod liver oil, mineral oil, olive oil, cough medicine, or other products, have been reported and toxicity has often resulted, primarily in infants and young children. Because of the potential hazard for poisoning to occur, the benefit from using any drug products containing camphor and labeled as "camphorated oil" or "camphor liniment," or any similar name such as "camphor oil" or "camphorated liniment," for any use, is insignificant when compared to the risk. Based upon the adverse benefit-to-risk ratio, any drug product containing camphor which is labeled as "camphorated oil" or "camphor liniment," or any similar name such as "camphor oil" or "camphor liniment," cannot be considered generally recognized as safe. Also, based upon lack of safety and effectiveness data and the adverse benefit-to-risk ratio, any drug product containing camphor in excess of 11 percent cannot be considered generally recognized as safe.

(b) Any drug product containing camphor and labeled as "camphorated oil" or "camphor liniment," or any similar name such as "camphor oil" or "camphorated liniment," or any drug product containing camphor in excess of 11 percent offered for any use is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is a new drug within the meaning of

section 201(p) of the Act for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD-1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any preparation containing camphor which purports to be or is represented as camphorated oil or camphor liniment or any preparation containing camphor in excess of 11 percent for any use is safe and effective for the purpose intended.

(d) Any such drug product in interstate commerce after the effective date of the final regulation that is not in compliance with this section is subject to regulatory action.

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 November 25, 1980. Comments should be addressed to the Hearing Clerk, Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. 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, 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: September 15, 1980.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 80-29964 Filed 9-25-80; 8:45 am]

BILLING CODE 4110-03-M

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21 CFR Part 341

[Docket No. 76-N-52]

Cold, Cough Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Reopening of the Administrative Record

AGENCY: Food and Drug Administration.

ACTION: Reopening of administrative record

SUMMARY: This notice advises that the Food and Drug Administration (FDA) is reopening the administrative record for over-the-counter (OTC) cold, cough, allergy, bronchodilator, and antiasthmatic drug products to allow for consideration of recommendations on camphor-containing drug products that have been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

DATES: Comments by November 25, 1980; and reply comments by December 26, 1980.

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: The Food and Drug Administration (FDA) published the report and proposed monograph of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (CCABA Panel) on OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products for human use on September 9, 1976 (41 FR 38312). Interested persons could have filed written comments regarding this proposal by December 8, 1976, and comments replying to comments by January 7, 1977. After the closing of the comment period following publication of the panel report, new data and information may be submitted for inclusion into the administrative record only through a petition to reopen the administrative record.

In a notice published in the Federal Register of March 21, 1980 (45 FR 18400), the agency advised that it had reopened the administrative record for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products to allow for consideration of data and information that had been filed with the Hearing Clerk's Office after the date the administrative record officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a tentative final order.

The CCABA Panel concluded that camphor is safe but the available data were insufficient to determine whether it is effective when labeled for use as an OTC expectorant, antitussive, and nasal decongestant. The Panel placed camphor in Category III (available data are insufficient to classify the ingredient as Category I or Category II) for different uses at different concentrations: expectorant (topical-5 percent ointment, steam inhalation-7 percent solution, lozenge-0.02 to 15 milligrams (mg)); antitussive (topical-5 percent ointment, steam inhalation-7 percent solution, lozenge-0.02 to 15 mg); and nasal decongestant (topical-5 percent ointment, steam inhalation-7 percent solution lozenge-0 02 to 15 mg). Following the publication of this panel's recommendation on camphor, the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) also reviewed camphor. The Miscellaneous External Panel, however, concluded that OTC products containing greater than 2.5 percent camphor have a low benefit-to-risk ratio and recommended that camphor be limited in OTC drug products for external use to less than 2.5 percent. The Miscellaneous External Panel also recommended that the quantity of camphor in a package be limited to a total of 360 mg per package, preferably in a child-proof container.

Because of the conflicting recommendations on camphor-containing drug products, FDA has concluded that resolution of this issue would be in the public's best interest. Therefore, the agency has concluded that the Miscellaneous External Panel's recommendations should be available to the agency in developing a tentative final order on cold, cough, allergy, bronchodilator, and antiasthmatic drug products. By this notice, FDA announces that it is treating the data and information on camphor received from the Miscellaneous External Panel as a petition to reopen the administrative record on cold, cough, allergy, bronchodilator, and antiasthmatic drug products. FDA is granting the petition by allowing the data and information contained therein to be included in the administrative record for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. This notice serves to inform interested persons of these recommendations, which appear below. This reopening of the administrative record relates only to the ingredient camphor in OTC drug products. Comments relating to portions of the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Proposed Monograph (41 FR 38312) other than on camphor will not be accepted at this time.

Statement of the Advisory Review Panel on OTC Miscellaneous External Drug Products Concerning OTC Drug Products Containing Camphor

The Advisory Review Panel on OTC Miscellaneous External Drug Products has reviewed the product camphorated oil as well as numerous other camphor-

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Camphor Poisoning: Over-the-Counter Dangers

Intoxication from camphor has been reported frequently in the literature for decades, most cases involving the accidental ingestion of camphorated oil, mistaken for castor oil or other similar products. Over 20 years ago, Smith and Margolis[1] collected 130 nonfatal and 18 fatal cases from literature dating back to 1833. Recent data from the National Clearinghouse for Poison Control Centers reveal an increasing proportion of ingestions of other over-the-counter camphor-containing preparations.[2,3]

Two cases with documented serum camphor levels have prompted this report and discussion of camphor's role in the self-medication over-the-counter armamentarium.

CASE REPORTS

Case 1

A 3-year-old girl was transferred to the University of Michigan Medical Center from a local emergency room. Recent medical history revealed four days of mild rhinorrhea, cough, and low-grade fever. Confusion and irritability with gastric upset and projectile vomiting preceded a generalized convulsion by two hours.

The seizure was controlled in 30 minutes by 25 mg of intramuscularly administered secobarbitol. Because of subsequent respiratory depression, oxygen was given by face mask and 0.2 gm of caffeine sodium benzoate was administered intramuscularly and the patient transferred.

Evaluation at this hospital disclosed a mildly depressed child with a spontaneous respiratory rate of 28 breaths per minute, pulse 126 beats per minute, temperature 36.4 C and blood pressure 120/90. Physical examination was unremarkable save for the distinct odor of camphor on the breath. Upon questioning, the mother related that the child had been found with an open jar of Vicks Vaporub (4.61% camphor) two hours before the convulsion, and she estimated one tablespoon (containing an estimated 0.7 gm of camphor) was missing. In addition, the patient had received twice daily intranasal administration of the product for five months and enjoyed the taste, often sucking the cotton-tipped applicators used for this.

Within 21 hours of admission she was asymptomatic and required no respiratory support or additional anticonvulsants. Laboratory studies revealed no abnormalities in CBC, electrolytes, liver functions, calcium, phosphorus, magnesium, glucose, blood urea nitrogen (BUN) creatinine, cerebral spinal fluid, and urinalysis.

Serum and cerebrospinal fluid were analyzed by gas liquid chromatography in the UMMC Pharmacy Drug Analysis Laboratory. Acidified specimens were extracted with chloroform and unconcentrated extracts injected into the gas chromatograph. Concentrations were calculated by comparison of peak areas with reference standards of camphor. Serum drawn seven hours after ingestion contained 1.95 mg of camphor per 100 ml, but cerebral spinal fluid and serum samples 21 hours after ingestion had no detectable level.

An electroencephalogram 18 hours after the seizure suggested a diffuse neuronal disturbance with excessive slow activity in the bianterior and bicentral regions with no specific paroxysmal discharges.

The patient was discharged 24 hours after admission phenobarbital 7 mg/kg/day, and has remained seizure free to this writing. A repeat electroencephalogram 15 after discharge was unchanged but was normal after months.

Case 2

A 2-year-old girl was brought to the emergency room minutes after ingesting an estimated 1 or 2 teaspoo Campho-Phenique (10.8% camphor and 4.7% phenol had vomited immediately and was given egg white by parents.

Physical examination showed an alert anxious girl with abnormal findings except a strong odor of camphor on breath. Gastric lavage was performed until the odor undetectable in the lavage fluids and the child released observation two hours later. Follow-up in 24 hours found to remain totally well.

A prelavage serum specimen drawn 20 minutes ingestion of approximately 0.5 to 1.0 gm of cam contained 0.610 mg of camphor per 100 ml as determ by gas liquid chromatography.

DISCUSSION

Camphor is a cyclic ketone for the hydroaromatic terpene group and has been used medicinal purposes for centuries. Obtained originally in the Far East by distillation of bark and from the camphor tree, *Cinnamomum Camphora*, it is now produced synthetically and available 20% cottonseed oil or 10% alcohol preparations well as an ingredient in an increasing variety other over-the-counter preparations. Table partial listing of such preparations with approximate percentage of camphor where information is available.

Pharmacologically, camphor is categorized an irritant rubefacient, acting locally on the and mucous membranes to induce hyperemia, feelings of comfort and warmth, with sensation of coolness when its vapors are inhaled. Subjective relief of pain is obtained by an induced counterirritation analgesic effect, representing masking of moderate to severe deeper visceral pain by a milder pain arising from skin or same segmented central nervous system level. The visible rubefaction and medicinal odor assure the patient that he is receiving an effective medication, producing a placebo effect and certainly having equal or greater pain-relieving value than the physiologic response elicited.

Camphor is classified in the toxicology rating system as "Class 4—very toxic" with a probable human lethal dose from 50 mg to 500 mg/kg. It is readily absorbed from mucous membranes and measurable serum levels demonstrated 15 minutes after ingesting approximately 0.5 to 1.0 gm. patient 2 and in an adult pregnant woman who ingested 12 gm.[4] Detoxification occurs by hydroxylation and then conjugation with glucuronic

TABLE I

A Partial Listing of Available Over-the-Counter Preparations Containing Camphor

Product	*Manufacturer*	*% Camphor*	*Dosage Form*
Camphorated oil	Various	20.00	External analgesic rub
Campho-Phenique	Glenbrook	10.80	External analgesic rub
Camphor spirits	Various	10.00	External analgesic rub
Soltice Hi-Therm Analgesic Balm	Chatterm	7.00	External analgesic rub
Ben-Gay Children's Rub	Pfizer	6.00	External analgesic rub
Soltice Quick-Rub (Adult)	Chattem	5.10	External analgesic rub
Sayman Salve	Carson	5.00	External analgesic rub
Vicks Vaporub	Vick	4.81	External analgesic rub
Panalgesic	Poythress	4.00	External analgesic rub
Heet	Whitehall	4.00	External analgesic rub
Soltice Quick Rub (Children's)	Chattem	3.75	External analgesic rub
Sloan's Liniment	Standard	3.40	External analgesic rub
ia-Camph	Dorsey	3.00	External analgesic rub
Soltice Hi-Therm Arthritic Lotion	Chattem	3.00	External analgesic rub
Lini-Balm Aerosol Foam	Arnar-Stone	2.00	External analgesic rub
Analbalm	Central	1.50	External analgesic rub
Sloan's Balm	Standard	0.50	External analgesic rub
Rhulicream	Lederle	0.30	External analgesic rub
Musterole	Plough	?	External analgesic rub
Penetro Quick Acting Rub	Plough	?	External analgesic rub
Va-Tro-Nol	Vick	?	Nose drops

by the liver, with excretion of the inactivated compound in the urine.[8] This detoxification occurs rapidly and accumulation by chronic intranasal application seems unlikely because cerebral spinal fluid and serum revealed no detectable camphor 21 hours after ingestion in case 1. Riggs *et al.*'s patient[7] had no detectable amount eight hours after ingesting 12 gm, but the placenta presented no barrier and camphor was identified in amniotic fluid, fetal blood, brain, liver, and kidney 36 hours after maternal ingestion. In a similar ingestion of 12 gm, large amounts were detected in maternal blood 24 hours after ingestion and were just detectable in infant blood 20 hours after maternal ingestion. The infant did well except for an early mild elevation of SGOT and SGPT.[9]

The major manifestations of camphor intoxication seem to be central stimulation associated with mouth, throat and gastric irritation. Nausea and vomiting with mental changes such as excitement, hallucinations, and delirium are common. Muscular excitability and tremors may herald the onset of generalized convulsions, often followed by depression and apnea.[10] Urinary retention, anuria, and albuminuria have been described[1] as well as transient mild hepatic changes.[7,9]

Rubin *et al.*[11] reported convulsions in five of 14

ingestions of camphorated oil. In Craig's series of children less than 5 years of age ingesting camphorated oil, none of 19 convulsed within 4 to 120 minutes after taking 0.7 to 6 gm.[10] Our patient 1 convulsed two hours after ingesting approximately 0.7 gm and had a documented serum level of 1.95 mg/100 ml five hours after the convulsion.

One gram resulted in the death of a 19-month-old child,[1] who suffered repeated tonic-clonic seizures, spasticity, and hyperreflexia before dying five days later. Necropsy disclosed hemorrhages of the skin, bowel, stomach, and kidneys, while brain tissue had extensive degenerative changes in the neurons, especially severe in Sommer's section of the hypocampus. Similar cerebral findings were noted in Riggs *et al.*'s newborn patient.[7] Neuronal damage could explain the diffusely abnormal EEG in case 1.

Statistics compiled by the National Clearinghouse for Poison Control Centers record 185 ingestions of camphor, 134 occurring in children less than 5 years of age in 1958 and 1959.[2] Forty-six percent of analyzed patients had symptoms and 20% had convulsions. Fifteen years later, in 1973, there were reports of 530 ingestions, 415 occurring in children less than 5 years of age.[3] Camphorated oil and spirits were implicated in 40% of the childhood poisonings, with the remainder involving other over-the-counter preparations. In all cases, symptoms were present in 15% and convulsions in 4%. Convulsions associated with Vicks Vaporub, quantitated serum camphor levels, and electroencephalographic abnormalities have not been reported previously.

Treatment should include immediate induction of vomiting, although both case 1 and case 2 suggest that early emesis did not completely empty the stomach and absorption continued. Gastric lavage may be helpful in removing remaining material and activated charcoal taken orally or placed into the stomach at the termination of lavage is also recommended to absorb residue.[12] Digestible oils and alcohol should be avoided because they enhance absorption of camphor.[6] Intravenously administered barbiturates are suggested for seizure control, and limited animal data suggest they have a protective effect on the central nervous system.[1] Appropriate respiratory support is indicated for depression and apnea, and close observation and minimized sensory input are important for symptoms of excessive central stimulation. Extracorporeal lipid dialysis has been successful in an adult who ingested 12 gm.[13]

Calls for abolish[ing] nonprescription sales of camphorated oil [and] spirits are found in both the British[10,14,15] and [American literature.[9,16] It has] been suggested that there is little therapeutic value to camphor[15-18] and that its dangers outweigh its alleged usefulness.[14-19] A large number of preparations containing camphor are now available for over-the-counter sale. One must ask whether products with tastes attractive to some children, [used] to soothe a baby's rash, decongest a nose, treat fever blisters, should contain convulsive or possibly fatal doses in teaspoon quantities.

It is hoped that the Food and Drug Administration panels investigating over-the-counter preparations will realistically evaluate the benefit-versus-risk ratio of drugs such as camphor and assume with greater rapidity an increasing public health advocacy. Pharmaceutical houses producing such products should voluntarily reassess toxicity and efficacy and market only preparations of proven value, with clear warning labels when high percentages of potentially dangerous preparations such as camphor are present.

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January 1, 1959

(For Complete Table of Contents, See Pages 4 and 6)

Medical Society of the State of New York
Annual Meeting, May 9 to 15, Hotel Statler Hilton Buffalo

BRIEFS ON ACCIDENTAL CHEMICAL POISONINGS IN NEW YORK CITY

From the Poison Control Center, New York City Department of Health

A series prepared by

HAROLD JACOBZINER, M.D., *Assistant Commissioner, New York City Department of Health*

HARRY W. HAYBIN, M.S., *Technical Director, Poison Control Center*

Oil of Wintergreen, Camphor, and Lye Ingestions

THE following ingestion accidents involving oil of wintergreen, camphorated oil, and lye and their mode of occurrence have been reported to the New York City Poison Control Center.

Incident Involving Oil of Wintergreen

The mother was cleaning the medicine cabinet and had placed the bottles and other contents of the cabinet on a chair. When her attention was distracted for a moment, her eighteen-month-old son picked up a half-full, three-ounce bottle of oil of wintergreen and ingested some of its contents. When the mother took the bottle away from the child, she noticed her son had ingested half of the contents. She did not know that oil of wintergreen was harmful. Later, however, when the child began to vomit, he was taken to the hospital emergency room where his stomach contents were evacuated. The child expired about eight hours after he was admitted to the hospital.

This needless death occurred because the medication was readily accessible to the child [illegible] of the fact that oil of wintergreen could have harmful effects.

Incidents Involving Camphorated Oil

While the therapeutic value of camphor is questionable, it is still widely used in the United States. Camphor, rather mistakenly, is looked on by the laity as a valuable therapeutic agent in infections. Some parents even put camphor bags on their children to ward off colds, polio, and other infections.

The ingestion of camphor preparations by children is a direct cause of camphor poisoning. Camphor stimulates the central nervous system and its action is more marked on the higher centers.

The symptoms of camphor intoxication occur quickly and include burning sensation in the epigastrium, thirst, nausea, vomiting, headache, a feeling of warmth, excitement, restlessness, confusion, delirium, hallucinations, unconsciousness, and convulsions. The face may be flushed. Pulse is rapid and the blood pressure is elevated. The patient [illegible]

is also a characteristic camphoraceous odor of the breath. (The odor should not be confused with the odor of naphthalene and paradichlorbenzene which are loosely and erroneously referred to as "camphor.") At times, depression may be the primary symptom.

MODE OF OCCURRENCE.—*Case 1:* A two-year-old boy obtained a bottle of camphorated oil from a table next to his bed in the bedroom and drank about two teaspoonfuls. His parents detected the odor on his breath and rushed him to the hospital. The child recovered.

Case 2: A twelve-year-old boy was sent to the drugstore for a bottle of castor oil.

The child was erroneously given two small bottles of camphorated oil. The parent failed to read the label and gave each of the three children a teaspoonful of the castor oil which was actually camphorated oil. (The other two children were a one-year-old girl and a ten-year-old boy.) The children immediately complained of abdominal pains and vomited. The oldest child also remarked about the odor of the preparation. All three recovered.

Case 3: While the grandmother was in the kitchen, her fifteen-month-old granddaughter climbed on a chair, took a bottle of camphorated oil from a dresser in the living room, opened it, and drank about a teaspoonful. The child immediately had abdominal pains, stupor, convulsions, etc. The child recovered completely.

Case 4: A seven-year-old girl complained of a cold, and her mother told her to go into the kitchen for a spoonful of cod-liver oil. The child disliked cod-liver oil so she went instead to the bathroom to take castor oil. She mistakenly obtained a bottle of camphorated oil and ingested one tablespoonful. The child immediately complained of a burning in the mouth and throat and was rushed to the hospital. She subsequently recovered.

Case 5: A two-year-old boy was playing in the bedroom and obtained a bottle containing spirits of camphor from the dresser. He drank about half an ounce. (The bottle was in an open dresser within the child's reach.) He immediately complained of burning in mouth and throat and had difficulty breathing. The child was rushed to the hospital. He made a complete recovery.

Case 6: A bottle of camphorated oil was on the dresser in the bedroom. While the mother was in the bathroom, her four children were playing in the bedroom. The mother smelled the odor of camphorated oil and went to the bedroom to investigate. She found her eighteen-month-old daughter covered with camphorated oil. The other children also had some on their faces and bodies. The infant soon had a convulsion and was taken to the hospital. She was admitted several hours after ingestion of the drug. At the hospital, the patient had generalized convulsions, right facial twitchings, and twitchings of the right leg. The infant soon became comatose and expired four hours after admission to the hospital. In camphor poisonings, death usually results from respiratory failure.

TREATMENT.—Camphor poisoning treatment consists of removal by lavage of the gastric contents. However, lavage should not be done during a convulsive attack. Convulsions may be controlled by sedatives. Short-acting barbiturates may be administered. Opiates should not be used. If respiration is impaired, artificial respiration and oxygen may be necessary. The best treatment, of course, is total prevention.

A teaspoonful of camphorated oil can be fatal to a child. It is obvious that all of the above cases of camphor poisoning could have been avoided if ordinary precautionary measures were taken. In every case, the toxic agent was made readily accessible to the child. In some instances, the children were given the wrong medication owing to the parent's failure to read the label on the bottle.

Physicians are requested to constantly remind parents to keep medications out of reach of children, to keep harmful drugs under lock and key, and

fully the label on any hold preparation. I quested to acquaint p tial dangers of medic hold preparations.

Incidents Involvin

Recently, there ha crease in poisonings establishment of the on March 9, 1955, a ings have been repo cent of these accider tween two and three

A fatal case of ly three-year-old boy the Center. While engaged in an interv from the Departme obtained a glass fille had been left on th attracted the mothe was taken to the ho symptoms: burnin throat, and vomitin emic, and the muco hyperemic and d was labored and th child was restless admitted to the ho for twenty days. twentieth day in s

It may be well to of lye poisonings, to their mode of o

MODE OF OCCU year-old boy obtai mercial lye prepar of its contents. for eleven days recovery.

Case 2: A two-y of lye which the the bed. The chil play with her dog and ingested recovered.

der lock and key, and always to read carefully the label on any medication or household preparation. Physicians are also requested to acquaint parents with the potential dangers of medications and other household preparations.

Incidents Involving Lye

Recently, there has been a noticeable increase in poisonings due to lye. Since the establishment of the Poison Control Center on March 9, 1955, a total of 225 lye poisonings have been reported. Twenty-five per cent of these accidents involved children between two and three years of age.

A fatal case of lye poisoning involving a three-year-old boy was recently reported to the Center. While the mother was busily engaged in an interview with a representative from the Department of Welfare, the child obtained a glass filled with lye solution which had been left on the sink. The child's cry attracted the mother's attention. The child was taken to the hospital with the following symptoms: burning in the mouth and throat, and vomiting. The lips were hyperemic, and the mucosa in the throat was also hyperemic and denuded. The breathing was labored and the lungs congested. The child was restless and drowsy. He was admitted to the hospital where he remained for twenty days. The child expired on the twentieth day in spite of therapy.

It may be well to cite a few other examples of lye poisonings, particularly with regard to their mode of occurence.

Mode of Occurrence.—*Case 1:* A two-year-old boy obtained a can of Drano (commercial lye preparation). He ingested some of its contents. The child was hospitalized for eleven days and made an uneventful recovery.

Case 2: A two-year-old girl obtained a can of lye which the mother had placed under the bed. The child crawled under the bed to play with her dog, obtained the preparation, and ingested some of the contents. She recovered.

Case 3: The mother used lye preparation for cleaning the clogged sink drain. Some pieces fell on the floor and her nine-month-old daughter picked up some of the fragments and ingested them. She recovered.

Case 4: The mother was cleaning the bathroom sink with Drano. She put the tablespoon she had used on the toilet seat. Her four-and-one-half-year-old daughter picked up the spoon and licked the residue. She recovered.

Case 5: A three-year-old girl found a can of Drano in the bottom of a clothes basket (her mother had put it there). She ingested some of the contents. The patient recovered.

Case 6: The grandmother had cleaned the stove with lye and put the container in the closet near the stove. Her one-year-old granddaughter obtained the container and ate some of the contents. She recovered.

Case 7: The can of lye was stored on the outside bedroom windowsill. While the mother was out of the room her two-year-old daughter obtained the can and ingested some flakes which she had picked off the can. She immediately complained of burning in the mouth and throat and was rushed to the hospital. The patient completely recovered.

Case 8: A three-and-a-half-year-old child obtained a can of lye from the kitchen closet while her mother was talking to a friend. The child took a kitchen knife, opened the can, and ingested some of its contents. She immediately started to cry because of burning in her mouth and throat. The mother first went to the pharmacist who advised her to put some milk of magnesia on the child's mouth. The mother then took the child to the hospital. In the emergency room the patient was treated with one-half a glass of vinegar followed by a glass of milk. The patient was further observed for three days and was finally discharged as improved. This child is apparently accident-prone. Last summer she fell from the stairway. The fall caused

only a stiff neck which was treated at home.

Case 9: While the mother was preparing lunch, her four-year-old daughter took a can of lye from the drawer in the kitchen, opened it with a kitchen knife, and ingested some of the contents. The mother said: "It all happened so fast." The child was taken to the hospital where her stomach was lavaged. Treatment consisted of spraying the mouth and throat, cortisone, and feeding by gavage. The child remained in the hospital for six weeks. Because of burns of the esophagus, the child had to make several follow-up visits to the clinic.

Case 10: Two male siblings, one two years of age, the other three years of age, obtained a can of lye which the mother had left in the soap closet in the kitchen. Before th[illegible]other awakened, they opened the can a[illegible]ested one-half teaspoon each. The ch[illegible] complained of burning of the tongue and [illegible]outh and were taken to the hospital where they were immediately treated with vinegar and water and vinegar solution. They were discharged from the emergency room with mild burns of the lips.

Lye is a common household article used extensively for grease cleaning purposes. It is a highly corrosive agent and m dissolve the mucous membranes. Burn of the mouth and throat and difficulty swallowing are common findings. It ma be emphasized that even small quantit may be fatal.

TREATMENT.—A weak acid of 0.5 to 1 p cent of hydrochloric or acetic acid admi istered orally is recommended. This shou be followed by the administration of sal oil and other demulcents.

It must be remembered, however, that t antidote must be administered as quickly possible after ingestion because of t possible danger of necrosis. The haza attendant with lavage must also be co sidered. In any event only a small, we oiled tube should be used in its administr tion.

Physicians are reminded that stricture scarring, and stenosis are frequently t result of lye poisonings. It is, therefo recommended that patients be hospitaliz and carefully observed for developing sym toms. Even in cases where no symptoms a presumably present and the patients a sent home, frequent follow-up visits a recommended to rule out any complication

(Number twenty-two in a series of Briefs on Accidental Chemical Poisonings)

Food Faddism Has Emotional Appeal

Food faddism, which is economically wasteful, scientifically unsound, and a source of great distrac-[illegible]n to physicians, nutritionists, and health agencies, [illegible]and grows in this country, according to [illegible]t E. Olson, Graduate School of Public [illegible]he University of Pittsburgh.

[illegible] in *Nutrition Reviews*, a monthly scientific [illegible]on of the Nutrition Foundation, Dr. Olson [illegible]pressed the view that the persistence of food faddism is based on the emotional rather than intellectual appeal used by faddists.

Food has always had an emotional value. One of the primordial human urges is the urge to eat, so today, with the scarcity of food no longer a problem, it is still meaningful as a symbol of acceptance, friendliness, and socialization. Studies suggest that infants regard food as being equated with love, [illegible], protection, and comfort, and [illegible] appreciate this symbolic value of food better than those concerned with the nutritional sciences.

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Camphor Intoxication Treated by Lipid Dialysis

H. Earl Ginn, MD; Karl E. Anderson, MD; Robert K. Mercier; Timothy W. Stevens, MD; and Billy J. Matter, MD

Lipid hemodialysis was successful in an elderly patient who had accidentally ingested camphorated oil.

POISONING by camphorated oil usually results from accidental ingestion. The lethal dose is estimated to be about 1 gm for a 1-year-old child. Two grams may produce toxic effects in an adult.[1] This report concerns the successful treatment by lipid hemodialysis of a patient who ingested approximately 12 gm of camphorated oil.

Report of a Case

The patient (VUH 326266), a 77-year-old man, was brought to the hospital following a seizure. He had mistakingly received a 20% solution of camphorated oil instead of a cough elixir from a local pharmacy and had ingested approximately 60 ml. Nearly 30 minutes later he vomited and had a grand mal seizure. The vomitus smelled strongly of camphor. He was brought t[illegible] the hospital in a postictal state but became increasing[illegible] agitated and had two more seizures despite intraven[illegible] barbiturate therapy. His vital signs were normal. [illegible]er, he was disoriented and agitated. His breath smell[illegible] strongly of camphor. His skin was flushed and dry. [illegible]teral mature cataracts were present. The remainder of [illegible] physical and neurological findings were normal. Results [illegible] urinanalysis, complete blood count and blood glucose, [illegible] urea nitrogen, and liver function tests were all w[illegible] normal ranges. The urine had an odor of camphor.

Hemodialysis was initiated wit[illegible] four hours after the ingestion of camphor. Eight lit[illegible] of soybean oil were warmed to 39 to 40 C. This was [illegible]irculated as dialysate through a Klung dialyzer at [illegible]/min by means of a pump. Blood from the left r[illegible] artery was pumped through the dialyzer at 300 cc/[illegible]n and returned via a superficial forearm vein (Fig 1). [illegible] patient had no further seizures and was alert and [illegible]nted after three hours of dialysis. The procedure was [illegible]ped after 4½ hours. There were no significant change[illegible] the hemogram or in plasma chemical determinations [illegible]pt for a decrement in lactic dehydrogenase (LDH) fr[illegible] [illegible]10 units to 160 units (Table). The higher predialysis [illegible]vel was attributed to his severe seizures. He was d[illegible]ed the following day with no residual effects of camp[illegible] toxicity. Analysis of the soybean oil by gas chromato[illegible]phy revealed 6.56 gm of camphor.

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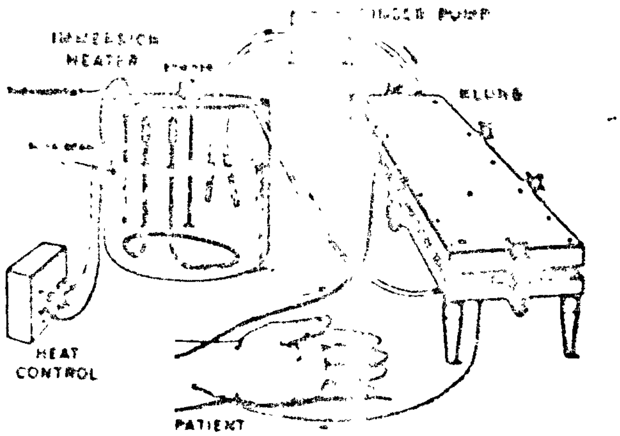


1. Diagram of lipid dialysate sy[illegible]m. Approximately 8 liters of soybean oil are heated [illegible]9 to 40 C by thermostat-controlled electric hea[illegible]. Oil is recirculated through dialyzer by pump[illegible] [illegible]d flow from patient may also require pump assista[illegible].

Commen[illegible]

Camphor is a cyclic keton[illegible] [illegible]f the terpene group that has been used for cent[illegible] [illegible]s in Chinese medicine for a variety of purpos[illegible]. It is a rubefacient[6] and has a mild local an[illegible]etic action. Small amounts produce a sensation [illegible] warmth and comfort. Large doses, however, a[illegible] irritating and cause nausea and vomiting.

Accidental poisoning occu[illegible] from mistaken substitution of camphorated oil [illegible]r castor oil or cough syrup. Suicidal and homocid[illegible] poisoning are infrequent. Ingestion of camphor[illegible]d oil to induce abortion has been reported.[1] As [illegible]le as 0.75 gm (teaspoonful of camphorated oil[illegible] [illegible]ave been fatal to a child. On the other hand, a [illegible]ealthy adult survived

	Patient's	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	42%	42%
[illegible]	140 mEq/L	138 mEq/L
[illegible]	4 mEq/L	3.8 mEq/L
[illegible]	108 mEq/L	110 mEq/L
[illegible]	20.5 mEq/L	22 mEq/L
[illegible]	9.4 mg/100 cc	9.1 mg/100 cc
[illegible]	6.9 gm/100 cc	6.5 gm/100 cc
[illegible]	3 mg/100 cc	2.8 mg/100 cc
[illegible]	6 units	3 units
Lactic acid dehydrogenase	510 units	180 units
Plasma urea nitrogen	10 mg/100 cc	10 mg/100 cc
[illegible]	1.1 mg/100 cc	1.1 mg/100 cc
Serum uric acid	5.4 mg/100 cc	5.3 mg/100 cc

the ingestion of 20 gm.[1] Young children, elderly and debilitated individuals apparently have a low tolerance to the drug.[1,2]

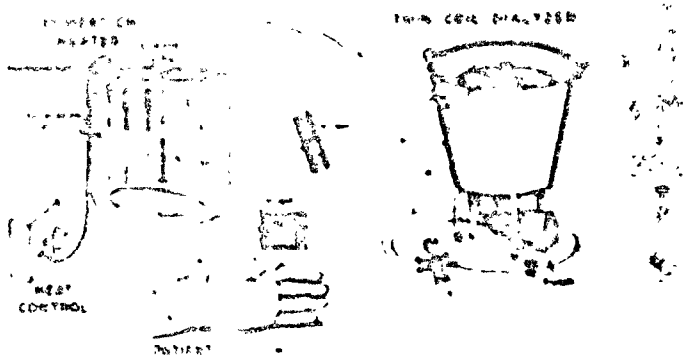
Absorption through mucous membranes occurs rapidly and toxic levels may be achieved within a few minutes after ingestion, thereby necessitating the earliest possible institution of therapy. Apparently, most of the camphor is promptly removed from the blood stream by entering entero the liver, where it is conjugated to glucuronic acid after being oxidized to camphorol, or the lipid depots, where it is highly soluble. Ultimately, the conjugated form is excreted by the lungs. The odor of camphor on the breath and the urine is characteristic and helpful in establishing the diagnosis.[1,2]

The symptoms of acute camphor poisoning include burning in the mouth and throat, thirst, epigastric pain, nausea, and vomiting. Eye manifestations include fixed, dilated pupils, strabismus, and amblyopia. In severe cases anxiety, twitching of facial muscles, confusion, spasticity, headache, dizziness, convulsions, hallucinations, depression, coma, and circulatory collapse may occur. In nonfatal cases, recovery is usually complete within 48 hours. However, a 19-month-old infant died five days after the ingestion of one teaspoonful of camphorated oil.[3]

Since there is no specific antidote, the treatment has consisted of eliminating the product from the body by emesis, gastric lavage, catharsis, and diuretics. Convulsions have been treated with anticonvulsive drugs and sedatives such as phenobarbital or amobarbital (Amytal). It should be remembered that oils and alcohol should not be administered since they hasten the absorption of camphor.[1]

This elderly patient was in good health except for cataracts of sufficient severity to prevent his reading the label on the bottle of camphor. Approximately 30 minutes following the ingestion of 2 oz of camphorated oil, he vomited and had a grand mal seizure. Three episodes of grand mal convulsions occurred despite barbiturate therapy.

The decision to dialyze this patient was stimulated by the successful experiments of Shinaberger



2. Alternate [illegible] employing a two-coil dialyzer. Approximately [illegible] of soybean oil are required to fill both warming [illegible] coil chamber.

and co-workers[4] [illegible]'s group has demonstrated that dialysis utilizing [illegible]ybean oil is a safe, practical procedure. Lipid [illegible]ble drugs, which cannot be removed or are p[illegible] removed by the usual water-electrolyte diviv[illegible] solution, may be readily removed from the [illegible]ent by lipid dialysis.

The lipid-di[illegible] procedure utilized in this patient employed [illegible]ung membrane system. Other systems, e.g. Kil[illegible]alyzers, could have been employed. Eight lit[illegible] of soybean oil (USP) were circulated past the [illegible]alysate side" of the membrane via a pump. Th[illegible] "blood side" of the membrane was primed with [illegible]ine and the patient's own blood. Standard dialys[illegible] procedures were otherwise used. To avoid the po[illegible]ility of oil entering the blood phase, in the ev[illegible] of membrane tear, the hydrostatic pressure o[illegible] oil dialysate phase should be maintained at a [illegible]l lower than the blood phase. An alternate sys[illegible] designed to employ two-coil dialyzers is depi[illegible]d in Fig 2. Approximately 20 liters of soybean [illegible] are required to adequately fill both the warmi[illegible]th and the coil chamber. This system has the [illegible]ntage of disposable coils, thus avoiding the te[illegible]s cleaning procedure required to remove the o[illegible]om permanent dialyzers.

Generic and Trade Names of Drug

Amobarbital—Amytal

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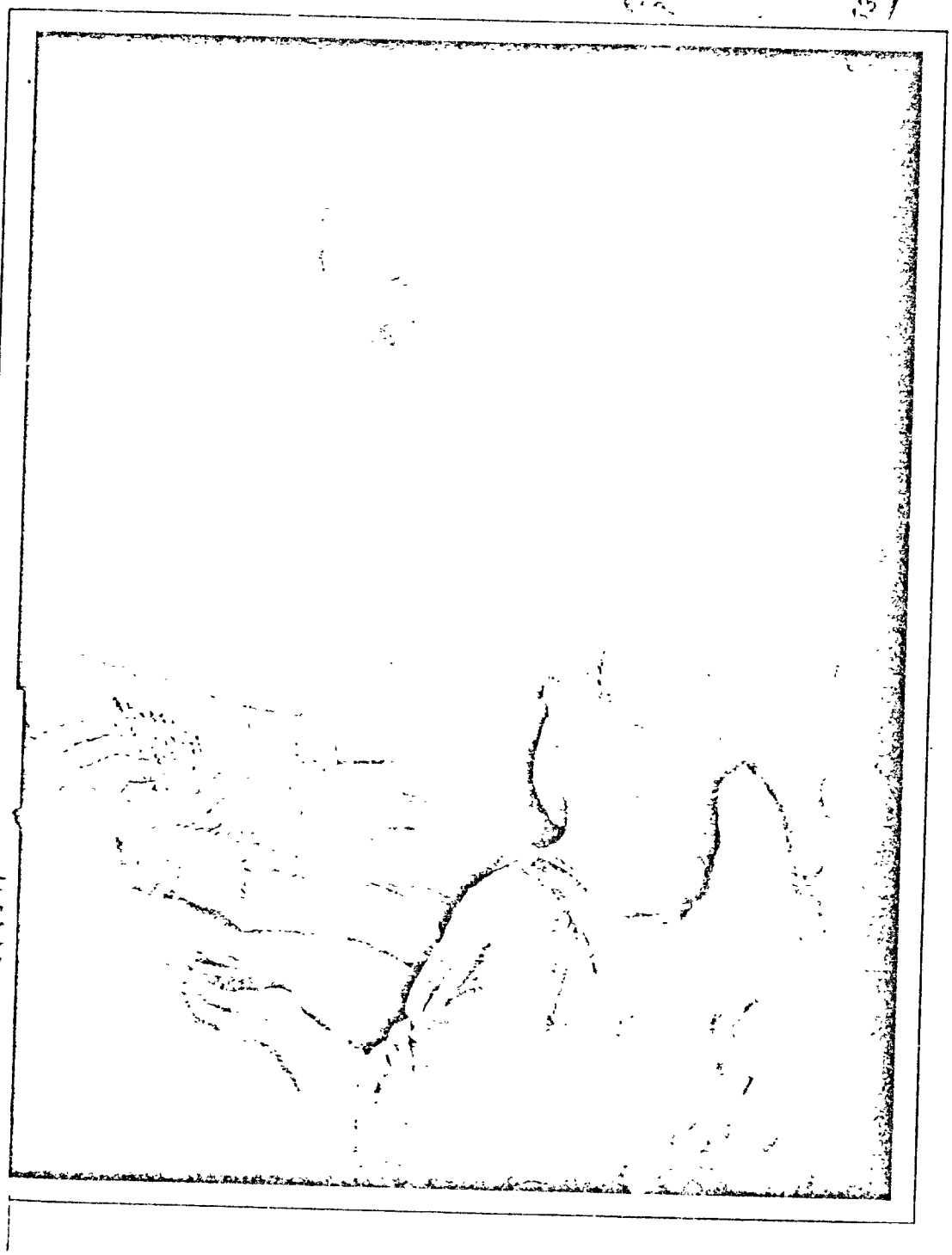

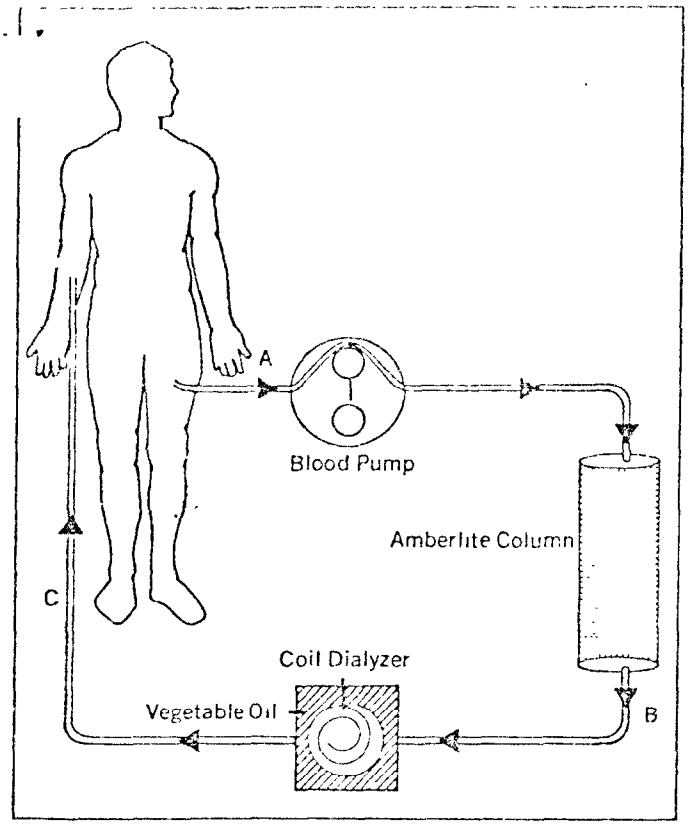

Fig 1.—Schematic diagram of dialysis system. Blood samples for dialysis obtained at points A, B, and C.

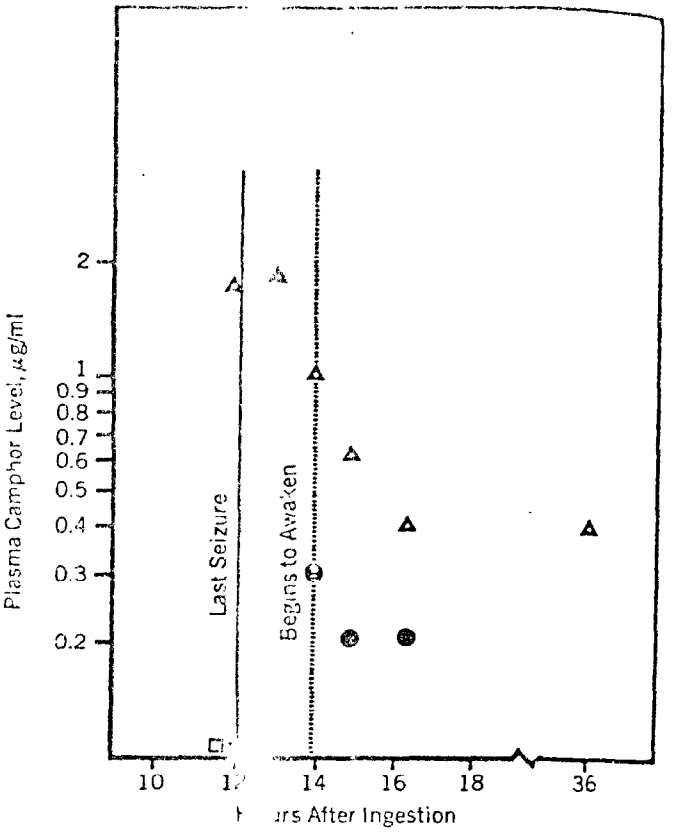

Fig 2.—Plot of plasma camphor levels obtained at points A, B, and C vs time. Major clinical events noted on vertical axis. Triangles represent venous, squares, posthemoperfusion; circles, postlipid hemodialysis.

skin. Once used as a reflex respiratory stimulant, it is now used exclusively for its local actions.[1] In a recent report of two cases of accidental ingestion in children, Phelan[9] compiled a list of 21 over-the-counter preparations containing as much as 20% camphor. Most reported cases of intoxication are accidental, either by inadvertent oral ingestion of a topical preparation or by confusion of camphor for cod-liver oil, a colic preparation, or castor oil.[1,2,4,5,9,10] Deaths have been recorded from ingestion of as little as one teaspoonful of a proprietary preparation.[1]

Description of the clinical aspects of intoxication have been remarkably consistent during the past three decades. Craig[10] describes four cardinal symptoms: increased muscular excitability, abrupt onset of convulsions, vomiting, and mental changes such as confusion and transient behavioral changes. Since camphor is absorbed in five to 90 minutes and its absorption is enhanced by coingestion of alcohol or fatty material, rapid intervention with induced emesis or gastric lavage is indicated in an attempt to prevent absorption.[4,10] Early reports of death by respiratory failure[2,10] may have been the result of aspiration or status epilepticus. The mechanism of neurotoxic effects from camphor is unknown, but several

dies suggest that neuronal damage occur.

tle information is available con ning toxic levels or distribution of mphor following absorption. Its h lipid solubility suggests accumu on in adipose and other tissues consequent delayed excretion.

is study was supported in part by funds grant DA 00900-03 from the National Inst of Drug Abuse.

avid Shlaes, MD, Barbara Vincenzo, RN, and y Lowinger assisted in the treatment of the nt.

Nonproprietary Name and Trademarks of Drug

erpromazine—*Chlor-PZ, Cromedazine, Pro achel, Thorazine.*

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Camphor Intoxication Treated by Resin Hemoperfusion

Robert Kopelman, MD; Sanford Miller, D, Raymond Kelly, PhD; Irving Sunshine, PhD

POISONING from camphor ingestion has been reported periodically for more than 140 years.[1] Morbidity is significant, and 20 deaths have been reported.[1,2] Camphor is listed in the Toxicology Rating System as "class 4, very toxic," with a probable human lethal dose in the range of 50 to 500 mg/kg.[3] It is rapidly absorbed after oral ingestion,[4] and there is no known antidote. Lipid hemodialysis has been the only reported technique for removal of absorbed camphor.[5] In the course of treating a patient who had ingested camphorated oil, hemoperfusion through amberlite resin was used and shown to be a new, effective, and less cumbersome therapeutic modality.

Report of a Case

A 37-year-old man came to the emergency department at 1:30 AM because of abdominal distress. A friend who accompanied him indicated that the patient had ingested part of the contents of a 120-ml bottle that contained camphorated oil (20% camphor) which he apparently had mistaken for castor oil. Approximately 30 ml remained in the bottle, suggesting that about 18 g of camphor may have been ingested. The camphor was ingested at 11:30 PM. The patient vomited at 12:10 AM and a second time before arrival. He was alert when he walked into the emergency department, but minutes later, grand mal seizures abruptly developed and he aspirated before he could undergo intubation. Following intubation, gastric lavage was performed. His vomitus, breath, and urine smelled strongly of camphor. During the first 12 hours of hospitalization, a total of 100 mg of diazepam, 50 mg of chlorpromazine, 300 mg of secobarbital, and 300 mg of phenobarbital were administered intravenously (IV) to suppress recurrent seizures activity.

During the night, the patient's blood pressure was maintained with 2 liters of normal saline IV. At 8 AM he underwent bronchoscopy for reexpansion of a collapsed right upper lobe secondary to the initial aspiration. While maintaining normal vital signs with adequate assisted ventilation, the patient remained comatose with recurrent seizure activity. Because he had ingested a potentially lethal dose of camphor and failed to show clinical improvement, an attempt to remove the absorbed camphor was indicated.

The only procedure reported at the time to be successful in removal of absorbed camphor was lipid hemodialysis against a soybean oil bath.[5] Ginn et al[5] reported clinical improvement in a patient and recovery of large amounts of camphor in soybean oil employed on the dialysate side of the membrane because of the high lipid solubility of camphor.

Amberlite hemoperfusion resin, a stable copolymer of polystyrene and divinyl benzene, recently has been used for the treatment of drug intoxication by hemoperfusion.[6] The amberlite resin is a nonionic absorbent with numerous aromatic functional groups that render it hydrophobic. Thus, it has high affinity for selected drugs and other nonpolar organic molecules.[6,7] Although these characteristics recommended its use for the removal of camphor, amberlite hemoperfusion resin had not been demonstrated to be effective in humans or in animals for removal of camphor. Therefore, it was decided to perfuse the patient's blood through the amberlite cartridge hemoperfusion system and to follow this by lipid hemodialysis, which not only would assure that a method demonstrated to be effective was used but also would permit evaluation of the amberlite hemoperfusion procedure.

The system employed is shown schematically in Fig 1. Blood samples were obtained for analysis at the points indicated (A, B, and C). Vascular access for hemodialysis blood was obtained from the left femoral vein via a catheter inserted by the Seldinger technique, with return to an antecubital vein. Blood flows were maintained at 200 ml/min. Combined hemoperfusion and lipid hemodialysis were performed for 45 minutes, when clotting occurred in the hemoperfusion cartridge because of an underestimation of the heparin sodium requirement for the combined system. Dialysis was resumed for an additional three hours and 45 minutes using liquid hemodialysis alone. This regimen was complicated by the cracking of the plastic casing for an EX-25 coil dialyzer on two occasions. Two hours into the hemodialysis, a Travenol U-II 1.5-59 m coil dialyzer was substituted for the EX-25 unit, and no further difficulties were encountered.

After 2½ hours of therapy, the patient began to awaken, and the procedure was terminated electively after an additional two hours. At that time, the initial strong odor of camphor on the breath was almost gone. His subsequent hospital course was uneventful. He was fully alert the next morning and was discharged the following day.

Plasma samples were analyzed for camphor by gas chromatography (Fig 2). The plasma concentration just before the start of the treatment was 1.7 μg/ml; a second sample taken 15 minutes into treatment disclosed a venous plasma level of 1.8 μg/ml. Simultaneous samples taken between the hemoperfusion cartridge and the hemodialysis system and after the lipid hemodialysis system contained no detectable camphor (less than 0.1 μg/ml). Plasma samples obtained before clotting of the hemoperfusion system thus showed essentially complete extraction of the camphor by resin. Subsequent samples obtained across the lipid hemodialysis system alone revealed about 60% extraction. Thus, the amberlite system appears superior to lipid dialysis in its ability to extract camphor from blood.

Comment

Camphor is an irritant that acts as rubefacient when applied to the

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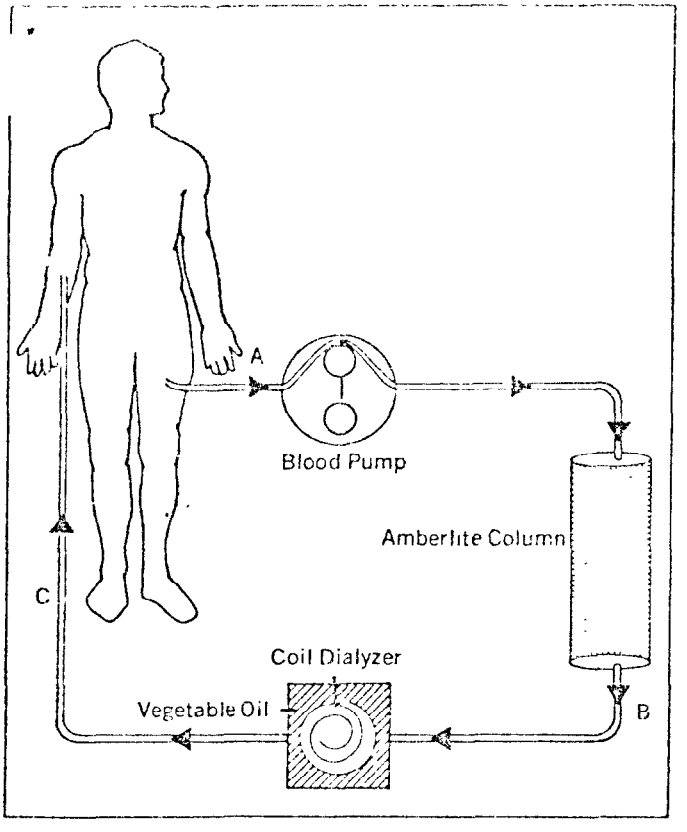

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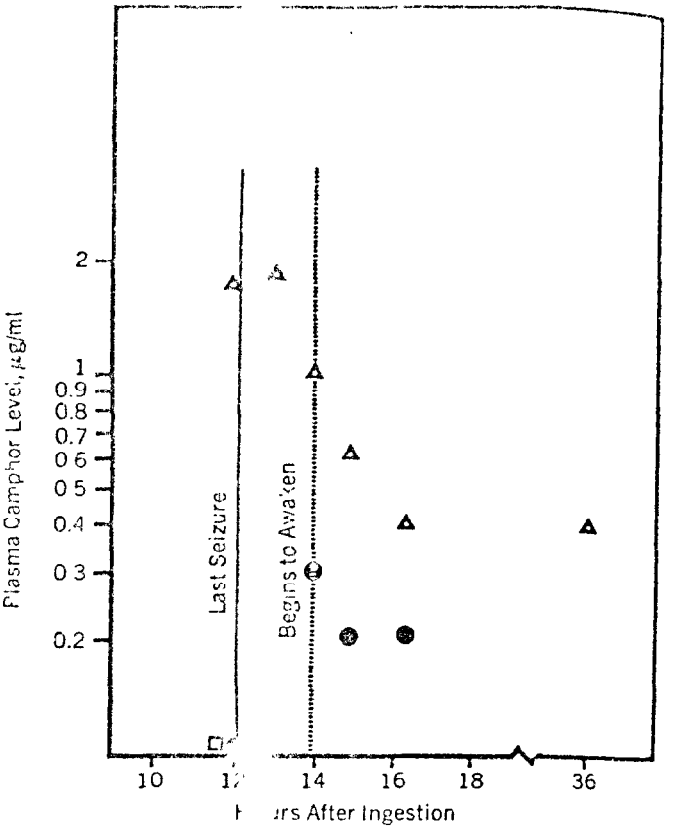

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OTC Volume

THE UNIVERSITY OF NEBRASKA MEDICAL CENTER
42ND AND DEWEY AVENUE
OMAHA NEBRASKA 68105

Ref. 6

October 14, 1976

Robert Pinco, Esq.
Director, OTC Drug Evaluations
Food and Drug Administration
9000 Rockville Pike
Rockville, Maryland 20852

Dear Bob:

I enclose five copies of my recent letter to the Commissioner concerning camphor along with a cited reprint and the 1974 data of the National Clearinghouse for Poison Control Centers - the 475 camphor ingestions leading to 77 hospitalizations represent an estimated 10% of the national cases. Since camphor is an ingredient of unproven benefit in the cold and cough remedies, hemorrhoidal remedies, external analgesics, miscellaneous external medicines and possibly other categories as well, I think some unanimity of opinion is in order.

I think I can speak for pediatricians in general and the American Association of Poison Control Centers in particular, in saying that if anything is to come from the OTC panels, it is the reduction of risk from toxic anachronisms such as camphor.

With best regards,

Carol

Carol R. Angle, M.D.
Professor of Pediatrics

CRA:mls
enclosures

THE UNIVERSITY OF NEBRASKA MEDICAL CENTER
42ND AND DEWEY AVENUE
OMAHA, NEBRASKA 68105

October 5, 1976

Hearing Clerk
Food & Drug Administration
Room 4-65
5600 Fishers Lane
Rockville, Maryland 20852

RE: Docket No 76-N 0052
21 CFR Part 341
Monograph for OTC Cold, Cough,
Allergy, Bronchodilator and
Antiasthmatic Drugs.

To the Commissioner:

There is sufficient pediatric concern with camphor poisor [illegible](1,2) to reconsider the safety of this ingredien[illegible]. As noted on page 38406 (F[illegible] Sept 9, 1976), "as little as 0.75 gm of camphor has been fatal to a child". [illegible]e there is no evidence that warning labels are any deterrent to childhood [illegible]soning, I would recommend that the camphor content of OTC cold and co[illegible] remedies and, in fact, of all OTC medicines, be reduced to less than 0.7[illegible]/30 gm or to less than 2.5% W/V. This would reduce the risk of serious [illegible]ental poisoning while allowing an adequate concentration of camphor.

Respectfully submitted,

Carol R Angle

Carol R. Angle, M.D.
Professor of Pediatrics
Past President, American Association
of Poison Control Centers

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CRA:mls

* included separately

15 CAMPHOR PRODUCTS

ALPHABETICAL LISTING WITHIN CATEGORIES

PRODUCT	UNDER 5 YRS	5 AND OVER	UNKNOWN AGES	SYMPTOMS UNDER 5	SYMPTOMS 5 & OVER	SYMPTOMS AGE UNK	HOSPITAL UNDER 5	HOSPITAL 5 & OVER	HOSPITAL AGE UNK	FATAL ALL AGES
CAMPHO PHENIQUE			-	-	-	-	-	-	-	-
15 134320	244	14	34	32	5	4	18	4	1	-
CAMPHO										
15 134400	11	5	6	6	2	2	9	1	-	-
CAMPHOR LINIMENT										
15 135760	89	51	24	22	20	6	21	16	5	-
CAMPHOR SPIRITS										
15 .35520	16	3	3	1	1	-	2	-	-	-
MOTHERS FRIEND										
15 528041	9	-	-	-	-	-	-	-	-	-
VASELINE CAMPHOR ICE										
15 870240	1	-	-	-	-	-	-	-	-	-
TOTAL	401	74	67	61	28	12	50	21	6	-

editorials

Camphor Poisoning

Extensively used in ancient Chinese medicine, considered the "balsam of disease" in the 16th century, and highly regarded as a "circulatory and heart stimulant" in the late 19th and early 20th century,[1] camphor is listed in the US *Pharmacopoeia* (ed 19 [revised], 1975) as a topical rubefacient to provide local analgesia and antipruritic effects. Few published studies, however, define camphor's precise pharmacologic activity or justify its inclusion in the *Pharmacopeia*. Because of its supposed mild expectorant and carminative effects, camphor remains a component of paregoric. Camphorated parachlorophenol is used in dentistry as an anti-infective for the treatment of root canals. Camphor is also used in flexible collodion. Apart from tradition, it is hard to justify the inclusion of camphor in these products. Spirits of camphor and camphorated oil (cottonseed oil containing 20% camphor) are readily available without prescription or limitation for either purchaser or use.

For more than 100 years, poisonings from these substances have been reported in the literature.[2] Recent statistics from the National Clearinghouse of Poison Control Centers show an annual increase of camphor poisonings that reached approximately 500 cases in 1973. From the literature and from experience (94 cases in 1974) at the Children's Hospital of Michigan, it is apparent that the majority of poisonings, in both children and adults, are due to confusion that results in the substitution of camphorated oil for other patented medications—most notably castor oil, cod liver oil, castoria, and cough and colic preparations. As little as 0.75 gm of camphor (one teaspoonful of camphorated oil) can result in life-threatening illness. Whether it is the toddler who takes a swallow from an accessible bottle or the adult who mistakenly takes several ounces, serious poisoning usually occurs. In addition, camphor crosses the placenta and has been implicated in neonatal death.[3]

Since camphor is easily absorbed through the mucous membranes and gastrointestinal tract, symptoms may begin 5 to 90 minutes after ingestion, progressing from nausea, vomiting, and excitability with tremors, to convulsions. The possible rapid onset of symptoms dictates the use of emergency transportation to bring the patient to a medical facility, and, if such transportation is not available, an adult should attend the patient while someone else drives. Even if the patient has had spontaneous emesis, lavage with normal saline is recommended. Because convulsions may occur suddenly, an emetic is contraindicated. Following lavage, a saline laxative such as sodium sulfate may be administered to assure complete emptying of the intestinal tract. Oils, which enhance the absorption of camphor, should not be used. Barbiturates have successfully controlled convulsions if the dose of camphor was limited. We have used diazepam slowly administered intravenously to control the convulsions in many of our patients. Lipid dialysis may be effective in the removal of camphor if instituted before the camphor enters the lipid deposits in the body.[4] However, if aspiration or repeated convulsions have not occurred, most patients recover completely within 48 hours.

A telephone survey of 283 drug stores in the metropolitan Detroit area disclosed that more than 94,000 oz of camphor and camphorated oil was sold through just these outlets in 1974. On the basis of information obtained from the US Food and Drug Administration, the national volume of camphor and camphorated oil sold in the United States is estimated to exceed 30 million ounces annually. This large volume, as well as the lack of inclusion of camphor under the Poison Prevention Packaging Act of 1970, the lack of distinctive labeling, and its easy availability in stores, compounded by adult carelessness and toddler curiosity, accounts for the continuing problem of serious camphor poisoning, especially from camphorated oil. Removal of camphorated oil and spirits of camphor from the *Pharmacopoeia* and market place as medications seems long overdue since there is no pharmacologic need for them and they pose a documented hazard. The Over-The-Counter-Review Committee of the US Food and Drug Administration should address itself to the problem of their removal.

Regine Arensow, MD
Children's Hospital of Michigan
Detroit

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Address editorial communications to the Editor, 535 N Dearborn St, Chicago, IL 60610

Ref 7
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Volume
160358

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA 19104

INTRAMURAL MEMORANDUM

DATE: 30 April 1979

TO: John T. McElroy

FROM: Harry E. Morton

SUBJECT: Camphor

At the last meeting of our Panel I was told to rework the material on camphor and have it sent to designated Panel members as a submission. Enclosed are 11 copies which I hope you will see fit to assign a submission number and mail a copy to each of the following Panel members:

Wm. E. Lotterhos
Rose Dagirmanjian
J. Robert Hewson
Yelva Lynfield
Harry E. Morton
Marianne N. O'Donoghue
Chester L. Rossi
Albert A. Belmonte
Jon J. Tanja
John T. McElroy
Thomas J. McGinnis

I tried to use only submission numbers and concentration of camphor, as you suggested, so liaison members of the Panel could see it but I found that in a couple of cases I needed to mention names of products. For that reason I guess the material ought to be sent to only those members of the Panel who are permitted to receive classified material.

I hope this finishes camphor as it has been worked over frequently. Either camphor is of equivocal value or some of the evaluators didn't do a good job, or maybe some of both. I see Lotterhos started it with the first draft in late 1975 or early 1976; Dagirmanjian followed with a second draft in May 1976; I took a shot at it as part of a review on ketones in December 1976 and evaluated camphor products in Februaiy 1978. Tanja revisited camphor in September 1978 and Lynfield took a swing at camphorated oil in October 1978. My memorandum of December 1978 on summarizing and evaluating the various actions taken by our Panel and Topical Analgesic Panel got emasculated. Now this is, I believe, the seventh attempt at getting some logical evaluation of the camphor products. I hope it will be acceptable.

If all goes well I hope to return from meetings on May 15 and look forward to seeing you on the 18th.

rw

Enc.

Harry E. Morton
04-25-79

Appraisal of Camphor as an Ingredient in OTC Preparations.

Camphor as an ingredient has been used for ages for various purposes by physicians and by individuals for self medication. However, since Tidscombe in 1897 first cautioned about its toxicity and recommended certain precautions in the sale of camphorated oil there have been frequent warnings during the past more than three-quarters of a century concerning its toxicity and lack of effectiveness and numerous recommendations have been made on restricting its availability to individuals in the treatment of others, especially children. These recommendations have been endorsed by groups of individuals interested in protecting the health of individuals, namely the Academy of Pediatrics and the American Pharmaceutical Association.

The pharmaceutical manufacturers and dispensing pharmacists have not taken the necessary precautions to protect the public from this poisonous ingredient so it becomes the responsibility of some administrative group to take the necessary action. Aronow and Spigiel in 1976 pointed out that "widespread availability coupled with human error account for camphor poisonings and suggest that administrative action is essential to remove these archaic and unnecessary products from the market place." In the same year Phelan stated "It is hoped that the Food and Drug Administration panels investigating over-the-counter preparations will realistically evaluate the benefit-versus-risk ratio of drugs such as camphor and assume with greater rapidity an increasing public health advocacy."

While it is frequently pointed out that currently death from camphor poisoning is rare, in all fairness it should be pointed out that

recovery from camphor poisoning is often due to heroic medical attention such as hemodialysis, peritoneal dialysis, stomach lavage, heavy sedation and laboratory tests which in some cases require sophisticated hospital procedures. It is stated in submission 160222 that during the calendar year 1974 there was a total of 542 cases of camphor poisoning reported to the U.S. National Clearinghouse Poison Control Centers and of these 77 cases, or 14.2 percent, were hospitalized. Assuming that the non-hospitalized cases required a visit to a physician or a hospital emergency room at a conservative average cost of about $50.00 each and the 77 hospitalized cases represent an average cost of $3,000.00 each, this represents an annual unnecessary medical expense of over a quarter of a million dollars to treat poisoning from a drug of dubious beneficial effect.

542 non-hospitalized cases @ $50.00	=	$ 27,100.00
77 hospitalized cases @ $3,000.00	=	231,100.00
Total		$258,000.00

* In submission 160222 a past president of the American Association of Poison Control Centers and a Professor of Pediatrics recommended that camphor in all OTC medicines be reduced to less than 2.5 percent (W/V) to reduce the risk of serious accidental poisoning.

A listing in order of decreasing concentration of camphor in all of the submissions made to the Panel for Miscellaneous External Drugs shows that the concentration of camphor varies from 55.8 percent to 0.1 percent, TABLE 1. The volume of the contents of individual containers sold OTC varies from 1 lb to 0.11 oz. A logical division between the

TABLE 1. Listing of Submissions in Decreasing Order Camphor Content.

Submission[1]	Camphor content and vehicle	Submission[2]	Camphor content and vehicle
1. #160225	65.8%, dressing		
		2. #060062	15.4%, ointment
3. #160136) #160231)	10.8%, oil		
4. #160002	7.4%, vehicle not stated		
5.cf 1.#160225	6.58%, cream		
6. #160078	6.0%, balm		
		7. #060051	5.78%, ointment
			5.7%, ointment
		8. #060040	5.57%, linament
9. #160262	4.75%, ointment		
10. #160136	4.4%, powder		
		11. #060008	3.75%, linament
		12. #060030	3.59%, linament
		13. #060031	3.0%, linament
14. #160106	2.5%, ointment		
15. #160058	1.6%, balm		
16. #160005	1.6%, ointment		
		17. #060029	1.5%, spray
18. #160004	1.48%, collodion		
19. #160174	1.48%, ointment		
		20. #060050	1.0%, ointment
		21. #060054	1.0%, ointment
22. #160096	1.0%, ointment		
23. #160016[3]	0.82%, linament	24. #060009[3]	0.8?%, linament
25. #160126	0.8%, balm		
26. #160084	0.649%, liquid		
27. #160076	0.6%, cream		

28.cf8#060040 0.5%, balm

cf27#160076 0.4%, liquid

#160147 0.37%, cream

.cf1#160225 0.34%, cream

#160080 0.3%, lotion

0.3%, cream

3. #160093 0.25%, powder

34. #160278 0.22%, liquid

35. #160059 0.2%, liquid

36, #160008 0.1%, tick

37. #160013 0.1%, stick

38. #160030 0.1%, lotion

0.1%, lotion

0.1%, spray

39. #160104 0.1%, cream

0.1%, lotion

40. #160213 0.1%, balm

41. #160019 not stated

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1) Submissions submitted to Panel for Reviewing Miscellaneous OTC External Drugs.

2) Submissions submitted to Panel for Reviewing OTC Topical Analgesic Drugs.

) Nos. 160016 and 0600[illegible] are the same product.

more toxic and less toxic preparations appears to be at 2.5 percent concentration of camphor. This is also the concentration of camphor recommended by Angle in 1976 (Submission 160222).

In addition to taking cognizance of the volume of a product and its concentration of camphor in evaluating the safety of a product, consideration has to be given to the effectiveness of camphor as a single ingredient or as a pharmaceutical aid because of a unique property of camphor. All of the products containing 2.5 percent or more of camphor contain more than a lethal dose of camphor in the individual container when ingested by a child and none of the products has been shown to have a beneficial pharmacological effect due to its camphor content when applied externally. Moreover, removal of the products from OTC classification would not be removing any essential preparation from the armamentarium of drugs available for alleviating a pathological process from the human body.

In TABLE 1 there are listed also the submissions made to the Panel on Topical Analgesics as one of these submissions contains a high concentration of camphor, one particular product was submitted to both Panels, this panelist was asked to review the report by the Topical Analgesic Panel and its submissions for possible additional information about camphor and the Topical Analgesic Panel rated camphor products quite differently than what this Panel proposes. In this way it is hoped to resolve the differences in the conclusions of the two Panels.

Upon examining the OTC Topical Analgesic Panel's report on Camphor, pp 234-243, it was found that the poor documentation of statements and erroneous citations of references made the conclusions arrived at in

the report unreliable. Only one original article in the scientific literature was cited in the report. For basic information to arrive at an opinion on camphor 9 books and compendia and over 80 original articles in the scientific literature were cited on camphor, pp 13-51, in a Review of Antimicrobial Properties of Ketones, 2nd draft 12-24-76, H.E. Morton. Some of the details of the errors of commission and omission are set forth in a MEMORANDUM dated 14 December 1978 to the voting members of Advisory Panel on OTC Miscellaneous External Drug Products and FDA OTC Staff by the same author. At this time there appears to be no reason why the same standards of safety for camphor can not be applied to the camphor products submitted to both panels.

There are two products (1) camphorated oil, containing 20 percent camphor, and (2) spirits of camphor, containing 10 percent camphor, that have been available as OTC products for a long time but are not listed in the current editions of the U.S. Pharmacopoea and the National Formulary. Their danger far outweighs their usefulness and, while they were not submitted to the Panel for evaluation, they should be placed in Category II for safety as are other products for external use containing more than 2.5 percent camphor.

Starting with the individual products, submission 160225 presents two products, one containing 65.8 percent camphor and the other containing 6.58 percent. Only two active ingredients are specified camphor and m-cresol, but the label on a package purchased OTC states that the product contains thymol iodide, an antifungal agent. The purpose of camphor is a pharmaceutical aid to detoxify the m-cresol and eugenol. The

camphor forms a complex with the 22.36 percent m-cresol and 2.23 percent m-cresol so as to release only 1.6 percent and 0.31 percent free m-cresol, respectively. Price stated (JAMA,111:1993-6, 1938) that 1 percent saponated cresol (equivalent to about 0.5 percent cresol) caused some burning and anesthesia of the skin and reduced the microorganisms on the skin no more rapidly than scrubbing with a brush, soap and warm water. The presence of camphor in the product defeats its intended purpose. While reducing the toxicity of the active ingredient for tissue it is concomitantly reducing other pharmacological activities such as antimicrobial and analgesic activities. The toxicity of the camphor-cresol complex is practically the same as for pure camphor. Other details of lack of adequate or sufficient data to support the claims of germicidal and antiseptic activities are provided on pp 47-62 in the Evaluation of Preparations containing camphor first draft 02-08-77 as amended 04-19-79. The two products discussed above can justifiably be placed in Category II for safety.

Submissions 160136, 160208, 160218 and 160231 pertain to the same product, a mixture of 10.8 percent camphor and 4.7 percent phenol in an aromatic oily solution.* The smallest container, 1 f oz, contains more than a lethal dose of camphor for a child or even an adult, if ingested, and the amount in the 1/4 fl oz container would be extremely dangerous to have in a household. This product causes more poisonings of humans than any other camphor product. During 1974 there were 5[illegible] poisonings due to camphor products reported to the National Clearinghouse Poison Control Centers and 292, or 53.87 percent, were due to this product. Of the 292 poisonings due to this product, 23 or 7.87 percent were hospitalized. Of the 250 poisonings due to all other camphor products, 54 or 21.6 percent were hospitalized.

Thus while this product is the camphor product most likely to cause poisoning, camphor liniment which contains nearly twice as much camphor is most likely to require hospitalization (160222). These figures for 1974 are concervative as the poisonings reported due to this product increased markedly in 1975 and 1976; increasing on the order of 27 to 34 percent.

Phenol is more soluble in the camphor-aromatic mineral oil vehicle than in water. When the product containing 4.75 percent phenol was brought into contact with water, the water phase was found to contain 1.026 percent phenol. Thus about one-fifth of the phenol went into the aqueous phase and four-fifths remained in the camphor-oil phase (160136). One study was made with the product and tissue cells in culture and it was found that 1:100 dilution of the product killed the tissue cells in an exposure of 10 min. If this represented a 1:100 dilution of phenol in the aqueous phase, 1:10,000, it is questionable that phenol was lethal under those conditions. Proper controls were not included in the test.

This product and the one described in 160225 are similar in that the function of camphor is in the role of a pharmaceutic aid to form a complex with highly poisonous substances. By using large amounts of camphor to form complexes with the toxic active ingredients to bind and thus inactivate the active ingredients, large quantities of the active ingredients can come in contact with the body with decreased harmful effect.

Nothing beneficial has been demonstrated for this product but, on the other hand, numerous poisonings have been recorded each year and it is destructive to tissue cells. Category II for safety appears justified for this product.

The smallest marketed amount contains several potentially toxic doses for a child and the largest available amount is too dangerous to have in a household. There is no evidence that the product would give temporary relief from throat irritations. Its use might be dangerous in conveying a false sense of security and causing effective therapy not to be sought. Category II for safety, submission 160002, 7.4 percent camphor.

There is no evidence that camphor is an emollient or moisturizer and is helpful in eliminating chapping of lips and skin. The vehicle in preparation 160078 may be providing the entire desired pharmacologic action. The 6 percent camphor in the marketed product may provide more than a lethal dose of camphor if the product was ingested. The danger of the presence of camphor in the product far outweighs any possible usefulness for the recommended purpose of the product so Category II for safety is a logical classification.

Camphor is present in the concentration of 4.75 percent in the product described in submission 160262. The camphor content in a 1.5 oz jar is more than a toxic dose for a child if ingested. There is one report of a child having a severe toxic reaction following the ingestion of an estimated teaspoonful of the product. There was altered brain activity for at least 15 days as detected by electroencephalograms. The claims for the product, as stated on the label, are that it is a decongestant and relieves coughs due to colds. Camphor is credited with neither of these pharmacologic properties (Merck Index). The pharmacologic properties of the other ingredients are as follows:

Menthol - topical antipruritic

Spirits of turpentine - solvent for oils, rubefacient, counterirritant

Eucalyptus oil - local antiseptic, expectorant

Cedar leaf oil -- substitute for oil of lavender

Myristic oil - ingestion of large quantities pr[illegible] luces narcosis, delirium, death

Thymol - antifungal

The purpose of the presence of camphor in the p[illegible]oduct cannot be ascertained readily. In any case it is obvious that [illegible]ts danger far exceeds any intended usefulness which justifies a clas[illegible]ification of Category II for safety.

The purpose of 4.4 percent camphor in a powder [illegible]th 2 percent phenol for a foot powder is not stated. It is not known to [illegible]e effective in the treatment of epidermatophytosis of the feet. Campho[illegible] has been placed in Category II for effectiveness in preparations for [illegible]reating the feet.

Submission 160058 covers a group of products in [illegible].15 oz stick form recommended for treating chapped lips. The composit[illegible]n of each product is essentially the same except for a flavoring agent [illegible] camphor, cherry, grape, mint or orange. While the camphor content is [illegible].6 percent in one of the products, which is a safe amount, it is not a [illegible]ecessary ingredient as it is replaced in other but similar products by f[illegible]avoring agents; cherry, grape, mint or orange. Category I for safe[illegible] and Category II for efficacy of camphor as an active ingredient for [illegible]e intended use of the product. A revised submission, 160126, covers t[illegible] same product with lesser amount of camphor.

The 1 oz package of the product described in 16[illegible]005 contains 16 ingredients, 7 of which are listed as active ingredi[illegible]nts. Camphor is

present in the concentration of 1.6 percent which could represent a toxic dose if ingested. The label states the product to be an ideal antiseptic pain relieving ointment particularly suitable as an application to boils. No evidence is produced that the product has antiseptic action or that it is efficacious in the treatment of boils. When the submission was made in January 10, 1974 it was stated that arrangements had been made for the performance of animal safety tests and the results would be submitted upon completion. No results have been received. No evidence is presented that the product as marketed is of the same composition as the material tested in vitro for the inhibition of bacterial growth. The ratio of camphor to phenol of approximately 4 to 1 might result in the camphor complexing with the phenol and thereby reducing the amount of free phenol. Category II for safety and Category II for efficacy are recommended for camphor.

The 1.48 percent camphor in the 0.31 fl oz of the product described in submission 160004 is a safe amount of camphor but camphor has been placed in Category II for efficacy by the Panel in the treatment of warts.

No justification is given for the presence of 1.43 percent camphor in the ointment described in submission 160174. The product is recommended for epidermophytosis of the feet, ring worm, relief of itching of the rectum and genitals, and itching due to eczema, superficial burns, abrasions, ivy poisoning, etc. The phenol has a much stronger antipruritic action than camphor and the chlorothymol, salicylic acid and benzoic acid have much stronger antifungal action than camphor. The

ratio of camphor to phenol of 1.5 to 1 raises the possibility of camphor complexing with the phenol and thereby reducing the amount of free phenol. While the amount of camphor in the 1 oz quantity of the product is safe but as an antifungal and antipruritic agent it should be classified as Category II for efficacy.

At the concentration of 1 percent the amount of camphor in the 0.42 and 0.14 oz packages of the product described in 160096 is safe. Camphor is not known to be effective against the virus of cold sores. Phenol has a stronger analgesic action and antiviral action than camphor. It was not demonstrated that 0.4 percent phenol has an antiviral action on the herpes virus within tissue cells. In the ratio of camphor to phenol of 2.5 to 1 the camphor may be complexing with phenol and thereby reducing the amount of free phenol. Category II for efficacy is recommended for camphor.

In submission 160016 camphor is listed as an active ingredient but present in the concentration of about 0.82 percent. At this concentration it has never been known to have analgesic or antiseptic activity. It is not mentioned in the list of active ingredients but it is stated in the label to contain Oil of Camphor. Camphor and Oil of Camphor are each rated very toxic chemicals. The 4 fl oz and 8 fl oz containers of the linament contain several toxic doses of camphor if ingested. In view of the product containing an unspecified amount of Oil of Camphor in addition to camphor, Category II for safety until adequate data are provided.

Submission 160126, dated May 7, 1975, covers a group of products in

0.15 oz stick form recommended for treating chapped lips. It is a more recent submission than 160058 (submission date January 10, 1974) and states the concentration of camphor to be 0.8 percent and is present as a flavoring and perfume substance. The total amount of camphor present is safe if ingested and no claim is made for medicinal action. Category I for safety.

In the antiseptic solution described in submission 160084 the 0.649 percent camphor is present as an official denaturant for the ethyl alcohol. One formula for denatured alcohol is 10 lbs camphor/100 gals alcohol, Formula 38-B. The amount of camphor could be reduced by 1 lb since the product contains 1 lb of peppermint oil and other essential oils which also are official denaturants in Formula 38-B. The product contains 40.26 percent ethanol by wt and requires a denaturant. The 4-1/4 oz and all larger quantities of the product contain more than a lethal dose of camphor, if ingested. It might be possible to select another denaturant without affecting the aroma of the product. If isopropyl alcohol was used, a denaturant would not be necessary. It might be worthwhile to investigate the use of a mixture of ethanol and n-propanal which Price (JAMA, 111:1993-6, 1938) reported to be powerfully germicidal.

This product has been rated Category I for safety for its ethyl alcohol content and for its benzoic content and Category II for safety for its boric acid content. Categoty II for safety has been proposed for its 0.649 percent camphor content.

The product has been rated Category II for efficacy for camphor for the claims that the camphor provides local analgesic and antipruritic properties and is utilized as a rubefacient.

The camphor content, 0.6 percent, is less than a toxic dose in the 1 oz package of cream described in submission 160076. The camphor content, 0.4 percent, in the 6 fl oz package of the liquid product contains a lethal dose of camphor and a portion of the contents might contain a toxic dose, if ingested. Category II for safety could be logical under such conditions. However, if the size of the package for the liquid preparation was reduced to 60 ml, the camphor would not be sufficient to be hazardous to health and the liquid product, like the cream, could be rated Category I for safety.

No reasons are given for designating camphor an active ingredient in the cream and in one liquid product but not in the other liquid product. Category II for efficacy until data are presented justifying the requirement of camphor in the products.

Product described in submission 160147 is marketed in 1 lb and 6 oz quantities. It is inconceivable that a person would ingest sufficient of the material to obtain a toxic dose of camphor since the concentration of camphor is only 0.37 percent. Category I for safety in regard to camphor. Only one of the claims "cools and alleviates the minor pain of ordinary sunburn" is of a medical nature and the small amount of camphor would not accomplish that in the presence of menthol, clove oil and phenol. The camphor might complex with some of the phenol to reduce the quantity of free phenol in the preparation. Category III for efficacy in regard to the ingredient camphor.

The amount of camphor contained in the unit package of Obtundia Calamine Cream, 0.11 oz, described in submission 160125 is so small as not to constitute a toxic dose for even the smallest child, if ingested.

Category I for safety in regard to camphor in this product. However, the product has been classified Category II for efficacy and labeling for lack of evidence to support the claims.

The two products described in submission 160080 each contain 0.3 percent camphor for a mild counterirritant action. The quantity in the individual carton of lotion is not stated so the safety of the product cannot be determined in regard to camphor. This is not important as the products have been classified Category II for safety because of their zirconium content.

The product described in submission 160093 containing 0.25 percent camphor is a foot powder and camphor has been placed in Category II for efficacy in foot preparations.

The product described in submission 160278 contains 0.22 percent each of camphor and menthol as official denaturants for the alcohol. The maximum single quantity marketed is 0.74 oz which contains about 45 mg camphor. This is not a toxic dose for a child so the product has to be given a rating of Category I for safety in regard to camphor. Efficacy of camphor is not applicable in this product.

The 3 fl oz of the product described in submission 160059 contains an estimated 0.180 g camphor. This would not constitute a toxic dose for a child, so Category I for safety in regard to the camphor component. Category II for efficacy for camphor since it is present in the concentration of 0.2 percent. At that concentration it would have no beneficial effect in the treatment of insect bites, acne pimples, heat rash, cold sores, dandruff, poison ivy, chafing and athlete's foot for which the product is recommended. Listing it as an active

ingredient might give a false sense of reliance on the product to the exclusion of more effective therapy. The product has been rated Category II for efficacy for the boric acid component.

Camphor is present as an active ingredient in the concentration of 0.1 percent in the product, a stick form, described in submission 160008. There would be less than 3 mg camphor in the stick weighing 0.1 oz. Category I for safety in regard to camphor. Category II for efficacy since data are lacking to prove that camphor in that concentration would have a beneficial effect in producing instant relief of chapped, dry lips; promote healing and ease the discomfort of cold sores, fever blisters, and cracked lips due to sun or wind burn. The product has no antibacterial action in vitro. The benzocaine and phenol would be expected to produce a slight analgesic action.

The camphor content is 0.1 percent in the outside of the stick described in submission 160013. Volume of the product is not stated as no labels are provided. Date of submission, January 16 1974. The company stated that arrangements have been made to perform animal safety tests and results of the tests will be submitted upon completion. The company also stated that a literature search is being performed on the ingredients as medicaments in the treatment of cold sores and the results of the study will be submitted upon completion. Results of the safety tests and literature search have not been submitted. Category II for safety, efficacy and labeling for lack of data.

There are three products described in submission 160030, each containing 0.1 percent camphor as an active ingredient. However, the recommended concentration of camphor is usually 1 to 3 percent for external

application so it is doubtful if 0.1 percent concentration would have any pharmacologic action. If it is present in the product as a pharmaceutical aid, such as a perfume or preservative, it should be so stated. The entire contents of the largest container represents less than a toxic dose of camphor. Category I for safety in regard to camphor. However, the Ziradryl Lotion contains zirconium oxide and was classified Category I for safety in regard to zirconium. Category III for efficacy in regard to camphor content.

The two products described in submission 160104 each contain 0.1 percent camphor as one of the active ingredients. The volume of the container is 4 fl oz which would not contain a toxic dose of camphor so the classification would be Category I for safety in regard to camphor. The product is recommended as an aid for cooling, soothing and healing of skin; relief of itching and discomfort in skin disorders such as contact dermatitis due to poison ivy, poison oak, sumac, insect bites, diaper rash, chafing and eczema. The concentration of camphor usually recommended for topical application is 1 to 3 percent. Since the product contains only 1/10 to 1/30 of the usually recommended dose, it is doubtful if the camphor content has the intended pharmacological activity. If camphor is present as a pharmaceutical aid it should be so stated and the reason for its presence. Category II for efficacy in regard to camphor due to lack of data to support a reason for its presence in the product.

The product weighing 4.26 g described in submission 160213 contains 0.1 percent camphor. Therefore, the entire contents of the package would not contain a toxic dose of camphor and would rate Category I for

safety in regard to camphor. The intended purposes o the balm are to relieve dry, chapped, sore lips and to protect againc , sun, wind and cold. No evidence is presented that camphor in the c ncentration of 0.1 percent will accomplish any of the claims of the oduct. Category II for efficacy for camphor for lack of supportive d n.

The product weighing 1/6 oz and in stick form d cribed in submission 160019 lists camphor as one of the ingredients. he product is intended for treating dry, cracked, chapped lips. The oncentration of the ingredients is not specified. Category II for afety and efficacy in regard to camphor for lack of data.

This paragraph, rightfully, should be paragraph on page 8. The ointment described in submission 160106 contains, amo , other ingredients, 2.5 percent camphor and 7.75 percent boric ac . The amount of camphor in a 1 lb jar of the ointment contains many t ic doses, if some of the product was ingested. There is no evidence th camphor contributes anything to the inhibition of bacterial growth c that the product, itself, has antiseptic properties. Category II is re mmended for safety in regard to camphor. The product has been rated Cat ory II for safety in regard to the boric acid component.

DISCUSSION

In evaluating some of the camphor-containing dr g products it has been necessary to take into consideration combinatio s of camphor with other drugs. Camphor is unique in forming complexes or complex mixtures, with other drugs which are eutectic mixtures nd not new stable chemical compounds. That is, two or more substances are soluble in each other. Upon coming in contact with water the c mplex may dissociate with some of the more water-soluble drug going into solution and possibly freeing some of the camphor. As more of the water-s luble drug in the aqueous phase is dissipated, more of the drug will b liberated from the complex to maintain an equilibrium between the aque s and camphor phases.

Physical chemical studies by Francis (JAPA, 30: 29-40. 1941) indicated that in a mixture of the two drugs a complex o one mole of camphor and one mole of phenol predominated. Since the molc ılar weights of camphor and phenol are 152.23 and 94.11, respectivel , this indicates that on a weight basis the two drugs are in the rati of 1:6 to 1, respectively. In the case of a mixture of camphor and -cresol, a complex of two moles of camphor and one mole of cresol predc inates. Since the molecular weight of m-cresol is 108.13 this indicat that on a weight basis the ratio of camphor to m-cresol is 2.81 to 1.

It is important to keep in mind that the pharma ological activity of a eutectic mixture depends upon the concentratio of the water-soluble drug that is in the aqueous phase and not u n the concentration of the drug in the camphor phase.

In the case of a camphor-cresol mixture, the mi ture has approximately the same toxicity for laboratory animals as amphor. In the

case of the camphor-phenol mixture, the toxicity of the mixture for laboratory animals has not been determined but it causes more cases of poisoning in humans than any other OTC camphor-containing compound. One contributing factor may be that there is a synergistic action of camphor and phenol in producing a toxic reaction. This was demonstrated by Bond and Haag (JAPA, 14:118-20. 1925) who reported that 0.3 g camphor/kg body wt and 0.3 ml phenol/kg body wt were not toxic orally for dogs when given individually but when both drugs in these amounts were given together, one given immediately after the other, the dogs died.

Many of the products in the 160--- series that were submitted to the Panel are aromatic or flavored so as to be a possible attraction to children. The containers are often attractive and small and might readily be left on the top of dressers, night stands, dressing tables, etc. or in the drawers of such pieces of furniture, or in a woman's handbag. Many of the products are used on children so may be in the environment of children. A child may be attracted to a product or having been treated with it. For various reasons precautions must be taken to protect children from camphor-containing OTC drugs. Assuming a child is mobile and inquisitive at 2 yrs of age when it weighs about 12 kg and by assuming a toxic dose of camphor is about 0.030 g/kg, then it is readily apparent that the amount of a drug containing 0.360 g camphor may be toxic for a child.

By applying a rule of thumb that volume of drug in individual container X percent concentration of camphor must be less than 0.360 g in order for the product to be safe for an OTC drug. Most of the drugs containing less than 2.5 percent camphor are safe. Of the submissions

containing less than 2.5 percent camphor only four contain a toxic dose of camphor for a small child. The 1 oz quantity of product 160005 contains 0.448 g camphor. If the volume of the product was reduced to 3/4 oz or the concentration of camphor was reduced from 1.6 percent to 1.25 percent the camphor would be at a safe level. The rosin, Oil of Cade and ichthamol in the product might make the product unappealing to a child but one never knows what a child will eat.

The Oil of Turpentine and ammonia might be enough to discourage an individual from swallowing the liniment described in 160016. The content of camphor needs to be investigated as the components stated on the label differ from the submitted list of ingredients.

The 4.25 to 32 fl oz quantities of product 160 4 contain many potentially toxic doses of camphor in the capacity of official denaturant for the alcohol. To eliminate the danger it might be possible to select a different denaturant, a different alcohol or a combination of the two.

If the volume of the product in submission 160 6 was reduced from 6 fl oz to 3 fl oz the entire contents of the bottle would possibly constitute a toxic dose but the tannic acid in the product might discourage ingesting the product.

Where the camphor content is low each product needs to be evaluated individually in order to keep the camphor within a safe range. For example, flexible collodion was not submitted for evaluation and 2 percent camphor is needed as a pharmaceutical aid to make flexible collodion. The product is usually employed as a vehicle and sold in

quantities of 0.5 fl oz or less. In this amount the camphor content is safe.

The submitted products containing 2.5 percent or more of camphor should present no great problem for categorization because of the great camphor content and/or lack of effective pharmacological action. Product 160225 has been inadequately tested and the submitted list of ingredients is not a true statement, product 160136 is the leading cause of the annual hundreds of cases of camphor poisoning and product 160002 is supported by no tests for safety and effectiveness. No evidence is presented in submission 160078 for the necessity of 6 percent camphor for treating sore lips. No evidence is presented that camphor in product 160262 contributes a beneficial effect to the product. It is recommended for congestion of the throat and chest which may give the patient a false sense of relief without correcting the illness. No evidence is presented that camphor is needed in product 160106. No person needing medication would be deprived of a useful drug if the above mentioned products were removed from the OTC market. When used as a pharmaceutical aid in some of the above products the camphor does not fulfill the combination drug policy for OTC products.

It appears to be possible to categorize the submission in the series 060---/on the same basis as submissions in the 160--- series. All of the submissions contain camphor and all except one also contain methyl salicylate and one also contains mustard oil. Here again the danger of the presence of camphor in the products outweigh any possible usefulness.

TABLE 2. Separation and Index

Submission No.	Camphor conc.	Volume of product	Toxic	Classification Safety	Classification Efficacy	Page
160225	- 65.8%	4 fl oz, 3-1/2 oz	Yes	I		5,6
	6.5%	16 oz, 1-1/4 oz	Yes	I		5,6
	0.34%	0.11 oz	No	I	II	13
160136) 160231)	- 10.8%	4,2,1 oz	Yes	I		6,7,8
160002	- 7.4%	7,2.5,1 oz	Yes	I		8
160078	- 6.0%	1.5 oz	Yes	I		8
160262	- 4.75%	1.5 oz	Yes	I		8,9
160106	- 2.5%	16 oz	Yes	I		17
160058	- 1.6%	0.15 oz	No	I	II	9
160005	- 1.6%	1 oz	Yes	I	II	9,10
160004	- 1.48%	0.31 oz	No	I	II	10
160174	- 1.43%	1 oz	No	I	II	10,11
160096	- 1.0%	0.42,0.14 oz	No	I	II	11
160016	- 0.82%	4,8 fl oz	Yes	I	II	11
160126	- 0.8%	0.15 oz	No	I	III	11,12
160084	- 0.649%	5/8,1 fl oz	No	I	III	12
		4-1/4,10,16,32 oz	Yes	I	III	12
160076	- 0.6%	1 oz	No	I	II	13
	0.4%	6 fl oz	Yes	I	II	13
160147	- 0.37%	6 oz, 1 lb	No	I	III	13
160225	- 0.34%	0.11 oz	No	I	II	5,6,13
160080	- 0.3%	? and 1.25 oz	No	I		14
160093	- 0.25%	3 oz	No	I		14
160278	- 0.22%	0.74 fl oz	No	I	N.A.	14
160059	- 0.2%	3 fl oz	No	I	II	14
160008	- 0.1%	0.1 oz	No	I	II	15
160013	- 0.1%	?	No	I	II	15
160030	- 0.1%	6 fl oz	No	I	III	15,16
160104	- 0.1%	4 fl oz	No	I	II	16
160213	- 0.1%	4.26 grams	No	I	II	16,17
160019	- ?	1/6 oz	?	I	II	17

SUMMARY

Camphor in concentrations of 2.5 percent or gre ter should be placed in Category II for safety and effectiveness for anti crobial, antiseptic, analgesic, antipruritic, counter-irritant, rubefacien or healing activities.

Product containing less than 2.5 percent campho may be placed in Category I for safety provided the individual OTC pa kage contains less than 0.360 g camphor, or that the product is rendere unpalatable to discourage it being taken orally, and providing no m dicinal activity is claimed for the ingredient camphor.

PEDIATRICS
OFFICIAL PUBLICATION OF THE AMERICAN ACADEMY OF PEDIATRICS
EVANSTON, ILLINOIS 60201

Committee on Drugs

Camphor: Who Needs It?

Camphor is a pleasant-smelling cyclic ketone of the hydroaromatic terpene group. Its history dates to ancient Chinese medicine. Originally obtained by distillation of bark chips from the camphor tree *Cinnamonum camphora*, it is now produced synthetically. Camphor was highly regarded as a circulatory and cardiac stimulant in the late 19th and early 20th centuries. Traditional uses have been as an abortifacient,[1] contraceptive,[2] cold remedy,[2] aphrodisiac,[1] antiaphrodisiac, suppressor of lactation,[1] and antiseptic.[4] Though no longer used for these purposes, camphor is an ingredient of a number of the over-the-counter remedies, particularly camphorated oil (20% camphor in cottonseed oil), spirits of camphor (10% camphor in alcohol), and many liniments, and is a component of paregoric (camphorated tincture of opium). While unfamiliar to many physicians, it is estimated that 380,000 liters (100,000 gal) of camphorated oil and 520,600 liters (137,000 gal) of spirits of camphor were produced in the United States in 1975, and marketed in packages *without* safety caps.[5]

When rubbed on the skin, camphor is a rubefacient, but if not vigorously applied it produces a feeling of coolness. The respiratory tract is particularly sensitive to this action, which is thought to be due to stimulation of nerve endings sensitive to cold. The initial response to the local irritation produces vasodilation or reactive hyperemia.

PROGRESSIVE SYMPTOMATOLOGY OF SEVERE CAMPHOR INTOXICATION

1. Nausea and vomiting
2. Feeling of warmth, headache
3. Confusion, vertigo, excitement, restlessness, delirium, & hallucinations
4. Increased muscular excitability, tremors, & jerky movements
5. Tremors, progressing to epileptiform convulsions, followed by depression
6. Coma, CNS depression
7. Death from respiratory failure or from status epilepticus
8. Slow convalescence

Relief of pain may be obtained by an indirect counterirritati of the same segmental CNS level.[6] Possibly because of these actions, plus its "medicinal" oma and tradition, camphor is marketed large in multi-ingredient liniments for symptomatic lief of "chest congestion" and muscle aches. These preparations contain from 1% to 20% ca phor.

Toxico gy

Camphor is classified as a class IV chemical, i.e., *very toxic substance*, with a probable human lethal dose of to 500 mg/kg.[7] The ingestion of 2 gm generally roduces dangerous effects in an adult (Table). lthough 42 gm (1.5 oz) have been ingested with ecovery,[8] and 0.7 to 1.0 gm (1 tsp camphorated l) has proven fatal in children.[9]

With mild poisoning, gastrointestinal tract symptoms are ore common than neurologic, and include irrit on of the mouth, throat, and stomach. Vo ing may be the only symptom, or it may prece or follow other symptoms. Symptoms of int ication following ingestion have occurred wit n 5 to 15 minutes, but may be delayed up t several hours if food is present in the stomach to interfere with absorption. Severe poisoning is aracterized by convulsions, which may be pun uated by periods of apnea and asystole. Pos onvulsive depression of the CNS follows stim tion.[7] Neuronal necrosis has been reported in l man fatalities, and similar lesions have been pr duced in mice.[9] Fatty degeneration of the liver a l kidney may also occur.[9]

Clinic l Reports

Reports of camphor poisonings have appeared in the literat re for more than 100 years. The National Cle inghouse of Poison Control Centers reported over 494 cases in 1973, of which 415 were in child n less than 5 years old.[5] In the s year, in Eng nd, Sibert reported that almost of all hospit lizations due to accidental poi ings in chile n aged 6 months to 5 years w due to camp or.[10] Aronow and Spigiel reported 94 cases of amphor poisoning from the Chil

's Hospital of Michigan in Detroit in 1974.[11] The majority of poisonings in both adults and children was due to *accidental substitution* of camphorated oil for other proprietary medications, most notably castor oil, Castoria, cod liver oil, and various cough and colic preparations. The similarity of size, shape, and label design of some manufacturers' bottles of castor oil and camphorated oil, plus similarities in the appearance of the product, leads to errors by consumers, drug store clerks, and pharmacists.[5,11,12]

Camphor is readily absorbed from all sites of administration, and several reports cite camphor intoxication secondary to vapor inhalation[11] or skin absorption.[13,14] A near-fatal case in a 6-month-old infant occurred after rubbing of the chest and nose with an ointment containing camphor, menthol, and thymol.[15]

Four cases of camphor ingestion during pregnancy have been reported. One resulted in neonatal death 30 minutes after delivery and 36 hours after ingestion of camphor.[16] Camphor was detected in maternal blood 15 minutes after ingestion, gastric lavage was performed, and camphor was not found eight hours later. At delivery, 36 hours after ingestion, camphor was found in amniotic fluid, cord blood, and fetal blood, as well as in the liver, brain, and kidney of the infant. Cause of death was failure to initiate respiration. The second case reported delivery of a healthy baby 20 hours after ingestion.[17] While high levels of camphor were measured in maternal blood 24 hours after ingestion and the amniotic fluid had a distinct odor of camphor, only very low levels were found in the infant's blood. In both these cases, the mothers mistakenly took camphorated oil, believing it to be castor oil, to induce labor. A third case reported the delivery of a healthy baby six days after ingestion[18]; no information on infant outcome was available concerning the fourth case.[19]

Although the rate and extent of transplacental transfer are unknown, even small amounts may produce toxicity to the fetus because of its limited capacity for hepatic hydroxylation and conjugation with glucuronic acid, the principal routes of detoxification.

The National Clearinghouse for Poison Control Centers reported a 20% incidence of convulsions for patients with camphor intoxication. Rubin et al.[20] reported convulsions in five of 14 ingestions of camphorated oil. In Craig's series of children less than 5 years of age who ingested camphorated oil, nine of 19 convulsed within 4 to 120 minutes after ingestion of 0.7 to 6 gm.[21]

While in most cases of camphor ingestion recovery is apparently complete, a case has been reported by Skoglund et al.[22] of a 15-month-old child who developed brief, generalized, major motor seizures which persisted for two days following the child's crawling through a spilled 10% camphor preparation. The child recovered, and subsequent observation revealed unremarkable findings on physical examination and a normal EEG. He had no further seizures until a year later, when a camphorated vaporizer preparation containing less than 5% camphorated oil was used by the mother to relieve symptoms of an acute, afebrile upper respiratory tract illness.

Conclusions

1. Camphor has no established, therapeutic role in scientific medicine.
2. Camphor has potent, serious toxicologic actions; the ingestion of relatively small amounts has proven fatal.
3. Although accidental oral ingestion is the most common route of intoxication, significant quantities can be absorbed percutaneously and via inhalation.
4. Transplacental transfer may be toxic to the fetus.
5. Camphorated oil, in particular, is the worst offender in accidental ingestions, because it is mistaken for a variety of over-the-counter products and is also accidentally ingested by toddlers.
6. As long as camphor-containing products continue to be marketed, pediatricians should warn parents of the dangers of camphor-containing products in the home, especially camphorated oil.

COMMITTEE ON DRUGS

Sydney Segal, M.D., Chairman; Sanford N. Cohen, M.D.; John Freeman, M.D.; Reba M. Hill, M.D.; Benjamin M. Kagan, M.D.; Ralph Kauffman, M.D.; Albert W. Pruitt, M.D.; Lester F. Soyka, M.D.; Stanley M. Vickers, M.D.
Consultant: Robert Kramer, M.S.

This statement has been endorsed by the Committee on Accident and Poison Prevention.

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ABSTRACT

An Epidemiologic Approach to School Absenteeism, b[illegible] Carlos E. Berganza, M.D., and Thomas F. Anders, M.D.

For pediatricians and family physicians who examine [illegible]ildren with multiple physical complaints associated with school absenteeism[illegible] there are few guidelines to aid in proper diagnosis and management. Cluste[illegible] of demographic and psychosocial variables associated with patterns of absen[illegible]eism might differentiate subgroups of school avoidance, which would e[illegible]iance diagnosis and disposition. In this study, we analyze the absentee r[illegible]es of 1,088 seventh graders in the Palo Alto Unified School District. A high[illegible] absentee group and a low absentee group are identified and traced backward[illegible] to the first grade and forward to the eighth grade. Absentee patterns are anal[illegible]ed. A methodology is applied which subdivides the groups into further poten[illegible]al categories of risk. *J Am Child Psychiatry* 17:117, 1978.

MAY 01, 1[redacted] POISON CO[redacted]SE REPORT SUMMARY
[redacted]ATIONAL CLEARINGHOUSE FOR POISON CONTROL CENTER[redacted]A BUREAU OF DRUGS, DIVISION OF POISON CONTRO[redacted]2240)

CATEGORY 15: CAMPHOR PRODUCTS
PRODUCT : ALL PRODUCTS
VICTIM AGE CATEGORY: ALL AGES

	ALL YEARS	1971	1972	1973	1974	1975	1976	1977	197[redacted]
ALL INCIDENTS ..	4,956	431	557	530	542	653	583	805	[redacted]55
TOXIC**	1,185	133	162	158	160	150	125	150	[redacted]17
SIGNS/SYMPTOMS	895	109	113	112	125	119	92	115	[redacted]10
FEVER	16	2	3		3		4	1	3
ATAXIA	13	3	3	1	2	1	2	1	
BURNS	40	9	4	4	4	10	5	1	[redacted]
LETHARGY	26	20	19	5	26	14	5	15	[redacted]1
CONVULSIONS .	147	26	15	24	20	19	14	10	19
RASH	7	1	1	1	1	1			2
DYSPNEA	25	3	1	4	7	4	2		4
HYPOTENSION .	5		1	1			1	1	1
COMA	21	4	3	4	3	2	2	1	2
CYANOSIS	11	1	1	3	1	2	2	1	
PNEUMONIA ...	3	1	1					1	
GI TRACT	371	46	52	46	44	50	36	46	[redacted]51
OTHER SIGNS .	389	41	52	51	56	49	38	60	[redacted]42
HOSPITALIZED .	552	74	89	86	77	63	55	53	[redacted]55
FATAL									
VICTIM AGES									
UNDER 5YO	3,878	315	398	415	401	549	467	631	[redacted]702
5YO AND OVER ..	666	82	107	79	74	59	70	136	[redacted]59
AGE UNSPECIFIED	412	34	52	36	67	45	46	68	[redacted]44
VICTIM SEX									
MALE	2,374	209	231	256	258	340	294	385	[redacted]401
FEMALE	1,915	156	217	205	223	231	218	315	[redacted]310
SEX UNSPECIFIED	667	66	109	69	61	82	71	105	[redacted]94
NATURE OF INCIDENT - ROUTE, MANNER, INTENT, ETC.									
ACCIDENT	4,548	402	509	494	486	625	539	717	[redacted]730
INGESTION	4,541	402	509	494	486	625	537	709	[redacted]713
[redacted]							[redacted]	[redacted]	
SUBSTANCE ABUSE	5		2		1			2	
SUICIDE	101	14	14	13	16	10	5	18	[redacted]11
OTHER MANNER ..	29	2	8	4	2	3	1	6	3
UNKNOWN	273	13	24	19	37	15	38	66	[redacted]61
PERSON CONTACTING POISON CENTER									
PROFESSIONAL ..	1,782	129	161	177	224	258	232	295	[redacted]306
LAY PERSON	2,568	213	297	299	274	344	278	429	[redacted]434
TYPE OF CASE									
TELEPHONE	3,382	211	294	306	356	460	427	628	[redacted]700
TREATED	1,574	220	263	224	186	193	156	177	[redacted]155
OTHER CHILDREN .									
INVOLVED	144	13	27	10	10	22	19	14	[redacted]29
TREATED	95	7	21	7	6	16	10	12	16

USE AND [redacted] OF EMESIS, LAVAGE									
SYR OF IPECAC .	1,252	106	153	132	113	121	134	1	249
COPPER SULF. ..	8	3	1	1	1	1		1	
APOMORPHINE ...	2		1					1	
SUCCESSFUL ...	645	68	86	83	54	79	69	107	39
UNSUCCESSFUL .	55	1	3	4	16	8	6	7	10
LAVAGED	586	86	99	94	85	74	43	54	51
SOURCES OF INFORMATION USED BY POISON CENTER									
BOOKS	1,030	154	188	143	132	140	88	112	73
NCPCC CARDS ...	2,005	161	186	239	278	309	207	321	304
PRODUCT LABEL .	228	28	46	35	25	24	25	21	24
MANUFACTURER ..	42	4	5	7	2	4	12	7	1
PREVIOUS KNWLDG	601	41	52	63	53	71	67	100	154
OTHER SOURCE ..	743	40	38	62	62	83	106	160	192
NOT AVAILABLE .	66	10	17	7	10	4	6	4	8
PACKAGING INFORMATION									
CLOSURE INFO									
SAFETY CAP ...	147		6	16	16	21	27	32	29
NON-SAFETY ...	730		44	118	102	115	68	125	158
OPEN	424		24	66	53	61	35	64	121
CLOSED	350		25	53	43	66	51	64	48
ORIGINAL CONTAINER OR TRANSFERRED									
ORIGINAL	367	168	121	47	17	10	1	2	1
TRANSFERRED ..	18	8	3	3	4				
WARNING LABEL									
YES	667		61	114	86	92	72	114	128
NO	222		22	52	35	34	21	27	31
CONTAINER STORAGE SITE									
USUAL PLACE ..	244	116	78	31	12	4	1	1	1
NOT USUAL	100	37	37	14	5	4	1	1	1

* TOXIC = CASES REPORTED WITH SIGNS AND SYMPTOMS, HOSPITALIZATION, OR DEATH

EPORT PREPARED BY MARK I FOW, PH.D. (HFD240)

NATIONAL CLEARINGHOUSE FOR POISON CONTROL CENTERS (FDA BUREAU OF DRUGS, DIVISION OF POISON CONTROL, HFD240)

CATEGORY 15: CAMPHOR PRODUCTS
PRODUCT : ALL PRODUCTS
VICTIM AGE CATEGORY: UNDER 5YO

	ALL YEARS	1971	1972	1973	1974	1975	1976	1977	1978
ALL INCIDENTS ..	3,878	315	398	415	401	549	467	631	[illegible]
TOXIC**	784	83	102	108	100	113	89	95	[illegible]
SIGNS/SYMPTOMS	546	64	65	70	73	86	60	62	[illegible]
FEVER	14	2	3		2		3	1	[illegible]
ATAXIA	4	1	2			1			
BURNS	27	4	3	2	3	7	4	1	[illegible]
LETHARGY	12	16	12	3	16	13	4	3	[illegible]
CONVULSIONS .	96	18	11	14	12	14	11	3	[illegible]
RASH	6		1	1	1	1			[illegible]
DYSPNEA	18	3	1	4	3	2	2		[illegible]
HYPOTENSION .	1		1						
COMA	13	3	2	2	2	2	1		[illegible]
CYANOSIS	8	1	1	3	1		2		
PNEUMONIA ...	2	1						1	
GI TRACT	204	24	27	24	23	39	20	22	[illegible]
OTHER SIGNS .	236	25	27	36	32	33	26	31	[illegible]
HOSPITALIZED .	404	49	60	66	50	54	43	43	[illegible]
FATAL									
VICTIM AGES									
UNDER 5YO	3,878	315	398	415	401	549	467	631	[illegible]
5YO AND OVER ..									
AGE UNSPECIFIED									
VICTIM SEX									
MALE	1,960	166	173	207	202	298	252	323	[illegible]
FEMALE	1,500	108	162	163	164	196	177	238	[illegible]
SEX UNSPECIFIED	418	41	63	45	35	55	38	70	[illegible]
NATURE OF INCIDENT - ROUTE, MANNER, INTENT, ETC.									
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	467	631	[illegible]
INHALATION ...									
SUBSTANCE ABUSE									
SUICIDE									
OTHER MANNER ..									
UNKNOWN									
PERSON CONTACTING POISON CENTER									
PROFESSIONAL ..	1,310	89	95	127	152	205	181	219	242
LAY PERSON	2,108	168	235	247	215	298	227	354	364
TYPE OF CASE									
TELEPHONE	2,643	158	197	237	265	388	332	489	577
TREATED	1,235	157	201	178	136	161	135	142	[illegible]
OTHER CHILDREN .									
INVOLVED	102	6	15	7	7	21	14	6	26
TREATED	64	1	10	5	5	15	9	5	[illegible]

USE AND SUCCESS OF EMESIS, LAVAGE									
SYR OF IPECAC .	1,027	81	113	105	85	102	116	210	215
COPPER SULF. ..	7	3	1		1	1		1	
APOMORPHINE ...									
SUCCESSFUL ...	520	52	58	67	44	66	58	86	89
UNSUCCESSFUL .	40	1	2	3	10	5	5	5	9
LAVAGED	447	64	71	72	63	59	36	41	41
SOURCES OF INFORMATION USED BY POISON CENTER									
BOOKS	732	110	129	104	93	109	63	73	51
NCPCC CARDS ...	1,583	115	134	192	200	260	162	265	255
PRODUCT LABEL .	181	21	32	27	21	21	21	19	19
MANUFACTURER ..	38	3	4	7	2	4	12	5	1
PREVIOUS KNOLDG	487	35	39	50	41	57	55	80	130
OTHER SOURCE ..	608	31	34	55	52	74	83	124	155
NOT AVAILABLE .	55	8	12	6	8	4	6	3	8
PACKAGING INFORMATION									
CLOSURE INFO									
SAFETY CAP ...	109		5	13	11	15	19	28	18
NON-SAFETY ...	635		33	97	87	104	63	111	140
OPEN	367		16	56	45	57	30	59	104
CLOSED	283		20	42	35	54	42	51	39
ORIGINAL CONTAINER OR TRANSFERRED									
ORIGINAL	274	123	88	38	15	7	1	1	1
TRANSFERRED ..	17	7	3	3	4				
WARNING LABEL									
YES	552		44	93	70	76	63	101	105
NO	188		13	43	31	32	18	25	26
CONTAINER STORAGE SITE									
USUAL PLACE ..	174	78	57	23	11	3	1		1
NOT USUAL	91	37	30	13	5	3	1	1	1

TOXIC = CASES REPORTED WITH SIGNS AND SYMPTOMS, HOSPITALIZATION, OR DEATH

JOB PREPARED BY MARK I FOW, PH.D. (HFD240)

The United States Pharmacopeia

TWENTIETH REVISION

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D. C., March 22, 1975. Prepared by the Committee of Revision and published by the Board of Trustees

Official from July 1, 1980

United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway, Rockville, Md. 20852

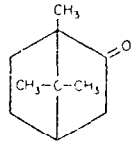
...sional mixing to dissolve the dibasic calcium phosphate, and heat for 30 minutes. Cool, add water to volume, and mix. If the preparation is not clear, filter, discarding the first 10 ml of the filtrate. Reserve portions of the solution for the *Identification* test. Transfer 25.0 ml of the solution to a 250-ml beaker equipped with a magnetic stirrer. Proceed as directed in the *Assay* under *Tribasic Calcium Phosphate*, beginning with "With constant stirring." Each ml of 0.08 *M* disodium ethylenediaminetetraacetate is equivalent to 8.604 mg of $CaHPO_4 \cdot 2H_2O$.

Calcium Phosphate, Tribasic—*see* Calcium Phosphate, Tribasic NF

Calcium Stearate—*see* Calcium Stearate NF

Calcium Sulfate—*see* Calcium Sulfate NF

Camphor



$C_{10}H_{16}O$ 152.24

Bicyclo[2.2.1]heptane-2-one, 1,7,7-trimethyl-

Camphor.

2-Bornanone [*76-22-2*]

» Camphor is a ketone obtained from *Cinnamomum camphora* (Linné) Nees et Ebermaier (Fam. Lauraceae) (Natural Camphor) or produced synthetically (Synthetic Camphor).

Packaging and storage—Preserve in tight containers, and avoid exposure to excessive heat.

Labeling—Label it to indicate whether it is obtained from natural sources or is prepared synthetically.

Melting range ⟨741⟩: between 174° and 179°.

Specific rotation ⟨781⟩: between +41° and +43° for natural Camphor, determined in a solution in alcohol containing 1 g in each 10 ml. Synthetic Camphor is the optically inactive, racemic form.

Water—A 1 in 10 solution in solvent hexane is clear.

Nonvolatile residue—Heat 2.0 g in a tared dish on a steam bath until sublimation is complete. Then dry the residue at 120° for 3 hours, cool, and weigh: the weight of the residue does not exceed 1.0 mg (0.05%).

Halogens—Mix 100 mg of finely divided Camphor with 200 mg of sodium peroxide in a clean, dry, hard glass test tube of about 25-mm internal diameter and 20-cm length. Suspend the tube at an angle of about 45° by means of a clamp placed at the upper end, and gently heat the tube, starting near the upper end, but not heating the clamp, and gradually bringing the heat toward the lower part of the tube until incineration is complete. Dissolve the residue in 25 ml of warm water, acidify with nitric acid, and filter the solution into a comparison tube. Wash the test tube and the filter with two 10-ml portions of hot water, adding the washings to the filtered solution. To the filtrate add 0.50 ml of 0.10 *N* silver nitrate, dilute with water to 50 ml, and mix: the turbidity does not exceed that produced in a blank test with the same quantities of the same reagents and 0.050 ml of 0.020 *N* hydrochloric acid (0.035%).

Camphor Spirit

» Camphor Spirit is an alcohol solution containing, in each 100 ml, not less than 9.0 g and not more than 11.0 g of $C_{10}H_{16}O$ (camphor).

Camphor	100 g
Alcohol, a sufficient quantity, to make	1000 ml

Dissolve the camphor in about 800 ml of the alcohol, and add alcohol to make 1000 ml. Filter, if necessary.

Packaging and storage—Preserve in tight containers.

Alcohol content ⟨611⟩: between 80.0% and 87.0% of C_2H_5OH.

Assay—Transfer 2.0 ml of Camphor Spirit to a suitable pressure bottle containing 50 ml of freshly prepared dinitrophenylhydrazine TS. Close the pressure bottle, immerse it in a water bath, and maintain at about 75° for 16 hours. Cool to room temperature, and transfer the contents to a beaker with the aid of 100 ml of 3 *N* sulfuric acid. Allow to stand at room temperature for not less than 12 hours, transfer the precipitate to a tared filter crucible, and wash with 100 ml of 3 *N* sulfuric acid followed by 75 ml of cold water in divided portions. Continue the suction until the excess water is removed, dry the crucible and precipitate at 80° for 2 hours, cool, and weigh. The weight of the precipitate so obtained, multiplied by 0.4581, represents the weight of $C_{10}H_{16}O$ in the specimen taken.

Camphorated Parachlorophenol—*see* Parachlorophenol, Camphorated

Candicidin

Candicidin.

Candicidin [*1403-94-4*].

» Candicidin conforms to the regulations of the federal Food and Drug Administration concerning antibiotic drugs (449.10) (see *Antibiotics* ⟨1011⟩). It is a substance produced by growth of *Streptomyces griseus* Waksman et Henrici (Fam. Streptomycetaceae). Candicidin has a potency of not less than 1000 µg per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, in a refrigerator.

Reference standard—*Candicidin Reference Standard*.

pH: between 8.0 and 10.0 in an aqueous suspension containing 10 mg per ml.

Loss on drying: not more than 4%.

Other requirements—It complies with the test for identification.

Candicidin Ointment

» Candicidin Ointment conforms to the regulations of the federal Food and Drug Administration concerning antibiotic drugs (449.610a, candicidin vaginal ointment) (see *Antibiotics* ⟨1011⟩). It contains not less than 90.0 percent and not more than 140.0 percent of the labeled amount of candicidin, the labeled amount being 0.6 mg per g.

Packaging and storage—Preserve in well-closed containers, in a refrigerator.

Water: not more than 0.5%.

Candicidin Vaginal Tablets

» Candicidin Vaginal Tablets conform to the regulations of the federal Food and Drug Administration concerning antibiotic drugs (449.610b) (see *Antibiotics*

NATIONAL CLEARINGHOUSE FOR POISON CONTROL CENTERS (FDA BUREAU OF DRUGS, DIVISION OF POISON CONTROL, HFD240)

ATEGORY 15: CAMPHOR PRODUCTS
ODUCT 135520: CAMPHOR SPIRITS
ICTIM AGE CATEGORY: ALL AGES

	ALL YEARS	1971	1972	1973	1974	1975	1976	1977	1978
ALL INCIDENTS ..	211	25	41	35	22	29	15	30	14
TOXIC**	54	4	9	11	6	8	6	5	5
SIGNS/SYMPTOMS	33	2	3	8	5	3	5	4	3
FEVER									
ATAXIA	1								
RUSHS								1	
LETHARGY									
CONVULSIONS .			1		1				
.....	1		1						
COMA									
HYPOTENSION .									
COMA									
CYANOSIS									
PNEUMONIA ...									
GI TRACT	21		3	3	4	2	4	2	3
OTHER SIGNS .	15	2	3	5	2	1	1	1	
HOSPITALIZED .	26	2	8	3	2	5	1	2	3
FATAL									
VICTIM AGES									
UNDER 5YO	160	13	34	31	16	24	10	22	10
5YO AND OVER ..	29	7	5	2	3	2	4	3	3
AGE UNSPECIFIED	22	5	2	2	3	3	1	5	1
VICTIM SEX									
MALE	94	8	22	13	10	17	5	13	6
FEMALE	82	12	12	14	9	8	10	9	8
SEX UNSPECIFIED	35	5	7	8	3	4		8	
FAILURE OF INCIDENT - ROUTE, MANNER, INTENT, ETC.									
ACCIDENT	190	21	40	34	20	28	12	25	10
INGESTION	190	21	40	34	20	28	12	25	10
INHALATION ...									
SUBSTANCE ABUSE									
SUICIDE	4	2							
OTHER MANNER ..	5	1		1	1		1	1	
UNKNOWN	12	1	1		1	1	2	2	4
PERSON CONTACTING POISON CENTER									
PROFESSIONAL ..	48	5	7	7	8	3	3	12	3
LAY PERSON	134	17	30	25	11	21	10	13	7
TYPE OF CASE									
TELEPHONE	130	15	20	22	13	21	9	23	7
TREATED	81	10	21	13	9	8	6	7	7
FOR CHILDREN .									
EXPOSED	4			1				3	
TREATED	2							2	

USE AND SUCCESS OF EMESIS, LAVAGE									
SYR OF IPECAC .	70	7	14	16	5	8	5	8	7
COPPER SULF. ..	1		1						
APOMORPHINE ...									
SUCCESSFUL ...	35	4	9	8	3	1	6	2	2
UNSUCCESSFUL .	3			1	2				
LAVAGED	27	2	8	2	9	4		2	
SOURCES OF INFORMATION USED BY POISON CENTER									
BOOKS	78	10	19	15	10	7	6	8	3
NCPCC CARDS ...	62	8	13	10	7	9	4	7	4
PRODUCT LABEL .	11	3	3		1		2	2	
MANUFACTURER ..	1							1	
PREVIOUS KNWLDG	30	3	4	5	5	4	4	3	2
OTHER SOURCE ..	28		5	5	1	8	2	3	1
NOT AVAILABLE .	2		1	1					
PACKAGING INFORMATION									
CLOSURE INFO									
SAFETY CAP ...	4			1				1	
NON-SAFETY ...	28		1	8	6	6	2	4	
OPEN	12		1	6	2	1		1	
CLOSED	20		1	4	3	4	2	4	
ORIGINAL CONTAINER OR TRANSFERRED									
ORIGINAL	21	6	14		1				
TRANSFERRED ..	2	1	1						
WARNING LABEL									
YES	26		5	5	4	3	2	5	2
NO	12		1	4	3	3			1
CONTAINER STORAGE SITE									
USUAL PLACE ..	17	9	8						
NOT USUAL	4		4						

** TOXIC = CASES REPORTED WITH SIGNS AND SYMPTOMS, HOSPITALIZATION, OR DEATH

REPORT PREPARED BY MARK I. FOIL, PH.D. (WED260)

CATEGORY 15: CAMPHOR PRODUCTS
PRODUCT 135520: CAMPHOR SPIRITS
VICTIM AGE CATEGORY: UNDER 5YO

	ALL YEARS	1971	1972	1973	1974	1975	1976	1977	1978
ALL INCIDENTS ..	160	13	34	31	16	24	10	22	10
TOXIC**	37	1	8	9	4	7	2	3	3
SIGNS/SYMPTOMS	17		2	6	3	2	1	2	1
FEVER									
ATAXIA									
BURNS									
LETHARGY			1		1				
CONVULSIONS .									
RASH	1		1						
DYSPNEA									
HYPOTENSION .									
COMA									
CYANOSIS									
PNEUMONIA ...									
GI TRACT	12		2	3	3	1		2	1
OTHER SIGNS .	8		2	3	1	1	1		
HOSPITALIZED .	23	1	7	3	2	5	1	2	2
FATAL									
VICTIM AGES									
UNDER 5YO	160	13	34	31	16	24	10	22	10
5YO AND OVER ..									
AGE UNSPECIFIED									
VICTIM SEX									
MALE	79	4	20	12	8	16	4	11	4
FEMALE	57	5	9	12	6	6	6	7	2
SEX UNSPECIFIED	24	4	5	7	2	2		4	
NATURE OF INCIDENT - ROUTE, MANNER, INTENT, ETC.									
ACCIDENT	160	13	34	31	16	24	10	22	10
INGESTION	160	13	34	31	16	24	10	22	10
INHALATION ...									
SUBSTANCE ABUSE									
SUICIDE									
OTHER MANNER ..									
UNKNOWN									
PERSON CONTACTING POISON CENTER									
PROFESSIONAL ..	36	1	7	7	8	3	2	7	1
LAY PERSON	100	10	23	21	6	17	6	11	6
TYPE OF CASE									
TELEPHONE	93	9	17	18	8	17	5	15	4
TREATED	67	4	17	13	8	7	5	7	6
OTHER CHILDREN .									
INVOLVED	4			1				3	
TREATED	2							2	

USE AND SUCCESS OF EMESIS, LAVAGE									
SYR OF IPECAC .	53	4	11	14	4	6	4	5	5
COPPER SULF. ..	1		1						
APOMORPHINE ...									
SUCCESSFUL ...	26	3	6	7	2		5	1	2
UNSUCCESSFUL .	3			1	2				
LAVAGED	24	1	8	2	7	4		2	
SOURCES OF INFORMATION USED BY POISON CENTER									
BOOKS	55	6	15	12	6	5	3	5	3
NCPCC CARDS ...	46	4	10	9	5	7	2	6	3
PRODUCT LABEL .	8	1	2		1		2	2	
MANUFACTURER ..									
PREVIOUS KNWLDG	22	2	3	3	4	3	3	3	1
OTHER SOURCE ..	25		5	5	1	7	2	2	3
NOT AVAILABLE .	2		1	1					
PACKAGING INFORMATION									
CLOSURE INFO									
SAFETY CAP ...	2			1				1	
NON-SAFETY ...	24			7	5	6	2	4	
OPEN	10			6	2	1		1	
CLOSED	16			3	3	4	2	4	
ORIGINAL CONTAINER OR TRANSFERRED									
ORIGINAL	18	4	13		1				
TRANSFERRED ..	2	1	1						
WARNING LABEL									
YES	21		4	4	3	3	2	5	
NO	10			4	3	3			
CONTAINER STORAGE SITE									
USUAL PLACE ..	12	5	7						
NOT USUAL	4		4						

* TOXIC = CASES REPORTED WITH SIGNS AND SYMPTOMS, HOSPITALIZATION, OR DEATH

EPORT PREPARED BY MARK I FOW, PH.D. (HFD240)

payroll, man-hours, capital expenditures, cost of materials consumed, gross book value of fixed assets, rental payments, supplemental labor costs, etc., in addition to information on value of products shipped and quantity data for selected classes of products. This survey, while conducted on a sample basis, will cover all manufacturing industries. Data on employment, payrolls and inventories for auxiliary establishments of manufacturing companies such as central administrative offices, manufacturers sales branches, warehouses, etc., will be included, as well as data on plants under construction but not in operation.

A survey of research and development costs will be conducted also. The data to be obtained will be limited to total research and development costs of work performed by the company, total cost of research and development work performed for the Federal Government and, for comparative purposes, total net sales and receipts and total employment of the company.

In addition, a survey on shipments to, or receipts for work done for, Federal Government agencies and their contractors and suppliers is planned. This survey has been conducted annually since 1966. It is designed to provide information on the impact of Federal procurement on selected industries and on the economy of States, standard metropolitan statistical areas, and geographic regions.

The report forms will be furnished to firms included in these surveys and additional copies are available on request to the Director, Bureau of the Census, Washington, D.C. 20233.

I have, therefore, directed the annual surveys be conducted for the purpose of collecting the data hereinabove described.

Dated: November 13, 1973.

EDWARD D. FAILOR,
Administrator, Social and Economic Statistics Administration.

[FR Doc.73-24496 Filed 11-15-73;8:45 am]

SURVEY OF DISTRIBUTORS' STOCKS OF CANNED FOODS

Notice of Determination

In conformity with Title 13, United States Code, sections 181, 224, and 225, and due notice of consideration having been published October 11, 1973 (38 FR 28091), I have determined that year-end data on stocks of 30 canned and bottled products, including vegetables, fruits, juices and fish, are needed to aid the efficient performance of essential governmental functions, and have significant application to the needs of the public and industry and are not publicly available from nongovernmental or other governmental sources. This is a continuation of the survey conducted in previous years.

All respondents will be required to submit information covering their December 31, 1973, inventories of 30 canned and bottled vegetables, fruits, juices, and fish. Reports will not be required from all firms but will be limited to a scientifically selected sample of wholesalers and retail multiunit organizations handling canned foods, in order to provide year-end inventories of the specified canned food items with measurable reliability. These stocks will be measured in terms of actual cases with separate data requested for "all sizes smaller than No. 10" and for "sizes No. 10 or larger." (In addition, multiunit firms reporting separately by establishment will be requested to update the list of their establishments maintaining canned food stocks.)

Report forms will be furnished to firms covered by the survey. Additional copies of the forms are available on request to the Director, Bureau of the Census, Washington, D.C. 20233.

I have, therefore, directed that this annual survey be conducted for the purpose of collecting these data.

Dated: November 13, 1973.

EDWARD D. FAILOR,
Administrator, Social and Economic Statistics Administration.

[FR Doc.73-24497 Filed 11-15-73;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

OVER-THE-COUNTER MISCELLANEOUS INTERNAL DRUG PRODUCTS

Safety and Efficacy Review; Request for Data and Information

The FDA is undertaking a review of all over-the-counter (OTC) drug products for human use currently marketed in the United States, to determine that these OTC products are safe and effective for their labeled indications. This review will utilize expert panels working with FDA personnel.

A notice outlining procedures for this review was published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464).

To facilitate this review and a determination as to whether an OTC drug for human use is generally recognized as safe and effective and not misbranded under its recommended conditions of use, and to provide all interested persons an opportunity to present for the consideration of the reviewing experts the best data and information available to support the stated claims for all dosage forms of OTC drug products taken or used internally and not previously the subject of a request for data and information for this OTC Review, the administration invites submission of data, published and unpublished, and other information pertinent to all active ingredients utilized in such preparations.

Examples of the types of products to be reviewed in this category include, but are not limited to internal dosage forms of:

Adsorbents.	OTC Cancer Cures.
Alcoholism Cures.	Reducing Aids
Antiflatulents.	Salt Tablets
Antiparasitics.	Smoking Deterrents
Aphrodisiacs.	Stomach Acidifiers
Bed Wetting Deterrents.	Sweeteners.
	Universal Antidotes.
Colic Remedies.	Urethral Creams for males.
Digestive Aids.	
Diuretics.	Weight Control Products.
Hair Growers.	
Hang-over Remedies.	Weight Increasing Products.
Impotency Cures.	
Menstrual Products.	Worm Remedies.

Published elsewhere in this issue of the FEDERAL REGISTER is a similar request for data for all OTC miscellaneous external drug products.

This request for data and information for all miscellaneous internal OTC drugs is the last opportunity for submission of data on OTC drugs to be reviewed by expert panels and the Food and Drug Administration pursuant to the procedures established in § 130.301. Any remaining OTC drug for internal use on which data have not been provided to the Food and Drug Administration should be submitted at this time. If any such submission relates to the work of an earlier panel, and there is still a reasonable opportunity for that panel to consider the data involved, it will be referred to the correct panel.

Submission of data has been, and remains, entirely voluntary. It is not required that any OTC drug be the subject of any such submission. The Commissioner advises, however, that the monographs resulting from the OTC drug review will, pursuant to § 130.301, be regarded by the Food and Drug Administration as fully applicable to every OTC drug, regardless whether any such submission has been made for a particular product. See *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973); *Warner-Lambert Company* v. *Federal Trade Commission*, 361 F. Supp. 948 (1973); and *United States* v. *Coli-Trol 80 Medicated*, CCH F.D.Cosm. L. Rep., para. 40,837 (N.D. Ga. 1973). The Commissioner is therefore giving final notice of the opportunity to submit data and information on any OTC drug for internal use on which no previous submission has been made.

Because of the diverse nature of the ingredients used in these drugs, FDA has not conducted a literature search and therefore, a bibliography is not available.

The FDA is aware that safety data on ingredients used in this category may be available as a result of testing related to nondrug products, such as cosmetics. All interested parties are encouraged to submit at this time all available safety data for these ingredients, so that the conclusions reached will reflect the best information available.

This panel is not charged with reviewing the safety or effectiveness of the use of these ingredients in nondrug products such as cosmetics. However, the conclusions of the panel with respect to these ingredients for drug use may be utilized by the Food and Drug Administration in determining whether their

use in cosmetics can continue to be justified. Thus, although the report and monograph prepared by this panel will cover only OTC drug use, the conclusions may well have a direct and substantial impact on all uses of these ingredients in consumer products.

To be considered, eight copies of the data and/or views must be submitted, preferably bound, indexed, and on standard size paper (approximately 8½ by 11 inches). All submissions must be in the format described below:

OTC DRUG REVIEW INFORMATION

I. Label(s) and all labeling (preferably mounted and filed with the other data—facsimile labeling is acceptable in lieu of actual container labeling).

II. A statement setting forth the quantities of active ingredients of the drug.

III. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

IV. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished product.

5. Pertinent medical and scientific literature.

V. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of the finished drug product.

5. Pertinent medical and scientific literature.

VI. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.

VII. If the submission is by a manufacturer, a statement signed by the person responsible for such submission, that to the best of his knowledge it includes unfavorable information, as well as any favorable information, known to him pertinent to an evaluation of the safety, effectiveness, and labeling of such a product. Thus, if any type of scientific data is submitted, a balanced submission of favorable and unfavorable data must be submitted. The same would be true of any other pertinent data or information submitted, such as consumer surveys or marketing results.

Submissions should be forwarded to:

Food and Drug Administration, Bureau of Drugs, OTC Drug Products Evaluation Staff (BD–109), 5600 Fishers Lane, Rockville, Maryland 20852.

Submission of data must be on or before January 15, 1974 (Federal Food, Drug, and Cosmetic Act, sec. 701; 21 U.S.C. 371).

Dated November 9, 1973.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.73-24506 Filed 11-15-73;8:45 am]

OVER-THE-COUNTER MISCELLANEOUS EXTERNAL DRUG PRODUCTS

Safety and Efficacy Review; Request for Data and Information

The FDA is undertaking a review of all over-the-counter (OTC) drug products for human use currently marketed in the United States, to determine that these OTC products are safe and effective for their labeled indications. This review will utilize expert panels working with FDA personnel.

A notice outlining procedures for this review was published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464).

To facilitate this review and a determination as to whether an OTC drug for human use is generally recognized as safe and effective and not misbranded under its recommended conditions of use, and to provide all interested persons an opportunity to present for the consideration of the reviewing experts the best data and information available to support the stated claims for all dosage forms of OTC drug products applied or used externally and not previously the subject of a request for data and information for this OTC Review, the administration invites submission of data, published and unpublished, and other information pertinent to all active ingredients utilized in such preparations.

Examples of the types of products to be reviewed in this category include, but are not limited to external dosage forms of:

Alcohol.
Astringents (styptic pencil).
Baby Cream (diaper rash, rash, Prickly heat).
Back and Medicated Plasters.
Bleaching Preparations—skin.
Blemish Remedies—skin.
Boil Ointment.
Bunion Remedies.
Bust Developers.
Callous Pads—Medicated.
Chafing and Chapping Aids.
Corn Pads, Plasters & Remedies.
Cradle Cap Remedies.
Depilatories.
Foot Balms, Baths, Creams, etc.
Girth, Weight Reducers (solutions, impregnated body wraps).
Hair Growers.
Hormone Cream.
Ingrown Toenail Remedies.
Liquid Bandages—Protective Skin Preparations.
Medicated Bath Preparations.
Mercurials and Mercury-containing Lotions, Salves, etc.
Nail Biting Deterrents.
OTC Cancer Cures.
Parasiticides.
Poison Ivy and Oak Remedies.
Premature Ejaculation Remedies.
Skin Healing Preparations.
Tattoo Removers.
Thumb Sucking Deterrents.
Wart Removers.
Wrinkle Removers.

Published elsewhere in this issue of the FEDERAL REGISTER is a similar request for data for all OTC miscellaneous internal drug products.

This request for data and information for all miscellaneous external OTC drugs is the last opportunity for submission of data on OTC drugs to be reviewed by expert panels and the Food and Drug Administration pursuant to the procedures established in § 130.301. Any remaining OTC drug for external use on which data have not been provided to the Food and Drug Administration should be submitted at this time. If any such submission relates to the work of an earlier panel, and there is still a reasonable opportunity for that panel to consider the data involved, it will be referred to the correct panel.

Submission of data has been, and remains, entirely voluntary. It is not required that any OTC drug be the subject of any such submission. The Commissioner advises, however, that the monographs resulting from the OTC drug review will, pursuant to § 130.301, be regarded by the Food and Drug Administration as fully applicable to every OTC drug, regardless whether any such submission has been made for a particular product. See *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973); *Warner-Lambert Company* v. *Federal Trade Commission*, 361 F. Supp.

ton, D.C. 20235 on or before September 26, 1975. The holding of such hearing is at the discretion of the Director.

All statements and opinions contained in this notice in support of this application are those of the Applicant and do not necessarily reflect the views of the National Marine Fisheries Service.

Dated: August 13, 1975.

GERALD V. HOWARD,
Acting Associate Director for Resource Management, National Marine Fisheries Service.

[FR Doc. 75-22694 Filed 8-26-75;8:45 am]

NORTHWEST FISHERIES CENTER

Issuance of Marine Mammals Permit

On July 2, 1975, notice was published in the FEDERAL REGISTER (40 FR 27958), that application had been filed by the Northwest Fisheries Center, National Marine Fisheries Service, Seattle, Washington 98112, for a permit to take an unspecified number of all cetacean species throughout the range of the group, for the purpose of Scientific Research, under the Marine Mammal Protection Act of 1972 (16 U.S.C. 1361-1407).

Notice is hereby given that, on August 21, 1975, the National Marine Fisheries Service issued a Scientific Research Permit, as authorized by the provisions of the Marine Mammal Protection Act of 1972, to the Northwest Fisheries Center, National Marine Fisheries Service, subject to certain conditions set forth therein.

The Permit authorizes the Northwest Fisheries Center to conduct a long-term study of cetacean population stocks by means of aerial and shipboard censuses, underwater observations/photography and sound recording. No cetaceans will be killed, captured, marked or handled during the course of this work.

The Permit is available for review by interested persons in the Office of the Director, National Marine Fisheries Service, Washington, D.C. 20235, and the Offices of the Regional Director, National Marine Fisheries Service, Northeast Region, Federal Building, 14 Elm Street, Gloucester, Massachusetts 01930; the Regional Director, National Marine Fisheries Service, Southwest Region, 300 South Ferry Street, Terminal Island, California 90731; the Regional Director, National Marine Fisheries Service, Northwest Region, Lake Union Building, 1700 Westlake Avenue North, Seattle, Washington 98109; the Regional Director, National Marine Fisheries Service, Southeast Region, Duval Building, 9450 Gandy Boulevard, North, St. Petersburg, Florida 33702; and the Regional Director, National Marine Fisheries Service, Alaska Region, P.O. Box 1668, Juneau, Alaska 99802.

Dated: August 21, 1975.

JACK W. GEHRINGER,
Acting Director,
National Marine Fisheries Service.

[FR Doc.75-22592 Filed 8-26-75;8:45 am]

EASTERN PACIFIC TUNA FISHERIES

Notice of Change of Place of Public Hearing

On or about August 27, 1975, a Notice was published in the FEDERAL REGISTER with respect to a hearing to aid the National Marine Fisheries Service in its investigations into the nature of foreign fishing operations in the Inter-American Tropical Tuna Commission's yellowfin regulatory area. The Notice stated that the hearing will be held at the United Portuguese Club, 2818 Addison Street, San Diego, California, beginning at 9:30 a.m., August 29, 1975.

This is to notify the interested public that the hearing will be held at the Sheraton Inn, San Diego Airport, 1590 Harbor Island Drive, San Diego, California.

Dated: August 25, 1975.

JACK W. GEHRINGER,
Acting Director.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Alcohol, Drug Abuse, and Mental Health Administration

NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND ALCOHOLISM

Notice of Meeting

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Public Law 92-463), announcement is made of the following National Advisory body scheduled to assemble during the month of September 1975:

NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND ALCOHOLISM

September 22-23; 9:30 a.m.
Conference Rooms I and J, Parklawn Bldg., Rockville, Maryland.
Open—September 22.
Closed—September 23, 11:00-12:30 p.m.
Open—Otherwise.
Contact David G. Orchard, Parklawn Building, Room 16-86, 5600 Fishers Lane, Rockville, Md. 20852, 301-443-4702.

Purpose: The National Advisory Council on Alcohol Abuse and Alcoholism advises the Secretary, Department of Health, Education, and Welfare, the Administrator, Alcohol, Drug Abuse, and Mental Health Administration, and the Director, National Institute on Alcohol Abuse and Alcoholism regarding policy direction and program issues of national significance in the area of alcohol abuse and alcoholism. Reviews all grant applications submitted, evaluates these applications in terms of scientific merit and coherence with Department policies, and makes recommendations to the Secretary with respect to approval and amount of award.

Agenda: September 22 will be devoted to discussions of (1) the FY 1978 budget status, (2) the future of public service media campaign, (3) Council methodology for evaluation of grant proposals, and (4) the receipt and review of grant applications during FY 1976.

September 23 will be devoted to a discussion of the recommendations from the January 10, 1975 Conference on Alcohol Research. From 11 a.m. to 12:30 p.m. the Council will conduct a final review of selected grant applications for Federal assistance and this session will not be open to the public in accordance with the determination by the Administrator, Alcohol, Drug Abuse, and Mental Health Administration, pursuant to the provisions of sections 552(b)(4), 552(b)(5), and 552(b)(6), Title 5 U.S. Code and Section 10(d) of Public Law 92-463 (5 U.S.C. Appendix I).

Agenda items are subject to change as priorities dictate.

Attendance by the public at the open portions of the meeting will be limited to space available.

Substantive program information may be obtained from the contact person listed above.

The NIAAA Information Officer will furnish summaries of the meeting and a roster of Council members. Dr. Harry C. Bell, Associate Director for Public Affairs, National Institute on Alcohol Abuse and Alcoholism, Room 16C-20 Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20852, telephone 301-443-3306.

Dated: August 21, 1975.

CAROLYN T. EVANS,
Committee Management Officer, Alcohol, Drug Abuse, and Mental Health Administration.

[FR Doc.75-22645 Filed 8-26-75;8:45 am]

Food and Drug Administration

[Docket Nos 75N-0106; FDC-D-667]

ACME SCIENTIFIC CO. ET AL.

New Animal Drug Applications; Notice of Withdrawal of Approval

Correction

In FR document 75-21264, appearing in the issue of Thursday, August 14, 1975, on page 34180, make the following changes:

1. On page 34180, third column, 12th paragraph from the top, in the sixth line the word reading "Octadecyl" should read "Octadecyl".

2. On page 34181, paragraph 28, in the last full line, the word reading "Solium" should read "Sodium".

3. On page 34181, paragraph 50, in the last full line, the numbers reading "12-606V" should read "12-608V".

[Docket No. 75N-0176]

OVER-THE-COUNTER (OTC) MISCELLANEOUS EXTERNAL AND INTERNAL DRUG PRODUCTS

Safety and Effectiveness Review; Request for Data and Information

The Commissioner of Food and Drugs is requesting supplemental and additional data and information for consideration by the OTC miscellaneous external and internal drug products panels. Submissions are due by October 28, 1975.

The Food and Drug Administration (FDA) is reviewing all over-the-counter

(OTC) drug products for human use currently marketed in the United States to determine if they are safe and effective for their labeled indications. The review is being expert panels working with FDA personnel. The review is being conducted pursuant to 21 CFR 330.10 (formerly 21 CFR 130.301), published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464).

Pursuant to § 310.10(a)(2) (21 CFR 310.10(a)(2)), a notice requesting data and information for OTC miscellaneous external drug products was published in the FEDERAL REGISTER of November 16, 1973 (38 FR 31697). Elsewhere in that issue, a notice requesting data and information for OTC miscellaneous internal drug products was published (38 FR 31699). Judging from the data and information received, it is evident that there are a number of drug products for which active ingredients are claimed and for which no submissions have been made. Also, FDA files were reviewed and many ingredients in various product categories were identified, and no data have been received for them.

The FDA wants the review by the OTC miscellaneous internal and external drug products panels to be as extensive as possible; any product not previously part of the OTC review should be included.

Accordingly, to aid manufacturers and other interested persons to determine those claimed active ingredients recommended for specific conditions for which little or no data has been received, the lists of product categories as previously established in the notices published in the FEDERAL REGISTER of November 16, 1973 (38 FR 31696, 31697) have been modified. The list below now includes ingredients (by product categories) known to be in products for which the manufacturer claims a specific action that is designated in the labeling. An ingredient's inclusion in the list should not be construed as approval of it by FDA for the designated effect. The purpose of the review is to make recommendations to the Commissioner on safety, effectiveness, and proper labeling of such ingredients. No claim is made that the list below is comprehensive or that the categorization will not be modified by the OTC miscellaneous external and internal drug products panels. It is merely offered as a guideline to manufacturers or other interested persons to indicate the kinds of ingredients and labeling for which data should be submitted.

Submission of data has been, and remains, entirely voluntary; no such submission is required for any OTC drug. The Commissioner advises, however, that the monographs resulting from the OTC drug review will, pursuant to § 330.10, be regarded by FDA as fully applicable to every OTC drug, regardless whether any such submission has been made for a particular product. See *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973); *Warner-Lambert Co.* v. *Federal Trade Commission*, 361 F. Supp. 948 (1973); and *United States* v. *Coll-Trol Medicated*, CCH F.D. Cosm. L. Rep., para. 40,837 (N.D. Ga. 1973). The Commissioner is therefore giving this opportunity to submit supplemental and original data and information on any OTC drug for external and internal use because any OTC drug product containing an active ingredient not listed in the appropriate monograph will be considered misbranded or a new drug requiring a new drug application.

Manufacturers or other interested persons who have previously submitted material to the OTC miscellaneous external and internal drug products panels do not have to resubmit such data and information, but they may supplement their submitted material if appropriate.

Examples of the types of products and ingredients for which supplemental and original data and information are being requested are as follows:

MISCELLANEOUS EXTERNAL DRUG PRODUCTS

Alcohol

Absolute alcohol 70 percent	Isopropyl alcohol 91 percent
Denatured alcohol	Isopropyl alcohol 99 percent
Ethyl alcohol 93 percent	Isopropyl alcohol with ethylene oxide
Isopropyl alcohol 70 percent	

Astringents (styptic pencil)

Aluminum chlorhydroxy complex	Ferric subsulfate
Aluminum sulfate	Oxyquinoline sulfate
Ammonium alum	Potassium alum
Benzalkonium chloride	Silver nitrate
Benzethonium chloride	Tannic acid

Astringents

Acetone	Polyoxyethylene monolaurate
Alcohol 14 percent	Potassium ferrocyanide
Aluminum acetate	Sodium diacetate
Aluminum sulfate	Starch
Benzethonium chloride	Talc
Boric acid	Tannic acid glycerite
Calcium acetate	Zinc chloride
Camphor	Zinc phenolsulfonate
Cresol	Zinc stearate
Cupric sulfate	Zinc sulfate
Isopropyl alcohol	
Menthol	
Phenol	

Baby cream (diaper rash, rash, prickly heat)

Alkyldimethyl benzylammonium chloride	Iron oxide
Allantoin (5-ureidohydantoin)	Lanolin
Aluminum acetate	Menthol
Aluminum hydroxide	Methapyrilene
Amylum	Methionine
Balsam peru	Methylbenzethonium chloride
Benzethonium chloride	Oil of eucalyptus
Benzocaine	Oil of lavender
Bicarbonate of soda	Oil of peppermint
Bismuth subnitrate	Oil of white thyme
Boric acid	Panthenol
Calamine	Para-chloromercuriphenol
Calcium carbonate	Petrolatum
Camphor	Phenol
Casein	Pramoxine hydrochloride
Cod liver oil	Salicylic acid
Cysteine hydrochloride	Silicone
Dibucaine	Sorbitan monostearate
Diperodon hydrochloride	Talc
Glycerin	Tetracaine
Hexachlorophene	Vitamin A
8-Hydroxyquinoline	Vitamin A palmitate
	Vitamin D
	Vitamin D_2

MISCELLANEOUS EXTERNAL DRUG PRODUCTS

Baby cream (diaper rash, rash, prickly heat)—Continued

Vitamin E	Zinc oxide
White petrolatum	Zinc stearate

Back and medicated plasters

Alkaloids of belladonna	Ethyl alcohol
Brown mustard	Eucalyptus oil
Capsicum	Nitrocellulose
Castor oil	Powdered mustard seed
Ether	

Bleaching preparations—skin

Ammoniated mercury	Hexachlorophene
Ginseng	Hydroquinone
Glyceryl para-aminobenzoic acid	Iodochlorohydroxyquin
	Oxyquinoline sulfate

Blemish remedies—skin

Allantoin (5-ureidohydrantoin)	Oil of peppermint
Benzocaine	Phenol
Benzoic acid	Resorcinol
Calamine	Salicylic acid
Camphor	Sodium alkylarylpolyether sulfonate
Ethyl alcohol	Sulfur
Eugenol	Triclocarban
Hexachlorophene	Zinc oxide
Menthol	
Oil of eucalyptus	

Boil ointment

Aminoacridine hydrochloride	Mercurous chloride
Benzocaine	Methyl salicylate
Bismuth subnitrate	Oil of cade
Camphor	Oil of sassafras
Cholesterol	Oxyquinoline sulfate
Extract of ergot	Petrolatum
Hexachlorophene	Phenol
Ichthammol	Pine tar
Isobutyl para-aminobenzoate	Rosin
Lanolin	Rosin cerate
Menthol	Thymol
	Zinc oxide

Chafing and chapping

Acetic acid	Diperodon hydrochloride
Alcohol	Ethyl amino benzoate
Allantoin	Fatty acid derivatives
Aluminum acetate	Fluoride of lime
Aluminum dihydroxyallantoinate	Fullers earth
Ammonia	Glyceryl monostearate
Ammonium carbonate	Glyoxylidureide
Amyldimethyl-aminobenzoate	Hexachlorophene
Amyl para-dimethylamino-benzoate	Hydrogenated vegetable oil
Beeswax	8-Hydroxyquinoline
Benzalkonium chloride	Isopropyl myristate
Benzocaine	Lanolin
Benzoic acid	Lanolin alcohol
Benzyl alcohol	Lecithin
Borax	Lime water
Butylated hydroxytoluene	Linear alcohol lactate
Calamine	Lipids complex
Calcium phosphate	Menthol
Camphor	Methyl salicylate
Carbamide	Microcrystalline wax
Carnauba	Microporous cellulose
Cetyl alcohol	Mineral oil
Cholesterolized petrolatum	Octyl salicylate
Chloride of potash	Oil of cajeput
Coal tar extract	Oil of clove
Colloidal oatmeal	Oil of eucalyptus
Corn starch	Oil of mink
Cotton seed oil	Organic protein
Dilsopropyl adipate	Oxyquinolin
Dimethyl polysiloxane	Panthenol
	Paraben

MISCELLANEOUS EXTERNAL DRUG PRODUCTS

...fing and chapping—Continued

...ra-chloro-meta-...ylenol	Sodium citrate
Peppermint oil	Sodium lauryl sulfate
Petrolatum	Sorbitan monostearate
Phenol	Sorbitan sesquioleate
Phosphate of iron	Soya sterol
Phosphate of magnesia	Spermaceti
Phosphate of potash	Squalene
Phosphate of soda	Stearic acid
Polyoxyethylene 25 propylene glycol stearate	Sugar of milk
Polyoxyl 40 stearate	Sulfate of potash
Potassium oleate	Thymol
Potassium stearate	Tincture benzoin
Propylene glycol	Tincture myrrh
Propylene glycol monostearate	Triethanolamine
Pyrilamine maleate	Turpentine
Quarta	Vanillin
Rose water	Vitamin A
Salol (phenyl salicylate)	Vitamin A palmitate
Sesame oil	Vitamin D
Silicone	Vitamin D_3
Sodium chloride	Vitamin E
	Xanthan gum
	Zinc oxide
	Zirconium oxide

Cold sore, fever blister

Alcohol	Lanolin alcohol
Allantoin (5-ureido-hydantoin)	Menthol
Ammonia	Mineral oil
Ammonium carbonate	Paraffin
Benzalkonium chloride	Peppermint oil
...ocaine	Petrolatum
...phor	Phenol
...olin	Sorbitan sesquioleate
	Soya sterol
	Tannic acid

Corn pads, plasters and remedies

Alkaloids of belladonna	Iodine
Allantoin (5-ureidohydantoin)	Lard
Ascorbic acid	Menthol
Beeswax	Methyl benzethonium chloride
Benzocaine	Methyl salicylate
Camphor gum	Oil of eucalyptus
Castile soap	Panthenol
Castor oil	Pyroxylin
Chlorobutanol	Salol (phenyl salicylate)
Chlorophyll	Sodium carbonate
Collodion	Thymol
Cotton seed oil	Turpentine
Ether	Vitamin A
Glacial acetic acid	Zinc chloride
Ichthyol	

Cradle cap remedies

Benzyl benzoate emulsion	Hexachlorophene

Detergent

Green soap tincture	Phenol sodium

Dry skin remedies

Beeswax	Paraffin
Colloidal oatmeal	Polyoxyethylene oleate
Deuterated lanolin	Pyridoxine hydrochloride
Hypoallergenic lanolin	Sesame oil
Glycerin	Vegetable oil
Liquid petrolatum	Vitamin A
Lanolin oil	White petrolatum
Lecithin	
Octyldodecanol	

Foot baths, baths, creams, etc.

...yl salicylate	Carbolic acid
...zalkonium chloride	Colloidal sulfur
...caine	Di-isobutyl phenoxy ethoxy ethyldimethyl benzyl ammonium chloride
Benzoic acid	
Cod liver oil	
Camphor	

MISCELLANEOUS EXTERNAL DRUG PRODUCTS

Foot baths, baths, creams, etc.—Continued

Essential oils	Propylene glycol
Formalin	Salicylic acid
Glyceryl monostearate	Sodium bicarbonate
Hexachlorophene	Sodium borate
8-Hydroxyquinoline	Sodium chloride
Iodized benzoic oil	Sodium hypochlorite
Iron sulfate	Sodium lauryl sulfate
Isopropyl alcohol	Sodium sesquicarbonate
Lanolin	Sodium sulfate
Lithium chloride	Talc
Magnesium sulfate	Thymol
Menthol	Tragacanth mucilage
Methyl salicylate	Trisodium phosphate
Natural pine needle oil	Water soluble chlorophyllins
O-Benzyl-p-chlorophenol	Witch hazel
Oil of eucalyptus	Zinc oxide
Oil of thyme	
Peppermint oil	
Potassium iodide	

Hair groomers

Amino acids	Lanolin
Ascorbic acid	Oil of eucalyptus
Benzoic acid	Olive oil
Essential oil	Proteins
Fatty acids	Tar oil
Hormone constituents	Vegetable oil
	Vitamins

Hormone creams

Estradiol	Natural estrogens
Estrogen	Pregnenolone acetate
Estrogenic hormones	Progesterone
Estrone	

Ingrown toenail remedies

Benzocaine	Para-chloro-meta-xylenol
Dibucaine	Sodium sulfide
Isopropyl alcohol	Tannic acid

Insect bites

Alcohol	Menthol
Ammonium hydroxide	Obtundia surgical dressing
Aqua ammonia	Oil of turpentine
Bicarbonate of soda	Peppermint oil
Calamine	Phenol
Camphor	Pyrilamine maleate
Ethoxylated alkyl alcohol	Sodium borate
Ferric chloride	Triethanolamine
Fluid extract ergot	Zinc oxide
	Zirconium oxide

Insect repellant

Oil of citronella

Itching

Alcohol	Oxyquinoline sulfate
Benzalkonium chloride	Panthenol
Benzoic acid	Petrolatum
Boric acid	Phenol
Calamine	Pine oil
Camphor	Precipitated sulphur
Chlorobutanol	Pyrilamine maleate
Coal tar	Resorcinol
Colloidal oatmeal	Rose geranium oil
Dehydroabietylamine hydrochloride	Salicylic acid
Ferric chloride	Triethanolamine
Glycerin	Tripelennamine hydrochloride
Hypoallergenic lanolin	Urea
Liquid petrolatum	Vitamin A palmitate
Menthol	Vitamin D_3
Methapyrilene hydrochloride	Vitamin E
	Zirconium oxide

Liquid bandages (sprays)—protective skin preparations

Acetyl triethylcitrate	Glycerin
Benzethonium chloride	Gum arabic
Benzocaine	Hexachlorophene
Chlorobutanol	Isopropyl alcohol
Di-isobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium chloride monohydrate	Menthol
Dipropylene glycol	Methacrylate resin
Ethyl acetate	Polyvinyl acetate
Ethyl alcohol	Polyvinyl pyrrolidone
Ethyl cellulose	Thimerosal
	Thiram
	White petrolatum
	Zinc oxide

Medicated bandages

Calamine	Glycerin
Gelatin	Zinc oxide

Medicated bath preparations

Acetylated lanolin	Sodium bicarbonate
Colloidal sulfur	Sodium carbonate
Iron sulfate	Sodium chloride
Isopropyl myristate	Sodium lauryl sulfate
Isopropyl palmitate	Sodium sesquicarbonate
Lanolin alcohols extract	Sodium sulfate
Liquid petrolatum	Tar distillate
Lithium chloride	Vitamin E
Magnesium sulfate	Water soluble chlorophyllins
Natural and essential oils	
Potassium iodide	

Mercurials

Ammoniated mercury	Mercury chloride
Bichloride of mercury	Mercury oleate
Calomel	Nitromersol
Mercuric salicylate	Para-chloromercuriphenol
Mercuric sulfide	Vitromersol
Mercurochrome	Yellow mercuric oxide
Mercury	Zylonin

Minor skin irritation

Aluminum sulfate	Mineral oil
Balsam peru	Oxyquinoline sulfate
Benzoic acid	Petrolatum
Bismuth subnitrate	Pine oil
Boric acid	Pine tar
Calamine	Precipitated sulfur
Calcium acetate	Resorcinol
Camphor	Rose geranium oil
Coal tar	Salicylic acid
Glycerin	Sodium borate
Juniper tar	Starch
Lanolin	Sulfur
Lanolin oil	White petrolatum
Menthol	Zinc oxide

Nail biting deterrents

Denatonium benzoate	Isopropyl alcohol
	Sucrose octa

Nasal ointments, jellies, etc.

Boric acid	Oil of lavender
Camphor	Petrolatum
Chlorobutanol	Phenol
Ephedrine	Sodium bicarbonate
Eucalyptol	Sodium borate
Iodized organic oil	Sodium chloride
Menthol	Wintergreen oil
Methyl salicylate	Zinc sulfate
Oil of cajeput	

Parasiticides

Alkaloids of sabadilla	Cyanoacetate
Aqueous coconut oil soap	Petroleum disulfate
	Picrotoxin
Benzocaine	Piperonyl butoxide
Benzyl benzoate	Pyrethrins
Dichloro diphenyl trichloro ethane	Sublimed sulfur
	Tricosyl acetate
Isobornyl thio-	

Poison ivy and oak remedies

[redacted]lcohol
[redacted]antoin (5-ureido-ydantoin)
[redacted]ochwood creosote
Benzethonium chloride
Benzocaine
Benzyl alcohol
Bicarbonate of soda
Bichloride of *mercury*
Bithionol
Calamine
Camphor
Cetyldimethyl-benzylammonium chloride
Chloral hydrate
Chloroform
Chlorpheniramine maleate
Dimethyl polysiloxane
Diperodon hydrochloride
Diphenhydramine hydrochloride
Endothermic hectorite
Ferric chloride
Glycerin
Hexachlorophene
Hydrogen peroxide
Hydrous zirconia
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Lidocaine
Menthol
Merbromin
Oil of eucalyptus
Oil of turpentine
Panthenol
Parethoxycaine
Phenol
Phenyltoloxamine dihydrogen citrate
Polyvinyl pyrrolidone
Pyrilamine maleate
Salicylic acid
Tannic acid
Tincture of impatiens bi-flora
Triethanolamine
Zinc acetate
Zirconium oxide
Zyloxin

Premature ejaculation remedies

Benzocaine
Benzyl alcohol
Ephedrine hydrochloride
Passion fruit

Psoriasis

Allantoin (5-ureidohydantoin)
[redacted]al tar
[redacted]olin oil
[redacted]uric oleate
[redacted]eral oil
Polyethylene glycol dilaurate
Saponated cresol *solution*
White petrolatum

Sebum hair loss

Allantoin (5-ureidohydantoin)
Ammonium lauryl sulfate
Dichlorophene
Di-isobutyl-phenoxy-ethoxy-ethyl-dimethyl-benzylammonium chloride
Estradiol
Isopropyl alcohol
Lauric diethanolamide
Methyl ethyl ketone
Polyethylene glycol
Propylene glycol
Sulfonated vegetable and mineral oils
Tetracaine hydrochloride

Skin cleansers

Colloidal oatmeal
Hypoallergenic lanolin

Skin healing preparations

Allantoin (5-ureidohydantoin)
Aloe vera gel
Aluminum acetate
Ammonium sulfoichthyolate
Balsam peru
Beeswax
Benzocaine
Benzyl alcohol
Benzyl cinnamate
Bismuth formic iodide
Bismuth subgallate
Bismuth subnitrate
Boric acid
[redacted]utyl amino-benzoate
[redacted]mphor
[redacted]l alcohol
[redacted]rophyllin
[redacted]ydroxy-quinoline
Glycerin
Hamamelis
Hexachlorophene
Hydrargyrum-nitrophenolate
Iodochlorhydroxy-quin
Lanolin
Lead iodide
Menthol
Mercury
Methyl salicylate
Mineral oil
Mineral wax
Oil of anitox
Oil of bay
Oil of spearmint
Oil of thyme
Olive oil
Ortho-hydroxy-phenyl mercuric chloride
Oxyquinoline sulfate
Pancreatin

Skin healing preparations—Continued

Panthenol
Paraffin
Petrolatum
Phenol
Picric acid
Pine oil
Potassium alum
Precipitated sulfur
Pyrilamine maleate
Resorcinol
Rose geranium oil
Safflower oil
Sesame oil
Sodium borate
Tannic acid
Triplennamine hydrochloride
Vitamin A
Vitamin D
Vitamin E
White petrolatum
Zinc oleate
Zinc oxide
Zinc phenol sulfonate
Zinc sulfate
Zirconium oxide

Skin protectants

Acetone
Alkyldimethyl benzyl ammonium chloride
Aluminum *powder*
Chlorinated solvents
Chlorothane
Cod liver oil
Dimethyl phthalate
Glycerin
Isopropanol
Lanolin
Para-chloro-meta-xylenol
Rosin
Sesame oil
Starch
Tincture benzoin
Vitamin A
Vitamin D
White petrolatum
Zinc oxide

Thumb-sucking deterrents

Denatonium benzoate
Isopropyl alcohol
Sucrose octa acetate

Wart removers

Acetic acid
Alcohol
Benzocaine
Camphor
Castor oil
Collodion
Ether
Glacial acetic acid
Iodine sublimed
Menthol
Salicylic acid

Wet dressing

Aluminum acetate
Aluminum sulfate
Calcium acetate
Calcium polysulfide
Calcium thiosulfate
Colloidal oatmeal
Sodium propionate

Wrinkle remover

Magnesium aluminum silicate
Sodium silicate

MISCELLANEOUS INTERNAL DRUG PRODUCTS

Adsorbents

Activated charcoal
Papaya
Peppermint oil

Antiflatulents

Activated Charcoal
Alcohol
Aluminum hydroxide
Anise seed
Aromatic powder
Asafetida
Belladonna alkaloids
Bismuth subcarbonate
Bismuth subgallate
Calcium carbonate
Capsicum
Carbon
Cascara sagrada extract
Catnip
Chamomile flowers
Chloroform
Cinnamon tincture
Colloidal kaolin
Dehydrated garlic
Diatase
Dorase
Ether
Fluid extract of capsicum
Fluid extract of myrrh
Ginger
Glutamic acid hydrochloride
Glycine
Hydrastis fluid extract
Hydrochloric acid
Iodine
Lactic acid
Magnesium hydroxide
Mannitol
Nux vomica extract
Oil of peppermint
Ox bile extract
Pancreatin
Pectin
Pepsin
Potassium bicarbonate
Potassium carbonate
Powdered extract belladonna leaves
Rhubarb fluid extract
Simethicone
Sodium bicarbonate
Sodium salicylate
Strychnine
Tincture of lavender compound

Antispasmotics

Aluminum hydroxide
Belladonna tincture
Atropine sulfate
Belladonna root extract
Bismuth subsalicylate
Hyoscine hydrobromide
Hyoscyamine sulfate
Magnesium hydroxide
Methenamine
Methylene blue
Phenyl salicylate (salol)
Quinine sulfate
Scopolamine hydrobromide
Zinc phenosulfonate

Aphrodisiacs

Don quai
Golden seal
Gotu-kola
Korean ginseng
Licorice
Sarsaparilla

Digestive aids

Activated charcoal
Aluminum hydroxide
Amylase
Aspergillus oryza enzymes
Bacillus acidophilus
Betaine hydrochloride
Black radish powder
Calcium gluconate
Cellulase
Citrus pectin
Dehydrocholic acid
Diastase malt
Duodenal substance
Fennel acid
Glutamic acid hydrochloride
Glycine
Hectorite
Hemicellulase
Hydrastis canadensis
Iron ox bile
Lactose
Lipase
Lysine hydrochloride
Magnesium hydroxide
Mycozyme
Natural papaya
Niacinamide
Nickel-pectin
Orthophosphoric acid
Ox bile extract
Pancreatin
Papain
Pepsin
Phenacetin
Prolase
Protease
Sodium chloride
Stem bromelain
Trillium
Vitamin B_1
Vitamin B_2
Vitamin B_6

Diuretics

Acetaminophen
Alfalfa leaves
Aloes
Ammonium chloride
Asparagus
Buroma
Caffeine
Calcium lactate
Corn silk
Couch grass
Dog grass extract
Ethyl nitrite
Essence pepsin
Extract buchu
Extract hydrangea
Extract stone root
Extract uva ursi
Extracts of bearberry (cascara sagrada)
Extracts of cascara
Ferric chloride
Hematropine methyl bromide
Hyoscyamine sulfate
Magnesium sulfate
Methenamine
Methylene blue
Oil of erigeron
Oil of juniper
Oil of nutmeg
Oleo resin capsicum
Pamabrom
Parsley
Phenacetin
Phenyl salicylate (salol)
Pipsissewa
Potassium acetate
Potassium nitrate
Pyrilamine maleate
Salicylamide
Saw palmetto
Sodium benzoate
Sodium nitrate
Spirit of peppermint
Sucrose
Sulfereted oils of turpentine
Theobromine sodium salicylate
Theophylline
Triticum
Urea
Venice turpentine

Hangover remedies

Acetaminophen
Aluminum hydroxide
Aspirin
Caffeine
Dextrose
Disaccharide
Fructose
Magnesium carbonate
Magnesium stearate
Magnesium trisilicate
Niacinamide
Oil of peppermint
Peat
Thiamine mononitrate
Xylem

Menstrual products

Acetaminophen
APAP
Aspirin
Ammonium chloride
Caffeine
Calcium

Menstrual products—Continued

pantothenate
Chlorprophenpyridamine maleate
Cinnamedrine hydrochloride
Cinnamyl ephedrine hydrochloride
Cnicus benedictus
Homatropine methyl bromide
Hydrastis canadensis
Methapyrilene hydrochloride
Natural estrogenic hormone
Niacinamide
Pamabrom
Phenacetin
Phenindamine tartrate
Pyridoxine hydrochloride
Pyrilamine maleate
Riboflavin
Salicylamide
Thiamine hydrochloride

Nausea

Acetaminophen
Aluminum hydroxide
Aspirin
Caffeine
Magnesium carbonate
Magnesium trisilicate
Niacinamide
Oil of peppermint
Thiamine mononitrate

Salt substitutes

Ammonium chloride
Ammonium glutamate
Calcium carbonate
Calcium silicate
Glutamic acid
Potassium chloride
Potassium glutamate
Potassium iodide
Sodium
Tribasic calcium phosphate

Salt tablets

Calcium carbonate
Dextrose
Potassium chloride
Sodium chloride
Vitamin B_1
Vitamin C

Smoking deterrents

Alcohol
Aloin
Aluminum hydroxide
Benzocaine
Calcium phosphate
Capsicum
Chlorophyllins
Cimicifuga
Extract of belladonna leaves
Extract of cascara sagrada
Extract of nux vomica
Lobelia
Lobeline sulfate
Magnesium carbonate
Methapyrilene hydrochloride
Natural lobelia alkaloids
Nicotinic acid
Potassium gentian root
Potassium nux vomica
Propylene glycol
Pyridoxine chlorhydrate
Quinine ascorbate
Silver nitrate
Sodium ascorbate
Sodium chloride
Solid extract of gentian
Thiamine mononitrate

Stomach acidifiers

Acidol
Dilute hydrochloric acid
Glutamic acid

Sweeteners

Anhydrous dextrose
Benzoic acid
Calcium saccharin
Casein
Dextrose
Gelatin
Glycerin
Honey
Isolated soya protein concentrates
Lecithin
Malt extracts
Potassium bitartrate
Skim milk powder
Sodium saccharin
Sorbitol solution
Vitain B_1

Universal antidotes

Activated charcoal
Alcohol
Magnesium hydroxide
Potassium arsenite
Syrup of ipecac
Tannic acid

Weight control products

Alcohol
Alfalfa
Alginic acid
Arginine
Ascorbic acid
Benzocaine
Biotin
Bone marrow-reticulocyte extract
Buchu
Caffeine citrate
Calcium
Calcium carbonate
Calcium caseinate
Calcium lactate
Carrageenan
Carboxymethylcellulose
Choline
Chondrus
Cnicus benedictus
Copper
Copper gluconate
Corn oil
Cupric sulfate
Cystine
D-calcium pantothenate
Dextrose
Dioctyl sodium sulfosuccinate
Ethyl aminobenzoate
Ferric ammonium citrate
Ferric pyrophosphate
Ferrous fumarate
Ferrous gluconate
Ferrous sulfate
Flax seed
Folic acid
Fructose
Gum guar
Gum karaya
Histidine
Hydrous dextrose
Hydrastis canadensis
Inositol
Iodine
Iron
Isoleucine
Lactose
Lecithin
Leucine
Liver concentrate
L-lysine
L-lysine mono hydrochloride
Magnesium
Magnesium oxide
Malt
Maltodextrin
Manganese citrate
Mannitol
Methionine
Methylcellulose
Niacinamide
Oil anise
Organic vegetables
Pancreatin enzymes
Pantothenic acid
Papain
Papaya enzymes
Pepsin
Phenacetin
Phenylalanine
Phenylpropanolamine hydrochloride
Phosphorus
Phytolacca berry juice
Pineapple enzymes
Potassium citrate
Potassium extract buchu
Potassium extract corn silk
Potassium extract juniper
Potassium extract uva ursi
Protein from soy bean
Psyllium
Pyridoxine hydrochloride
Riboflavin
Rice polishings
Saccharin
Sea kelp
Sea minerals
Sesame seed
Sodium
Sodium bicarbonate
Sodium caseinate
Sodium carboxymethylcellulose
Soy meal
Thiamine hydrochloride
Thiamine mononitrate
Threonine
Tricalcium phosphate
Tryptophan
Tyrosine
Uva ursi
Valine
Vitamin A
Vitamin A acetate
Vitamin A palmitate
Vitamin B_1
Vitamin B_2
Vitamin B_6
Vitamin B_{12}
Vitamin D
Vitamin D_2
Vitamin E
Wheat germ
Xanthan gum
Yeast

Worm remedies

Gentian violet
Pyrantel pamoate

This request is for supplemental and original data and information for all miscellaneous external and internal OTC drug products. Any data for an OTC drug for external or internal use which have not been provided to FDA should be submitted promptly in order to be properly considered by expert panels and FDA pursuant to the procedures set forth in § 330.10.

Because of the diverse nature of the ingredients used in these drugs, FDA has not conducted a literature search, and therefore a bibliography is not available.

The FDA is aware that safety data on ingredients used in these categories may be available as a result of testing related to nondrug products, such as cosmetics. All interested parties are encouraged to submit all available safety data for these ingredients, so that the conclusions reached will reflect the best information available.

The Commissioner has concluded that the OTC miscellaneous external and internal drug products panels shall not review the safety or effectiveness of the use of these or other ingredients for conditions that have previously been reviewed by other OTC panels. The Commissioner further notes that these panels are not charged with reviewing the safety or effectiveness of the use of these ingredients in nondrug products, such as cosmetics. However, the conclusions of the Panel about these ingredients for drug use may be used by FDA in determining whether their use in cosmetics can continue to be justified.

Interested persons are invited to submit supplemental and original data on any claimed active ingredient that is designated in the labeling and offered for OTC use for treating miscellaneous internal or external conditions not covered by previous OTC panels.

To be considered, eight copies of the data and/or views must be submitted, preferably bound, indexed, and on standard size paper (approximately 8½ x 11 inches). All submissions must be in the format described below:

I. Label(s) and all labeling (preferably mounted and filed with the other data—facsimile labeling is acceptable in lieu of actual container labeling).

II. A statement setting forth the quantities of active ingredients of the drug.

III. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

IV. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.
5. Pertinent medical and scientific literature.

C. Finished drug product.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination as to the safety of the finished drug product.
5. Pertinent medical and scientific literature.

V. Efficacy data.
A. Individual active components.
1. Controlled studies
2. Partially controlled or uncontrolled studies.
3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.
5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination on the efficacy of combinations of the individual active components.
5. Pertinent medical and scientific literature.

C. Finished drug product.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination on the efficacy of the finished drug product.
5. Pertinent medical and scientific literature.

VI. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.

VII. If the submission is by a manufacturer, a statement signed by the person responsible for such submission, that to the best of his knowledge it includes all unfavorable information, as well as any favorable information available to him pertinent to an evaluation of the safety, effectiveness, and labeling of such a product, including information derived from investigations, consumer complaints, commercial marketing or published literature.

Supplemental and original data and information must be submitted on or before October 28, 1975, to the Food and Drug Administration, Bureau of Drugs, Division of OTC Drug Evaluation (HFD-510), 5600 Fishers Lane, Rockville, MD 20852.

Dated: August 21, 1975.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.75-22644 Filed 8-26-75;8:45 am]

[Docket No. 75F-0156]

SANDOZ COLORS & CHEMICALS, INC.

Filing of Petition for Food Additive

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409 (b)(5), 72 Stat. 1786 (21 U.S.C. 348(b)(5))), notice is given that a petition (FAP 3R2851) has been filed by Sandoz Colors & Chemicals, Inc., East Hanover, NJ 07936, proposing that the food additive regulations (21 CFR Part 121) be amended to provide for safe use of 7-(2*H* - naphtho[1,2 - *d*]triazol - 2 - yl) - 3-phenylcoumarin as an optical brightener in polyolefin articles intended to contact food.

Dated: August 18, 1975.

HOWARD R. ROBERTS,
Acting Director, Bureau of Foods.

[FR Doc 75-22643 Filed 8-26-75;8:45 am]

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No D-75-362]

REGIONAL ADMINISTRATOR, REGION IX (SAN FRANCISCO)

Redelegation of Authority

On February 5, 1975, the Assistant Secretary for Community Planning and Development of the Department of Housing and Urban Development published in the FEDERAL REGISTER (40 FR 5386) a redelegation of authority to each Regional Administrator, Deputy Regional Administrator, Area Director, Deputy Area Director and the Director of the Anchorage, Alaska Insuring Office to exercise, with certain exceptions not here applicable, the power and authority of the Assistant Secretary for Community Planning and Development with respect to the Community Development Block Grant program under Title I of the Housing and Community Development Act of 1974. The Regional Administrators and Deputy Regional Administrators for Regions I through VII, IX, and X were authorized to retain the authority including final program authority in the jurisdiction of those subordinate field offices from which the Regional Administrator or Deputy Regional Administrator determines that such authority should be withheld or withdrawn. The Regional Administrator for the San Francisco Regional Office has made the determination that the Community Development Block Grant program administered by the San Francisco Area Office for Hawaii, Guam, American Samoa and the Trust Territories of the Pacific Islands should be administered in the San Francisco Regional Office. Said determination was approved by the Assistant Secretary for Community Planning and Development on August 20, 1975. In accordance with the redelegation of authority published in the FEDERAL REGISTER (40 FR 5386), notice is hereby given that authority for approval of Community Development Block grant applications from the Directors and Deputy Directors of the San Francisco Area Office for Hawaii, Guam, American Samoa and the Trust Territories of the Pacific Islands is revoked and shall be administered by the San Francisco Regional Office. Applications for Community Development Block grants to recipients within Hawaii, Guam, American Samoa and the Trust Territories of the Pacific Islands shall be submitted to: Director, Honolulu Insuring Office, 1000 Bishop Street, P.O. Box 3377, Honolulu, Hawaii 96813 (40 FR 5386, February 5, 1975)

Effective date. This notice and redelegation shall be effective as of August 22, 1975.

ROBERT H. BAIDA,
Regional Administrator Region IX (San Francisco).

[FR Doc.75-22685 Filed 8-26-75;8:45 am]

DEPARTMENT OF TRANSPORTATION

Materials Transportation Bureau

ROLF JENSEN & ASSOCIATES, INC. ET AL.

Special Permits Issued

Pursuant to 49 CFR § 170.13 of the Department's Hazardous Materials Regulations, issued May 22, 1968 (33 FR 8277), following is a list of new DOT Special Permits upon which action was completed during July 1975.

Special Permit No.	Issued to—Subject	Mode or modes of transportation
SP 7018	Rolf Jensen & Associates, Inc., on behalf of CBF Systems, Inc., Covina, California, to ship bromotrifluoromethane (Halon 1301) over-pressurized with nitrogen in ASME welded steel cylinders not exceeding 2.5 pounds water capacity each.	Motor vehicle.
SP 7021	Hercules Incorporated, Wilmington, Delaware, to ship high explosives (Dynamite) in cartridge lengths not exceeding 60 inches in DOT-12B fiberboard boxes.	Motor vehicle.
SP 7025	Airco Industrial Gases, Murray Hill, New Jersey, to ship liquefied helium and hydrogen in a 12,500 gallon nominal water capacity cargo tank.	Motor vehicle.
SP 7026	Industrial Air Gases Corp., Fullerton, California on behalf of HR APCO Division, Hydraulic Research, Inc., Pasadena, California, to ship bromotrifluoromethane pressurized with nitrogen in DOT specification spherical steel pressure vessels patterned after DOT specification 4DS.	Motor vehicle, Passenger carrying Aircraft, Cargo only aircraft.
SP 7029	United States Energy Research and Development Administration, Washington, D.C., to make limited shipments of various Class A explosives in certain rail cars equipped with brake valves authorized prior to July, 1975.	Rail freight.

ALAN I. ROBERTS,
Director, Office of Hazardous Materials Operations.

[FR Doc 75-22714 Filed 8-26-75;8:45 am]

1. 2

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INDEX FOR THE STATEMENT OF THE ADVISORY REVIEW PANEL ON OTC MISCELLANEOUS EXTERNAL DRUG PRODUCTS CONCERNING OTC DRUG PRODUCTS CONTAINING CAMPHOR

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MEETING OF THE PANEL ON REVIEW OF
MISCELLANEOUS EXTERNAL OTC DRUG PRODUCTS

Seventh Meeting
November 9 and 10, 1975

Ramada Inn
Bethesda, Maryland
and
Parklawn Building
Rockville, Maryland

Panel Members

William E. Lotterhos, M.D., Chairman
Chester L. Rossi, R.Ph., D.P.M.
Rose Dagirmanjian, Ph.D. (Absent)
Harry E. Morton, Sc.D.
Vincent J. Derbes, M.D.
George C. Cypress, Jr., M.D.
Marianne N. O'Donoghue, M.D.

Liaison Representatives

Marvin M. Lipman, M.D.
Consumer Liaison (C.U.)
Bruce Semple, M.D.
Industry Liaison (P.A.)
Saul A. Bell, Pharm.D.
Industry Liaison (CTFA)

FDA Members

Robert G. Pinco, Esq., Director, OTC Division
Thomas D. DeCillis, Panel Administrator
Joseph Hussion, Drug Information Analyst
John M. Davitt, Executive Secretary

Invited Presentation

Renate Kimbrough, M.D., NCDC, Atlanta

Also Present (Open Session)

William Trudell (USV Pharmaceuticals)
Richard Bourne (Block Drug)
Myron Lower (Reed & Carnrick)
David Oppenheimer (Pfizer)
Philip Dodd (The "Pink Sheet")

Statements made herein are provisional in nature and may be modified or revised in subsequent meetings of the Panel or in their final complete report to the Commissioner.

Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Liaison Members, Consultants, or FDA Staff Members.

20 Jul 1976
Adopted

Chairman

draft of the minutes with appendices will be circulated to the Panel members for comments and corrections prior to acceptance.

The following ingredients were discussed:

Alcohols. The initial sections of the Panel report on "Antimicrobial Drugs for Topical Use" were presented. These sections deal in general with the alcohols and specifically with methyl, ethyl, isopropyl, cetyl, stearyl and benzyl alcohols, and menthol. The uses of and claims associated with ethyl alcohol in the OTC products submitted to the Panel for review were discussed in some depth. (Appendix 2)

Pyrethrins. A revised Panel report was presented. The following categories were assigned with regard to efficacy as a pediculocide:

Category I. Pyrethrins 0.3% or pyrethrins 0.2% plus piperonyl butoxide (synergist) 2%.

Category III. Pyrethrins alone at lower than 0.3% concentration.

With regard to safety, all pyrethrins preparations have been placed into Category III, mainly because of the lack of information on percutaneous absorption and possible hazards in pregnancy. (Appendix 3)

Judgement on safety of the synergists has been deferred to a future meeting.

Camphor. A preliminary report, for background information only, was presented.

Acetone. A revised draft of a report on this ingredient was presented.

Salicylic Acid. Briefly discussed. A new Panel report is being prepared.

AEP-16.1

SUMMARY MINUTES OF THE OTC REVIEW PANEL ON MISCELLANEOUS EXTERNAL DRUG PRODUCTS

Eleventh Meeting
May 16 and 17, 1976

Holiday Inn
Bethesda, Maryland

Panel Members

William E. Lotterhos, M.D.
Chairman
George C. Cypress, M.D. (absent)
Rose Dagirmanjian, Ph.D.
Vincent J. Derbes, M.D.
Harry E. Morton, Sc.D.
Marianne N. O'Donoghue, M.D.
Chester L. Rossi, D.P.M.

Liaison Members

Consumer
Marvin Lipman, M.D.
Consumers Union

Industry
Bruce Semple, M.D.
Proprietary Association

Saul A. Bell, Pharm.D.
Cosmetic, Toiletry & Frangrance Assoc.

FDA Staff Members

John M. Davitt - Executive Secretary
Michael Kennedy - Panel Administrator
Victor Lindmark, Pharm.D. - Drug Information Analyst

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Adopted 12 June 1976

William E. Lotterhos, M.D.
Chairman

Open Session

No formal open session was held, since there had been no requests for open session discussion or presentations. On May 17, the Panel members attended the Third Conference on Cutaneous Toxicity (Marriott Twin Bridges Motel, Washington, D.C.), jointly sponsored by the American Medical Association and the Society of Toxicology. This was a two-day conference; Dr. Dagarmanjian and Mr. Davitt attended on the second day (May 18) as well.

Closed Session

Minutes

Minutes of the previous (10th) meeting were reviewed and approved.

Tannic Acid (Tannins):

The preliminary draft report presented at the seventh meeting (November 9 and 10, 1975) has been revised and expanded. The expanded draft (Addendum A) was discussed during this session. The current Panel positions on tannic acid preparation of several therapeutic classes are as follows:

1. Treatment of contact dermatitis due to Rhus spp. and/or other plants of the Anacardeaceae family: efficacy has not been established. Because of the possiblity of significant absorption (and consequently an increased potential for systemic toxicity) when applied to large areas of the integument, these preparations fall into Category II.

2. Treatment of minor wounds: although clinical efficacy has not actually been established, it is possible that tannic acid would precipitate tissue proteins in an abraded area, forming a protective coating, checking excessive secretion and stopping superficial hemorrhage (Category III). This use of tannic acid for this indication would be acceptable from the safety standpoint (Category I), provided application is limited to an area of 1 sq cm or less.

3. Herpes simplex (labial fever blisters): efficacy has not been established for this indication, but tannic acid may be beneficial inasmuch as any topically applied astringent would be expected to have a desirable effect on this type of herpetic lesion (Category III).

4. Treatment of ingrown toenails: efficacy and safety not yet completely reviewed.

5. Antimicrobial claims: to be discussed at a future session.

Zirconium Compounds

Both zirconium oxide and zirconium carbonate are currently used in OTC poison ivy remedies. There is insufficient evidence of efficacy in treatment of rhus dermatitis, although a report from one group of investigators (Maibach and Epstein, Postgrad. Med. 35:571, 1964) indicates efficacy as a rhus dermatitis preventive.

The Panel is concerned about the known potential of certain zirconium compounds for producing adverse local reactions (granulomata) in sensitive individuals. Hence, these compounds have tentatively been placed into Category II, re: safety.

Camphor

A preliminary report had been presented at the seventh meeting (November 9 and 10, 1975). A expanded draft was discussed and revised at this session.

The Panel feels that additional information on the percutaneous absorption of camphor is needed in order to assess risk in pregnancy (camphor crosses the placenta) and in the newborn (glucuronidation is an important detoxication mechanism). Industry liaison members will request industry to provide whatever pertinent information is available.

Denatonium Benzoate:

The Panel has received an interim (13 week) report on the chronic oral toxicity study in rats currently being conducted by the International Research and Development Corp. under contract with HUD. Denatonium benzoate is being administered to male and female rats by gavage, at dose levels of 1.6, 8 and 16 mg/kg/day. Five rats of each sex from each dosage group were sacrificed and necropsied at 13 weeks.

Alcohols

A revised report on preparations containing isopropanol for antimicrobial activity was presented, discussed, and received for information by the Panel.

Pyrethrins

To date, health officials of 21 states have responded to the Panel's inquiry regarding pyrethrins hypersensitivity. Thus far, the replies have not indicated an allergy problem (Addendum B).

Future Meetings

The next meeting of the Panel has been rescheduled for Sunday and Monday, July 11 and 12, 1976. During the open session (July 12) representatives of Block Drug Co, Inc. will make a presentation on the safety and efficacy of pyrethrins-piperonyl butoxide pediculocides.

TANNIN

In 1611 Cotgrave[1] defined tan as: "The barke of a young Oake, wherewith being small beaten, leather is tanned". According to Reid[2] tannin is a generic term for a widely occurring group of substances of vegetable origin, capable of rendering raw hides into leather. Common tannin (tannic acid) occurs in oak gallnuts (Turkish nutgall contains 50-60%, Chinese nutgall about 70%); tannins are also present in tea, sumac, oak bark, and mangrove bark. Tannin from the latter source is known as cutch, and is produced on a large scale, especially in Malaya.[2]

The usual method of preparation involves breaking or crushing the bark or gallnuts into small pieces; these are then washed and boiled with water until the tannin has been extracted. After separation of insoluble matter, the thick, reddish-brown, viscous extract is evaporated, leaving the crude tannin as a hard cake. Purification may be effected by extracting the crude material with an alcohol-ether mixture; evaporation deposits the tannic acid as a colorless, noncrystalline mass. Tannic acid may also be prepared by heating gallic acid with phosphorus oxychloride.[2]

Substances capable of tanning, and hence called tannins, are often of greatly different chemical structure; all tannins, however, have the property of converting the gelatin of hides into insoluble nonputrefying material, thus changing the hide into leather. In general, tannins are noncrystalline when solid, but readily soluble in water or

alcohol to give colloidal solutions that are strongly astrigent. Tannins have long been used in compounding inks, because they form greenish-black or bluish-black colors with ferric salts.[2]

Tannins may be divided into three main classes: (1) condensed tannins that cannot be hydrolyzed either by acids or enzymes (these include the acacatechin and isoacacatechin tannins and the gambir catechin tannins; all contain highly substituted phloroglucinol nuclei); (2) hydrolyzable tannins, for example, gallotannins, ellagitannins, and caffetannins, and (3) tannins of unclassified nature.

Gallotannin, from which is obtained the tannic acid of commerce and medicine, is present in oak galls. It is a mixture of the gallic acid esters of glucose, one of which is pentadigalloylglucose. These esters are called depsides. Tannic acid, USP, is a mixture of compounds of gallotannin type. It is a light-yellow powder of very astrigent taste, used in styptic preparations and ointments. Tannic acid was formerly widely used in medical practice as may be seen from these quotations from an article published in 1850.[3] "I have been accustomed to use the tannin in every case where a strong and active astrigent seemed to be indicated and have never had reason to regret its exhibition...more than one thousand cases of dysentery, diarrhea, cholera infantum and other bowel affections... there is no danger in the use of tannin to almost any extent...except for constipation...I have used it in the sweating of the last stages of phthisis..in hemorrhage...in threatened abortion...in hemorrhoids...in aphthae and other diseases of the mouth...in old sores and phagedenic

ulcers."

By contrast one of the leading textbooks of pharmacology, that of Goodman and Gilman[4] in the section dealing with tannic acid states: "there are few if any legitimate medical uses for this substance". A review of the use of tannic acid in the treatment of burns and in barium enemas will explain its fall from favor among physicians.

A half century ago Davidson[5] introduced the use of tannic acid in burns. His method consisted of covering the burned areas with dry sterile pads which pads were then soaked with a 2.5% aqueous solution of tannic acid. This treatment was modified by Wells[6] in 1936, whereby a bath of tannic acid was prepared and the patient was immersed in it. The precise percentage of tannic acid was not considered important but enough was put in the water to give it "a good muddy appearance". The tub bath was followed by transferring the patient to a dry bed and for about 72 hours the burned areas were sprayed more or less constantly with a 5% solution of tannic acid immediately and thoroughly dried with a blower.

In 1941 Buis and Hartman[7] described the histopathology of the liver following burns. At the Henry Ford Hospital tissue examination was possible in five instances of death following superficial burns. Unfortunately deaths following burns fall under the jurisdiction of the coroner and tissue examination was limited to that which could be obtained at the usually incomplete autopsy. A brief clinical summary and the histopathological finds were presented. The gross findings merited no official comment with the exception of the extent and degree of the burned areas.

Treatment, while adapted to individual needs followed the principles as discussed in detail by McClure and Lam[8, 9, 10] and consisted of: a) combatting primary shock if present; b) adequate sedation; c) débridement--general anesthetic was not advocated; d) tanning with tannic acid jelly; e) restoration of fluid balance; f) transfusions of blood plasma and whole blood as indicated by repeated hemoglobin or hematocrit determinations; g) oxygen therapy if indicated.

Case 1. White man, age 21. Steam scald of head, neck, entire skin of lower extremities, hands, wrists, and forearms. Survived 18 hours.

Liver: Focal areas of degeneration centrally located, varying in degree from necrosis and complete dissociation of the cords to indefinite cellular detail. Diffuse infiltration of lymphocytes in the periportal areas. Small deposits of bile pigments.

Case 2. White man, age 45. First degree burn of chest and shoulders, estimated at 25 per cent of body surface, by caustic soda. Survived 90 hours.

Liver: Extreme destruction of the parenchyma; some sections could hardly be identified as liver. Only a few hepatic cells near the periphery of the lobule retained a semblance of structure. Tissue consisted for the most part of large vacuolated areas, cellular debris, pigments, phagocytic cells and some exudate. The periductal areas were infiltrated with lymphocytes and an occasional polymorphonuclear leukocyte. The cells of the small bile ducts were better preserved but also showed degenerative change. The picture was quite characteristic of a toxic

hepatitis.

Case 3. White girl, age 6. Clothing caught fire from stove. An estimated 45 per cent of body surface burned involving mainly the trunk and thighs. Treatment included cortin and immersion in a tannic acid bath. Succumbed in 50 hours.

Liver: Fairly uniform throughout. Hepatic cords intact. No evidence of necrosis. Slight decrease in intensity of stain. No proliferation of ducts or infiltration with inflammatory cells.

Case 4. White man, age 43. Fell into a pit of steaming sand up to hips with second degree burns of both legs and thighs. Survived 20 days. Icterus index varied from 60 to 80 units from the 4th to the 8th day and leveled off at 15-20.

Liver: Marked widespread degeneration of the parenchyma varying from true necrosis to congestion. Extensive vacuolization. Change not zonal in distribution. Some regeneration of the cord cells. Slight increase in periportal fibrous tissue. No increase in ducts.

Case 5. White man, age 19. Burned by flame, head, neck, hands and legs, the area was estimated at 25 per cent of body surface. Survived 90 hours. Icterus index gradually increased up to 83 on the 3rd day.

Liver: Similar to Case 2. Extensive necrosis of cord cells with only an occasional recognizable cluster of cells near the periphery of the lobule. The nuclei did not show as extensive fragmentation as the cytoplasm. Ghost outlines of sinusoids could be detected. Considerable pigment, cellular debris, and exudate. Fairly intense infiltration with

inflammatory cells, mostly lymphocytes. Slight increase in the periductal fibrous tissue which also supported many lymphocytes. No evidence of regeneration of cord cells or ducts, the latter being better preserved. In view of this a series of animal experiments was planned to determine if similar changes could be produced, two phases of which are reported here.

Normal, healthy animals, ranging from 12 to 15 kilograms in weight were shaved over the back and sides. Under adequate anesthesia the skin was exposed to a bunsen burner sufficient to cause second and third degree burns. The average time of this process was five minutes. Approximately 35 to 65 per cent of the body was burned. The burned areas was immediately covered with resorcitannol jelly, the same as that used in the clinical treatment of burns, and the animals returned to their cages. Sedation was administered as indicated (morphine sulphate), in no instance for more than 36 hours post burn. The animals had access to food and water. No other treatment was given. Daily determinations for the first five days and on alternate days thereafter were made of the erythrocyte count, hemoglobin, plasma protein, and icterus index. The animals were allowed to survive until the eschar was broken, exposing raw granulating surface, and the animals showed signs of discomfort. This period varied from 10 to 18 days.

The blood changes were those characteristically described as following burns, increased erythrocyte count, increased hemoglobin, and an immediate fall of plasma protein which gradually returned to within normal limits. The icterus index did not vary beyond normal limits in any case. There were three deaths in the series.

At autopsy there was no evidence of infection in the burned area. A thin layer of jelly-like organizing serum was present in the subcutaneous tissue. Nothing noteworthy was found in the gross examination of the viscera. The livers were uniform in appearance, the surface smooth, a dark reddish brown color, and dry. On section some blood could be expressed from the cut surface, the latter having a lightly mottled nutmeg appearance. There was no suggestion of ulceration in the stomach and duodenum.

Microscopically, the findings in the animals living a number of days and in those dying within 48 hours differed sharply. In the first group the positive findings were confined to the lungs, liver and brain. The liver showed dilatation of the sinusoids which were either empty or engorged with red blood cells. The liver cells, especially those near the center of the lobule, were correspondingly compressed and in various stages of granular and vacuolar degeneration. There was moderate congestion in the lungs, but no consolidation. The brain presented congestion of the small vessels with perivascular and pericellular edema and degeneration of cells in a few instances.

In the animals dying in 48 hours or less, all organs were congested and the kidney showed definite changes, as did also the liver, lungs and brain. In these animals the liver changes were identical with those observed in the human cases dying within a few days of the injury; that is, marked congestion of the sinusoids, extensive necrosis of the liver cells involving from one-fourth to three-fourths of the lobule, accompanied by hemorrhage. Hemorrhagic infiltration was seen in the lungs. The kidneys showed granular and vacuolar degeneration of the tubules and the brain

pericellular and perivascular edema with degeneration of the pyramidal cells of the cortex and the ganglion cells of the base.

In 1962 Wells, Humphrey and Coll[11] reported four patients of theirs who had died of "toxemia" following burns; an additional case was drawn to their attention by Milton Helpern then Assistant Medical Examiner of New York City.

The four patients who died of "toxemia" were of particular interest, and their cases were briefly presented because each one exhibited central lobular liver necrosis as an outstanding lesion or as the sole cause of death. Treatment of these patients followed the general principles laid down by Wells:[6] the employment of a tannic acid tub in which a careful débridement was done without an anesthetic, a thin, sterile tan being secured in every case; the tan was subsequently maintained by the use of a tannic acid spray, and for the most part was kept perfectly dry by a current of warm air from a commercial hair drier.

Case 1. A 17 year old boy, was admitted on July 1, 1937. Practically all his clothing had been burned off when a can of gasoline he was holding became ignited from a bystander's cigarette. The burns were estimated to involve not less than five-sixths of the entire body surface. The patient was immediately put in a tub of tannic acid solution, the loose skin removed and the hair shaved. He remained in the tub 4 1/2 hours and, after being transferred to bed, was sprayed repeatedly with a tannic acid solution and immediately dried with a commercial hair drier.

Autopsy. On microscopic examination, all organs except the liver

showed nothing but cloudy swelling and congestion. In the central two-thirds of the liver lobule, the parenchymal cells showed a granular, deep-pink-staining cytoplasm in contrast to the relatively normal cells in the peripheral area. Throughout this central zone, the nuclei were slightly enlarged, and there were numerous necrotic foci. A moderate number of mitoses were present in the peripheral zone. The sinusoids were distended with blood. There was no leukocytic infiltration.

Case 2. A 23 year old man, was admitted on August 18, 1938. An electric flash in a transformer room had ignited his clothing. The entire head, the torso to the waistline, both upper extremities and wide patches on both thighs, both anteriorly and posteriorly, were burned. The patient was put in a tub of tannic acid solution and carefully and thoroughly débrided. He remained in the tub 2 3/4 hours. This treatment was followed by repeated spraying with a tannic acid solution, which was immediately dried with a commercial hair drier. Three transfusions were given, and no gross fluid imbalance was clinically apparent until the last 24 hours of life, when edema of the lower extremities developed. About two hours before death, the patient became restless, complained of severe pain in the upper abdomen, and vomited several times. He died 96 hours after admission.

Autopsy. The liver weighed 2000 gm., and the cut surface showed a fine mottling, with hemorrhagic points. The gall bladder and biliary ducts were not unusual. No ulceration of the duodenal mucosa was found. On microscopic examination, significant histologic changes were limited to the liver. The central three-fourths of the liver lobules showed extensive

hemorrhagic necrosis, with complete disruption of the cords of liver cells. A few cells in the peripheral region were still intact, and some of these were in mitotic division. A slight diffuse infiltration of polymorphonuclear leukocytes was present throughout, together with a scattering of fat globules. There was no increase in fibrous tissue.

Case 3. A 23 year old man was admitted on April 26, 1940. An explosion of illuminating gas had resulted in burns involving the entire face and neck, upper chest, back and both arms except for the palms of the hands. The patient was immediately put in a tub of tannic acid solution, where a thorough débridement was carried out. He remained in the tub for 2 1/4 hours. After being removed, he was repeatedly sprayed with a tannic acid solution and immediately dried with a commercial hair drier.

Autopsy. The liver weighed 1240 gm., and was soft and flabby. The cut surface revealed a finely mottled red-and-yellow appearance. There was dark thick concentrated bile in a small thin-walled gall bladder. The bile ducts were not remarkable and contained thin, clear bile. Microscopic examination showed extensive central hemorrhagic necrosis involving more than three quarters of the liver lobule, with disruption of the liver cords. Only a narrow zone of intact cells remained in the peripheral areas. These cells varied markedly in size and staining reaction. Many had large nuclei, with irregularly clumped chromatin. Mitotic figures were present, some of which were bizarre forms with scattered chromosomes. Definite evidence of regeneration was not demonstrated. Fat globules were present in slight degree through the area of necrosis and in the remaining liver cells. A moderate number of polymorphonuclear leukocytes infiltrated the interstitial tissue.

Case 4. A 26 year old man, was admitted on September 18, 1940. While the patient was working under his own car, a pan of gasoline caught fire and the flames spread to his clothing. Diffuse burns involved the left side of the face, neck, chest, whole left upper extremity and the fingers of the right hand. The patient was put immediately in a tub of tannic acid solution and débrided. He remained in the tub 4 1/2 hours. This treatment was followed by repeated spraying with tannic acid solution, which was immediately dried with a commercial hair drier.

Autopsy. The liver weighed 2390 gm. There were multiple areas of subcapsular hemorrhage. The cut surface was a pale yellow brown, with small hemorrhagic areas throughout. The gall bladder and bile ducts were not remarkable. On microscopic examination almost the entire liver lobule was involved in hemorrhagic necrosis. Only in small foci in the periportal areas were intact cells present, and mitoses were infrequent. Slight diffuse leukocytic infiltration was present. Fat globules in moderated amount were noted in both necrotic and viable tissue. There was very little evidence of bile stasis.

In the case of Dr. Milton Helpern, a thirteen-month-old boy was severely scalded over the face, trunk and extremities. The local treatment was tannic acid and silver nitrate. The patient died eighty-two hours after the burn was sustained.

Autopsy. The liver weighed 340 gm. The organ was of normal shape; it was firm but showed a moderate yellow discoloration. The central parts of the lobules were red. In the central half of the lobule the liver cells

were more pale-staining than in the peripheral half. The nuclei of many liver cells were pyknotic, and some cells contained no nuclei. Some of the liver cells were eosinophilic. The liver cells in the peripheral half contained many fat vacuoles but were otherwise normal.

On review of the reported cases and particularly the proved cases coming to necropsy, the common denominator appeared to be that tannic acid had been employed in the treatment. Because it seemed to be of interest to investigate the possible role of tannic acid in the production of liver damage, a series of experiments was planned by Wells et al[11] to determine the effect of subcutaneous injections of tannic acid on the liver in rats.

Albino rats weighing 70 to 90 gm. were selected. Tannic acid (Mallinkrodt, U.S.P., fluffy) was employed. Subcutaneous injections of a 5 or 10 per cent solution of tannic acid were given in doses that did not exceed 1.5 cc at any one site, to avoid leakage and to facilitate absorption. No anesthesia was used. Rats that survived were killed on the third or fourth day. The tissues were fixed by formalin or Zenker's fluid, and suitable sections were stained with hematoxylin and eosin.

The rats were injected, usually in groups of 6, with varying amounts (0.05 to 0.40 gm.) of tannic acid in from one to eight sites over a period of forty-eight hours. Of the 77 rats injected, 8 failed to survive. Every one of the remainder showed some degree of liver damage, which, in general, varied directly with the amount of tannic acid injected and the number of injection sites employed. All other organs examined presented a normal appearance except for a slight cloudy swelling.

The liver damage produced by these injections of tannic acid solution was characterized by: necrosis of the liver cells in the central portion of the lobule; a variable zone of intact cells in the peripheral area exhibiting a granular cytoplasm and enlargement of the nuclei, with irregular clumping of hyperchromatic nuclear material; regular and bizarre mitoses, some with dispersion of chromosomes, prominent in the liver cells at the periphery or the lobule; and hemorrhage and leukocytic infiltration, which were present in minor degree in areas of necrosis.

Attention was called particularly to the fact that in these experiments the degree of liver damage varied directly with the total amount of tannic acid solution injected.

The patients in the cases presented above died largely or solely as the result of a central liver necrosis. Such a necrosis has been observed only when the patient has been treated with tannic acid. Tannic acid is no longer used in the treatment of burned patients.

In 1946 Hamilton[12] published a brief article advocating the use of tannic acid in barium enemas. He observed that better mucosal patterns on the evacuation films could be obtained by adding one level tablespoonful of powdered tannic acid to each two quart barium and water mixture prior to the administration of the enema. Results were so satisfactory that this became routine at the Army General Hospital at which he was stationed. Following this article the addition of tannic acid to barium sulfate suspensions in the roentgenographic examination of the colon was recommended by a number of authors[13, 14, 15, 16].