k. Noscapine (noscapine hydrochloride). The Panel concludes that noscapine is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) Safety. Clinical experience has confirmed that noscapine is safe in the dosage ranges used as an antitussive. Noscapine belongs to the isoquinoline alkaloids of opium and, like papaverine, has a weak spasmolytic (relieves spasm) effect on smooth muscle but little or no effect on the heart or gastrointestinal tract (Ref. 1). There is no evidence that it causes addiction, and it is not subject to the Federal Controlled Substances Act. A large margin of safety in both animals and man has been reported (Refs. 2 and 3). Nausea, drowsiness, and lightheadedness have been reported in a few instances, but this was similar to the incidence in placebo reactors (Ref. 4). Bellville et al. (Ref. 5) found no depression of respiration with doses as high as 90 mg.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of noscapine as an antitussive. Effectiveness has not been established by objective, controlled clinical trials.

For the most part, the animal studies employing a variety of methodologies for inducing cough by mechanical

and chemical means have shown noscapine to have an antitussive effect equivalent to codeine (Refs. 6, 7, and 8). Controlled studies in man using experimentally induced cough have been conflicting (Refs. 4, 9, and 10). Most of the clinical trials reported have been poorly controlled subjective studies. The majority of these studies indicate that noscapine is equal to codeine in clinical effectiveness (Refs. 3 and 11 through 15).

Unlike the narcotic antitussives, respiratory depression and constipation have not been reported for noscapine. Doses as high as 90 mg have been given with no significant increase in toxicity (Ref. 16).

(3) Proposed dosage. Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed a total of 180 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above--Category I Labeling.) In addition, the Panel recommends the following specific claims referable to its central mechanism of action and its nonnarcotic designation:

(i) Indications. (a) "Calms the cough control center and relieves coughing".

(b) "Non-narcotic cough suppressant for the temporary control of coughs".

(c) "Calms cough impulses without narcotics".

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below--Data Required for Evaluation.) The Panel recommends that one experimentally induced cough study and one controlled study in patients with cough due to respiratory illness employing objective cough-counting techniques be performed in order to establish effectiveness as an antitussive.

REFERENCES

(1) Jaffee, J. H., "Narcotic Analgesics," in "The Pharmacological Basis of Therapeutics," 3d Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan Co., New York, p. 281, 1965.

(2) Krenger, H., M. B. Eddy and M. Sumwalt, "Narcotine and its Derivatives," Public Health Reports (Supplement), 165:1053-1075, 1943.

(3) Segal, M. S., M. M. Goldstein and E. O. Attinger, "The Use of Noscapine (Narcotine) as an Antitussive Agent," Diseases of the Chest, 32:305-309, 1957.

(4) Bickerman, H. A. and A. L. Barach, "The Experimental Production of Cough in Human Subjects Induced by Citric Acid Aerosols. Preliminary Studies on the Evaluation of Antitussive Agents," American Journal of the Medical Sciences, 228:156-163, 1954.

(5) Bellville, J. W. et al., "Effect of Noscapine and Codeine on the Respiratory Response to Carbon Dioxide," Anesthesiology, 19:545-551, 1958.

(6) Winter, C. A. and L. Flataker, "Antitussive Compounds: Testing Methods and Results," Journal of Pharmacology and Experimental Therapeutics, 112:99-108, 1954.

(7) Konzett, H., "Recent Points of View in the Pharmacology of Narcotine," (English translation), "Neuere Gesichtspunkte zur Pharmakologie des Narkotins"), Wiener Klinische Wochenschrift, 67:306-309, 1955.

(8) Laßarre, J. and H. Plisnier, "Antitussive and Bronchodilator Properties of Narcotine Hydrochloride," (English translation), ("A Propos des Proprietes Antitussigenes et Bronchodilatatrices du Chlorhydrate de Narcotine"), Archives Internationales de Pharmacodynamie et de Therapie, 119:205-213, 1959.

(9) Bickerman, H. A. et al., "The Cough Response of Healthy Human Subjects Stimulated by Citric Acid Aerosol, Part II: Evaluation of Antitussive Agents," American Journal of the Medical Sciences, 234:191-205, 1957.

(10) Eddy, N. B., H. Friebel, K. J. Hahn and H. Halbach, "Codeine and Its Alternates for Pain and Cough Relief. 4. Potential Alternates for Cough Relief," Bulletin of the World Health Organization, 40:639-719, 1969.

(11) Janschulte, B., "Experience with Narcompren, a New Antitussive," (English translation), ("Erfahrungen mit Narcompren, einem neuen Hustenmittel"), Medizinische Klinik, 42:1788-1789, 1955.

(12) Peeters, E. G. "Antitussive Properties of Noscapine," (English translation), ("Les Proprietes Antitussives de la Noscapine"), Le Scalpel, 114:945-954, 1961.

(13) General Practitioner Research Group, Report #21, "General Practitioner Clinical Trials. A Long Acting Antitussive Preparation," The Practitioner, 188:249-252, 1962.

(14) Bergmann, M. and H. Stolzer, "Clinical Experience with Narcotine as a Cough Suppressant," (English translation), ("Klinische Erfahrungen mit 'Narkotin' als hustenreizstillendes Mittel"), Wiener Medizinische Wochenschrift, 106:232-233, 1956.

(15) Blankart, R., "Clinical Experience with an Antitussive Containing Narcotine," (English Translation), ("Klinische Erfahrungen mit einem narcotinhaltigen Hustenmittel") Therapeutische Umschau, 20:403-406, 1963.

(16) Barasz, Z. et al, "The Comparative Antitussive Effect of Noscapine Hydrochloride and Dihydrocodeine Bitartrate," (English translation), ("Effet Antitussif Compare du Chlorhydrate de Noscapine et du Bitartrate de Dihydrocodeine"), Praxis, 12:317-319, 1962.

1. Thymol (topical/inhalant). The Panel concludes that thymol is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) Safety. Clinical experience has confirmed that thymol (topical/inhalant) is safe in the dosage ranges used as an antitussive.

Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal and anthelmintic properties (Ref. 1). When hydrogenated, thymol is converted to the closely related drug, menthol (Ref. 2). The LD_{50} of thymol in mice is 1800 mg/kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymol's relative inactivity compared to menthol, of which 50 to 120 gm "would have to be absorbed to cause poisoning" (Ref. 4), thymol is presumably relatively nontoxic.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of thymol (topical/inhalant) as an antitussive. Experiments in anesthetized rabbits have indicated that thymol administered by steam inhalation augmented the concentration of soluble mucous in the respiratory tract fluid (Ref. 2). The dose administered was unknown but the concentration in the vaporizer was in excess of 81 mg/kg. The volume of secretions did not change. Much lower concentrations of

menthol were effective (1 mg/kg). In man no data on effectiveness of thymol alone were found although a mixture containing thymol, menthol, eucalyptol and propylene glycol appeared to suppress citric acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the antitussive activity of thymol were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8 and 9), and in steam inhalations (Refs. 10 and 11). Although significant antitussive activity as compared to placebo was demonstrated, it was not evident whether the thymol component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term, double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder cough symptoms in individuals using the medicated mouthwash as compared to placebo. Although the medicated mouthwash contained 0.63 mg/ml thymol the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 0.1 percent preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For inhalation use as a 0.13 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 0.1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at 1/2 to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour.

(v) For use as a mouthwash 0.63 mg/ml solution: Gargle with 2/3 oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above--Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth".

(5) Evaluation. The Panel made the following recommendations: (i) For topical use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below--Data Required for Evaluation.)

(ii) For inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below--Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below--Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below--Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) "The Pharmacological Basis of Therapeutics," 3d. Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, p. 1027, 1965.

(2) Boyd, E. M. and E. P. Sheppard, "A Bronchomucotropic Action in Rabbits From Inhaled Menthol and Thymol," Archives Internationales de Pharmacodynamie et de Therapie, 182:206-214, 1969.

(3) Summary of Animal Safety Data is included in OTC Volume 040298.

(4) Leiber, B., "Menthol - A Critical Stock Taking," (English Summary), ("Menthol - eine kritische Bestandsaufnahme"), in "Menthol and Menthol-Containing External Remedies," Edited by Dost, F. H. and B. Leiber, Georg Thieme Verlag, Stuttgart, Germany, pp. 30-31, 1967.

(5) Calesnick, B., J. A. Christensen, G. Hoff and G. Weintrub," Antitussive Effect of Aerosolized Medication on Experimentally Induced Cough in Man," Clinical Medicine, 71:1938-1944, 1964.

(6) Letter to Beckley, J. H. from M. S. Sadove is included in OTC Volume 040298.

(7) Blanchard, C. L., S. J. Borsanyi and T. C. Grubb, "Evaluation of Nasal Decongestant Drugs," The Eye, Ear, Nose and Throat Monthly, 43:76-82, 1964.

(8) Stamos, E., "Vaporub. Nasal Decongestant Study: Vick Rhinorheometer. CRD 71-1," Draft of unpublished data is included in OTC Volume 040298.

(9) Carter, V. H., "Vaporub. Nasal Decongestant Study - Vick Rhinorheometer. CRD 72-7," Draft of unpublished data is included in OTC Volume 040298.

(10) Shapiro, M., "Steam Alone vs. Vaposteam in Steam," Draft of unpublished data is included in OTC Volume 040298.

(11) Ciampi, L. A. "Vaposteam. Nasal Decongestant Vick Rhinorheometer. CRD 71-5," Draft of unpublished data is included in OTC Volume 040298.

(12) OTC Volume 040278.

m. Turpentine oil (spirits of turpentine) (topical/inhalant). The Panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) Safety. Clinical experience has confirmed that turpentine oil is safe when applied topically or used as an inhalant in the dosage ranges used as an antitussive. The Panel concludes that oil of turpentine is safe when applied externally or vaprized in boiling water as a steam inhalant. However, the Panel has determined elsewhere in this document that it is not safe for OTC use when used orally as an antitussive. (See part III. paragraph B.2.b. above--Turpentine oil (spirits of turpentine) (oral).)

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from Pinus palustrus. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4).

Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway, resistance, or compliance (Ref. 5). One study in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold" no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years with approximately two complaints per million packages purchased (Ref. 14).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of turpentine oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to a lack of properly controlled studies of the substance by itself.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may

be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

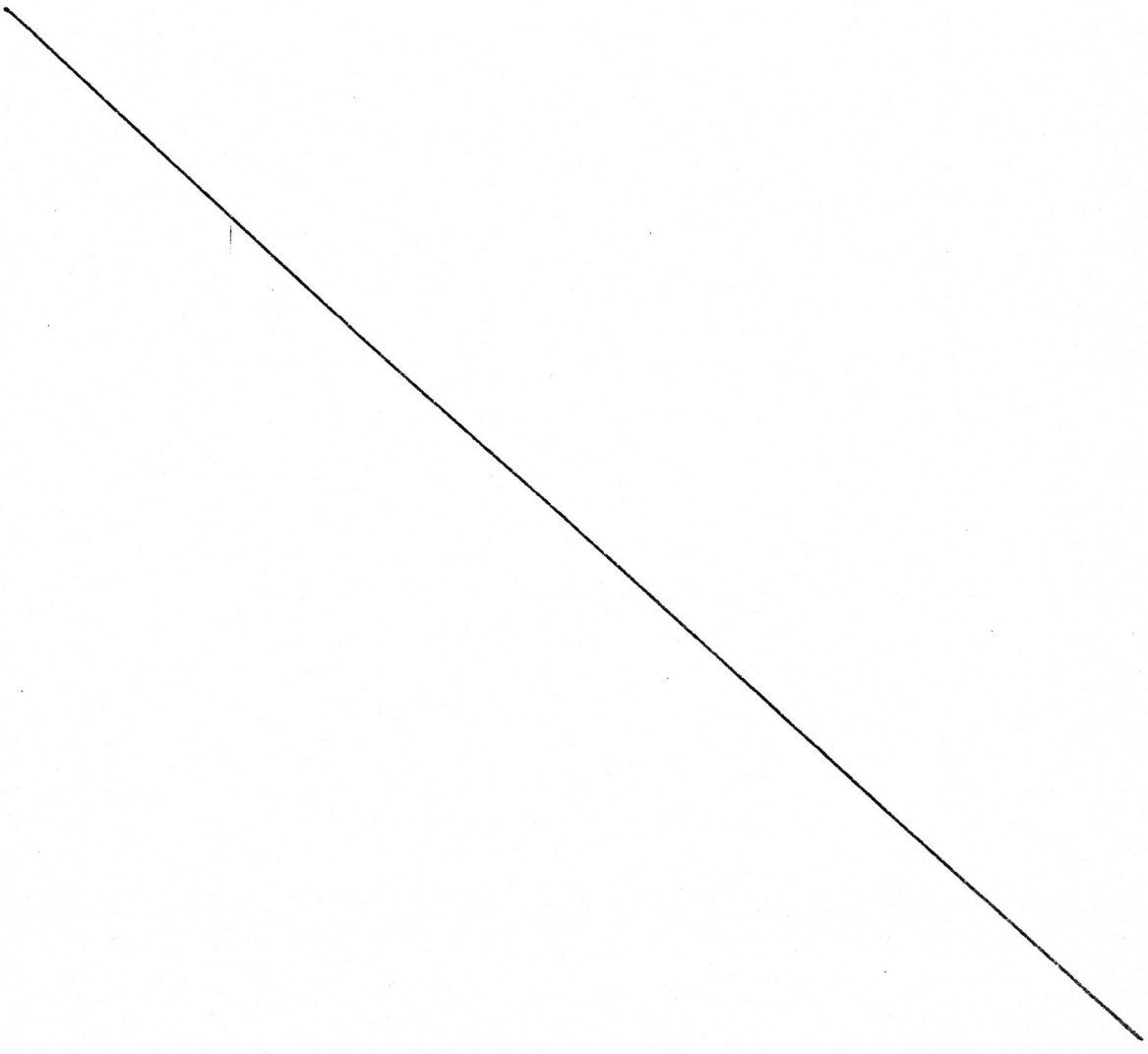
(4) Labeling. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B. 1. above--Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth".

(5) Evaluation. The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below--Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below--Data Required for Evaluation.)



REFERENCES

(1) Nelson, K. W. et al., "Sensory Response to Certain Industrial Solvent Vapors," Journal of Industrial Hygiene Toxicology, 25:282-285, 1943.

(2) Memo to Hoffnagle, G. F. from A. R. Blanchette, "Vaporub--Levels of Aromatics from a Vaporizer," is included in OTC Volume 040298.

(3) Memo to Those Concerned, from A. F. Summa, "Vaposteam--Vaporizer Testing Program," is included in OTC Volume 040298.

(4) Sperling, F., W. T. Allcercus and C. Collins, "Acute Effects of Turpentine Vapor on Rats and Mice," Toxicology and Applied Pharmacology, 10:8-20, 1967.

(5) Watanabe, T., and D. M. Aviado, "Cardiopulmonary Effects of Turpentine in Mice," Draft of unpublished data is included in OTC Volume 040298.

(6) Huber, G. L., "Speaking Manuscript: Vicks Paper," Draft of speech is included in OTC Volume 040298.

(7) Jakab, G. J. and G. M. Green, "The Effect of the Vapors of a Commonly Used Remedy for Colds on Pulmonary Antibacterial Defenses," Chest, 68:389-390, 1975.

(8) Goldstein, E. A., D. Cooper and B. Tarkington, "Effect of Inhaling Medication Vapors from a Colds Preparation on Murine Pulmonary Bacterial Defense Systems," Draft of unpublished data is included in OTC Volume 040298.

(9) Larkin, V. D., "Efficacy and Safety of Vaposteam Liquid," Draft of unpublished data is included in OTC Volume 040298.

(10) Litchfield, H. R., "Efficacy and Safety of Vaposteam Liquid," Draft of unpublished data is included in OTC Volume 040298.

(11) Ghadini, H., "Broad Clinical Effectiveness and Safety CRD #70-34," Draft of unpublished data is included in OTC Volume 040298.

(12) Larkin, V. D., "Evaluation of Vaporub in a Vaporizer," Draft of unpublished data is included in OTC Volume 040298.

(13) Larkin, V. D., "VAPORUB in Hot Water," Draft of unpublished data is included in OTC Volume 040298.

(14) OTC Volume 040279.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antitussives. The Panel concludes that certain words used in the context of claims for antitussives are statements which have no scientific meaning and therefore are misleading to the consumer. Additional data are required to support the following antitussive claims:

a. The term "soothing" in labeling such as "Calms coughing by soothing the irritated throat".

b. The term "throat soothing" in labeling such as "Throat soothing and recommended for coughs due to colds and dry, husky or tickling throats".

c. The term "smooth coating" in labeling such as "Produces a smooth coating that gives quick comfort to irritated throats and helps relieve coughs".

d. The terms "demulcent action" and "soothes" in labeling such as "Demulcent action which gently sooths cough-irritated throat membranes".

e. Statements referring to "duration of action" unless there is acceptable documentation to verify this.

f. Terms relating to sleep such as "Quiets annoying cough and lets you sleep". An antitussive is capable of quieting annoying cough, but has not been demonstrated to be directly related to sleep.

g. The term "soothing" has not been scientifically demonstrated to have an antitussive effect. In fact, none of the antitussive ingredients reviewed by the Panel have any "soothing" properties since the Panel cannot determine what such a property would be. The same is true for the term "smooth". Again, the Panel is unaware of how the ingredients act to smooth an irritated throat or sooth membranes by a "demulcent" action.

C. Data Required for Evaluation.

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. Principles in the design of an experimental protocol for testing antitussive drugs. a. General principles. The effectiveness of an antitussive agent is dependent on its ability to relieve the coughing of patients with a variety of disease conditions associated with cough. Relief of coughing may occur with a reduction in the frequency or number of coughs, or with a decrease in the intensity of the coughing, or both. Because coughing is such a common symptom occurring in health as well as disease, adaptation readily occurs to the extent that many patients are unaware of the extent of their coughing, and hence any subjective evaluation is apt to be highly variable and with an unacceptable margin for error. Objective studies employing the actual recording of the cough are required to document a decrease in cough frequency and/or intensity.

b. Selection of patients. The study design will depend on whether the patients in the study have chronic lung disease or acute self-limiting illnesses. For a cough study in patients with chronic lung disease, a crossover design could be used in a small group of 10 to 20 patients whose underlying chronic pulmonary disease is relatively stable so that daily fluctations in the recorded cough counts performed prior to drug administration are minimized. The smoking habit of the patients must be carefully documented and maintained at the same level throughout the clinical trials. No smoking would be permitted during the actual recording sessions. For a cough study in patients with acute upper respiratory infection, a larger number of patients, averaging between 50 and 100, would have to be studied because of the marked variation in cough from day to day and hour to hour in upper respiratory infection. The patients would have to be assigned in a randomized design to either the placebo or drug groups. The sensitivity of this type of study could be improved by matching the groups for age, sex, severity of cough, and smoking habit.

c. Methods of study. To establish effectiveness of a drug as an antitussive, objective controlled studies employing cough-counting techniques are recommended. Two types of investigation are acceptable to the Panel. These are:

(1) A study may be done in a small group of healthy volunteers, approximately 10 to 20 in number, who are preferably nonsmokers. If smokers are included, their smoking habits must be well documented and remain at the same level during the entire course of the study. Any departure from smoking habits must be documented and made part of the evaluation of data. The data obtained in such a study including smokers and nonsmokers should be evaluated separately before combined. A challenge technique employing an irritant aerosol such as citric acid is used to assess effectiveness, dose, and time responses against the experimentally induced cough. This is performed under controlled laboratory conditions with a double-blind or suitably blinded, crossover design in suitably trained individuals.

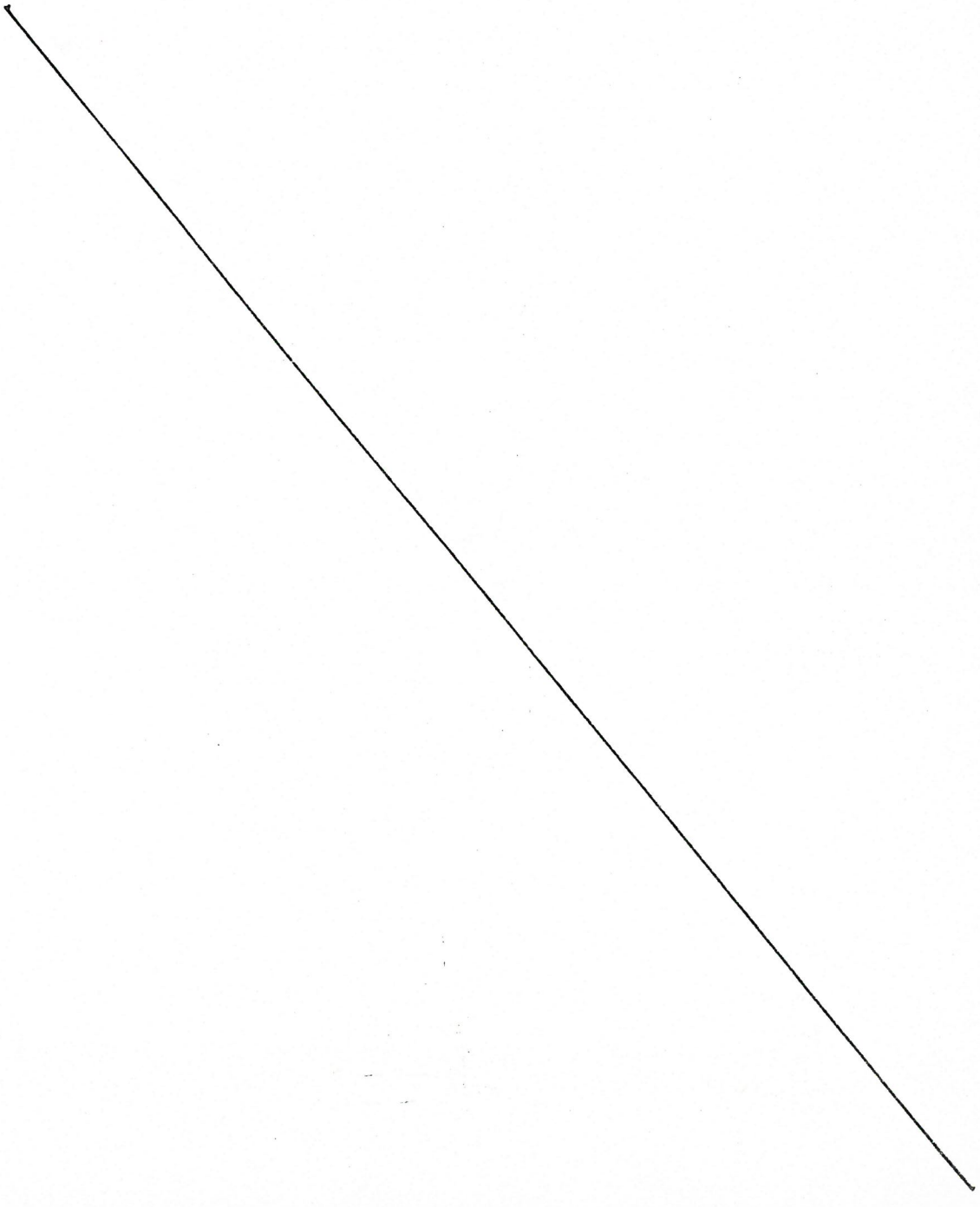
(2) A double-blind, controlled study may be done in patients with cough due to respiratory disease. The dose and formulation of the drug to be tested would be as recommended for OTC use. Coughs are recorded and counted for stated periods before and after giving the drug or placebo so that adequate comparisons can be made concerning the onset and duration of antitussive activity following a single dose,

as well as the effect of multiple doses. As a model for OTC drugs, however, the requirement for long periods of testing would be unnecessary since effective relief should be obtained fairly rapidly and, in most instances, after 1 or, at most, 2 days.

d. Interpretation of data. Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories. All of the required studies in man should employ objective cough-counting techniques for recording the cough reflex. In the reevaluation of those drugs for which there was insufficient evidence of antitussive effectiveness and for the assessment of drugs that have not been submitted for review by the Panel, the two required studies should consist of either one challenge study with experimentally induced cough plus a study with cough in respiratory disease, or, alternatively, two studies by different investigators in patients with respiratory disease. A significant reduction in cough when compared with placebo by acceptable statistical analysis of the data will permit re-classification of such drugs into Category I.

All data submitted to the Food and Drug Administration must present both favorable and unfavorable results.

e. Evaluation of safety. Tests for safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.



IV. EXPECTORANTS

A. General Discussion.

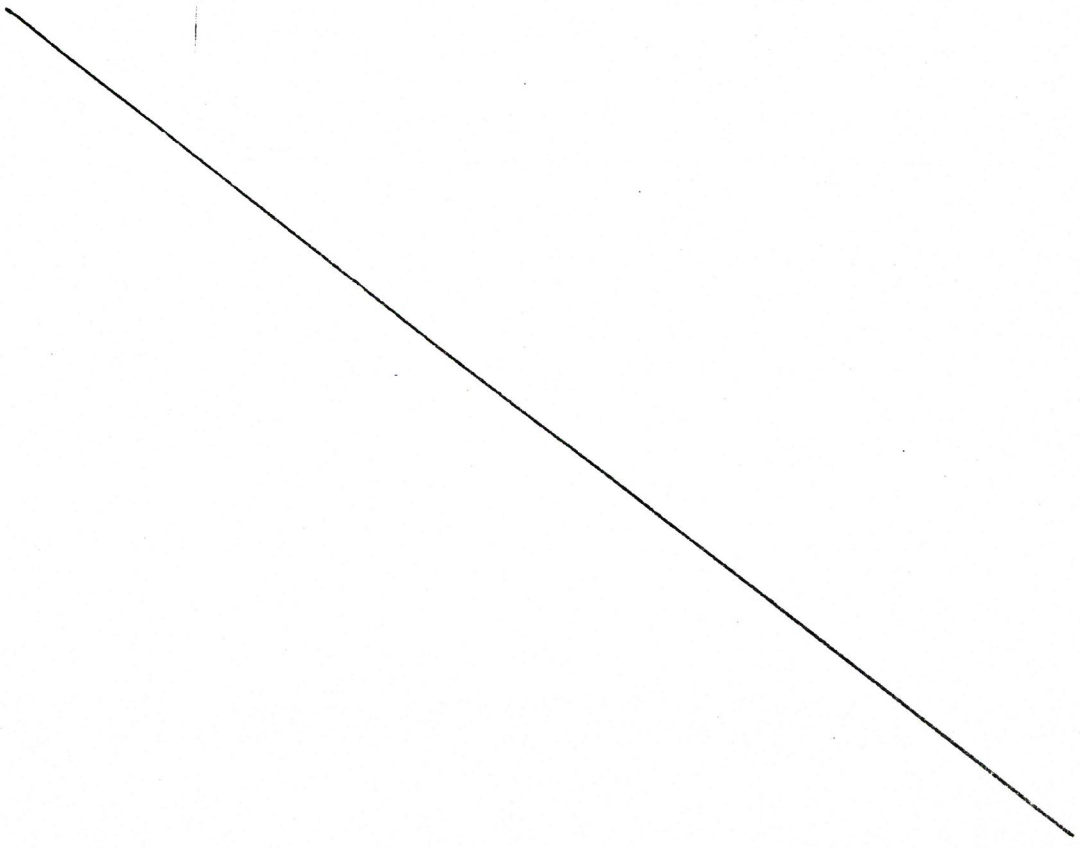
Expectorants are agents that are used to promote or facilitate the evacuation of secretions from the bronchial airways to provide for the temporary relief of coughs due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The secretions (sputum or phlegm) expectorated consists in part of respiratory tract fluids (RTF) together with a varying mixture of saliva and postnasal secretions.

In general, the mechanisms of action of the expectorants have been shown to be due to one or more of the following: The stimulation of reflexes from the stomach (the major action of certain drugs that are irritants to the gastrointestinal tract and act through their nauseant effect which increases the output from the secretory glands of the gastrointestinal as well as the respiratory tracts); stimulation of vagal nerve endings in the glands of the bronchial tubes; direct effect on the secretory cells lining the airway when administered by inhalation or if excreted by the respiratory tract; and stimulation of centers in the brain such as the vomiting center.

By facilitating the evacuation of secretions from the bronchial airway, local irritants are removed. In addition, by increasing the amount of mucous that covers and protects the lining of the throat and the bronchial airway, it is claimed that a "soothing" or "demulcent" action is exerted which relieves irritated membranes in the respiratory passages. While these effects may indirectly serve to diminish the tendency to cough, the mechanism of this indirect action is quite different from that of an antitussive which is specifically designed to inhibit or suppress cough. Any claim relating to the amelioration of cough must be supported by the type of studies suggested above for evaluation of antitussives. (See part III. paragraph C. above--Data Required for Evaluation.) Expectorants would be expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions.

As a group, the expectorant drugs have been widely used for many decades in the form of liquid preparatons. By and large, in the dosages used for OTC administration, these drugs have had a good safety record. The few exceptions, where hypersensitivity reactions or cumulative toxicity

represents a distinct hazard, have been discussed under the individual sections. While the expectorants have been traditionally used for their effect on aiding in the expectoration of phlegm (sputum) and thus relieving certain aspects of difficulty in breathing, there is little or no evidence to document this. In summary, the Panel concludes that while many of the expectorants on the market with long usage are generally safe, most lack evidence of efficacy and furthermore, all expectorants must be clearly identified on the labels of drug products as having a primary effect on respiratory sputum and not primarily as an antitussive.



B. Categorization of Data.

1. Category I conditions under which expectorant ingredients are generally recognized as safe and effective and are not misbranded.

Category I Active Ingredient

The Panel was unable to classify a claimed expectorant active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for expectorant active ingredients to be generally recognized as safe and effective and not misbranded:

a. Indications. (1) "Helps loosen phlegm (sputum)".

(2) "Helps rid the passageways of bothersome mucus".

(3) "Expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(4) "Helps drainage of the bronchial tubes by thinning the mucus".

(5) "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow".

b. Warnings. (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) "Caution: A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

2. Category II conditions under which expectorant ingredients are not generally recognized as safe and effective or are misbranded. The use of expectorants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following expectorant active ingredients as not generally recognized as safe and effective or as misbranded:

Antimony potassium tartrate

Chloroform

Iodides

Calcium iodide anhydrous

Hydriodic acid syrup

Iodized lime

Potassium iodide

Ipecac fluidextract

Squill preparations

Squill

Squill extract

Turpentine oil (spirits of turpentine) (oral)

a. Antimony potassium tartrate. The Panel concludes that antimony potassium tartrate is not safe for OTC use as an expectorant.

(1) Safety. Antimony potassium tartrate is not safe in the dosage range used as an expectorant.

The trivalent salts of antimony are potent inducers of vomiting; they act on centers in the brain as well as locally on the stomach walls. Because the antimony ingredient in this preparation tends to accumulate in the body and not to be excreted in a manner similar to arsenic, the danger of toxic reactions increases with repetitive or chronic use. These toxic reactions consist of marked irritation of the stomach and intestinal mucosa. Pain in joints and muscles are common, and the muscles of the heart may be depressed. Abdominal pain, rash and vascular collapse as well as a number of cases of hemolytic anemia, some fatal, have been reported (Ref. 1). Such toxic effects have been seen with the use of the trivalent compound at higher doses for the treatment of helminthic infections; but even in doses

suitable for expectorant activity, antimony potassium tartrate is considered too toxic because of its cumulative properties to be used as an OTC product (Ref. 1).

(2) Effectiveness. There is no evidence that antimony potassium tartrate is effective as an expectorant.

When administered in subemetic doses, antimony potassium tartrate theoretically exerts its expectorant activity through reflex stimulation of the salivary and bronchial glands (Ref. 2). There is, however, not one documented study in either animals or man demonstrating its effect on cough, sputum production or respiratory tract secretions (Ref. 3).

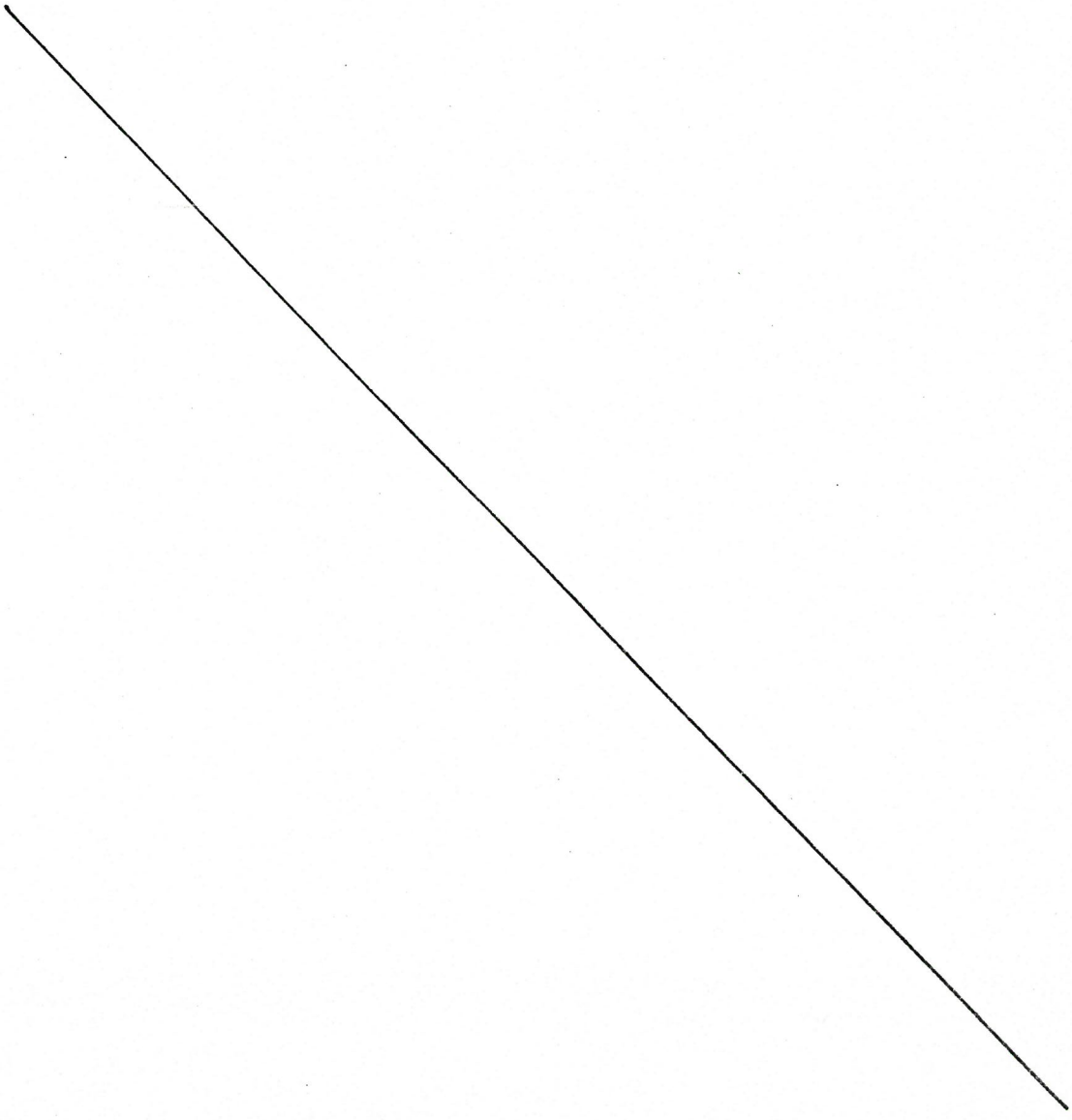
(3) Evaluation. Because of its toxicity and tendency to accumulate in the body, the Panel is of the opinion that even subemetic doses present risks which outweigh whatever benefit theoretically might occur since there is no evidence to support effectiveness.

REFERENCES

(1) Harvey, S. C., "Heavy Metals," in "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan Publishing Co., Inc., pp. 928-930, 1975.

(2) "Drill's Pharmacology in Medicine," 2d Ed., Edited by DiPalma, J. R., McGraw-Hill, New York, p. 689, 1958.

(3) OTC Volume 040190.



b. Chloroform. The Panel concludes that chloroform is not effective for OTC use as an expectorant. The Panel is aware that the safety of chloroform is being questioned at present and has therefore limited its use only as a flavoring agent in CCABA preparations.

(1) Safety. The Panel concludes that the question of safety is dependent on dosage and abuse potential.

In doses of 4 to 8 ml orally, chloroform has been known to produce a narcotism similar to that occurring when administered by inhalation but developing more slowly and of longer duration (Ref. 1). The mean lethal dose by ingestion is approximately 30 ml (Ref. 2), although as little as a teaspoonful has produced serious illness. Symptoms of toxicity due to chloroform ingestion are often delayed for 2 or more days (Ref. 3). The problem of abuse at a "chloroform party" has recently been reported (Ref. 4).

Three documents concerning the safety of chloroform were submitted to the Panel for review and appropriate action. These pertained to the possible carcinogenicity of chloroform (Refs. 5 and 6) and the acute toxicity of chloroform in rats with an extrapolation to a suggested "maximum permissible limit" in humans (Ref. 7).

The first document was a review of a report by Harris on the implications of cancer causing substances in Mississippi River water (Ref. 5). A detailed analysis of the epidemiological data, presented

together with a review of the statistical methods and the animal studies, is reported in full in the minutes of the 17th meeting of the Panel, Appendix 9 (Ref. 8). The Panel recognizes that there are serious inconsistencies in the report which makes the extrapolation of the data to possible risks of cancer from chloroform in drinking water unacceptable. Furthermore, the evidence of carcinogenicity in mice is conflicting and inconclusive and its extrapolation to another species, man, is open to serious question. Accordingly, the Panel concludes that for the report pertaining to the possibility of chloroform being a carcinogen in drinking water there is no evidence to support this possible carcinogenic hazard in the recommended dosages. This view is supported by an ad hoc Study Group on "Assessment of Health Risk from Organics in Drinking Water" in their report to the Hazardous Materials Advisory Committee of the Environmental Protection Agency (Ref. 9).

The second document (Ref. 7) attempts to establish some guidelines on permissible limits of solvent residues in chemicals. The authors list the obvious limitations of their study, i.e., the difficulty of extrapolating from rat to man; an acute single dose study does not provide an answer regarding the effect of chronic exposure; and the questionable use of arbitrary conversion factors that have no scientific basis. Their revised figure for the permissible limit for chloroform

is 0.25 ml/60 kg. The Panel's recommended concentration of 0.4 percent by volume is therefore well within the authors' suggested permissible limit. The Panel recommends that chloroform be available only as a flavoring agent at a maximum concentration of 0.4 percent which represents 0.004 ml/ml or 0.02 ml/5 ml (teaspoon) of a product dosage. This is well within their revised permissible limit of 0.25 ml/60 kg of body weight.

The third document is a preliminary report from the National Cancer Institute entitled, "Report on Carcinogenesis Bioassay of Chloroform" dated February 1976 (Ref. 6). The protocol consisted of a total of 400 rats and mice with suitable control animals receiving daily doses of chloroform orally for a total of 546 days. The treated animals were divided into low and high dose groups.

For rats, the results of the study showed a decreased survival rate which appeared dose related. Clinical evidence of toxicity appeared during the first 10 weeks but became more apparent during the second year of the study. The control groups also showed these signs by the 70th week. Transient palpable nodules were noted in both test and control groups by the end of the second year. The

incidence of "all tumors" in both treated and control rats did not differ. Significant differences from control groups occurred with kidney tumors in male rats which appeared dose related and thyroid tumors in the female rats but the thyroid tumors were not considered relevant to the study because of the known incidence of spontaneously occurring thyroid tumors in this strain of rat. Neoplastic nodules of the liver occurred with equal frequency in test and matched controls (5 percent). Necrosis of hepatic parenchyma occurred with slightly greater frequency in the chloroform-treated rats.

For mice, results of the study showed that there was no significant differences in survival rate between the controls and treated mice except for the high dose female group. Beginning after 42 weeks of treatment, the chloroform-treated mice began to exhibit a bloated appearance with abdominal distention. The incidence of "all tumors" in the treated groups was significantly higher, and this was solely due to the presence of hepatocellular cancer.

The conclusions to be drawn from this study are that orally administered chloroform can produce hepatic neoplasms in this strain of mice when administered at these levels and for a prolonged period of time. There was a less striking correlation of kidney tumors with

chloroform ingestion in the rat species. But the lack of any increase in hepatic tumors in the rats or kidney tumors in the mice is attributed by the authors as illustrating "species differences in organ specificity and sensitivity." The Panel questions whether this then can be extrapolated to other species such as dog or man.

The Panel has considered the dosage of chloroform administered in the study. The average 400-gm rat received 36 to 80 mg/day for 546 days or a total of 19.656 to 43.680 gm. The average 30-gm mouse received 4 to 14 mg/day for 546 days or a total of 2.184 to 7.644 gm. In terms of an average 60-kg human, the equivalent doses would be 5.4 to 12.0 gm/day or a total of 2,984.4 to 6,552 gm for 546 days. If the mouse dosage is extrapolated, the human dose would be 8.0 to 28.0 gm/day or a total of 4,368 to 15,288 gm. The Panel finds that the use of chloroform as a flavoring agent at a maximum allowable concentration of 0.4 percent or 0.4 gm/100 ml would require the consumption of 1.35 to 7 liters/day for a total of 737.1 to 8,822 liters in 546 days. If the usual cough mixture is dispensed in a 120 ml bottle, this would represent the consumption of 31,850 bottles in a 2-year period. The Panel questions how many other drugs, food stuffs, flavoring agents, etc. would be toxic or even carcinogenic at these levels.

In the final analysis, the Panel is unable to determine from the available data the lack of safety of chloroform in man at the 0.4 percent concentration proposed for use as a flavoring agent. Obviously, there is a dose-response relationship with respect to toxicity and the potential for abuse exists just as with alcohol.

(2) Effectiveness. There is no evidence that chloroform is effective as an expectorant or that it ameliorates cough.

There is no documentation of the expectorant activity of chloroform. One report (Ref. 9) states that it is "probably harmless as well as useless in the dosages used." The U. S. Dispensatory reports that chloroform has been added to cough mixtures as a respiratory sedative, but its action is too fleeting to be of any great value (Ref. 1). Remington's Practice of Pharmacy (Ref. 10) classifies chloroform as a pharmaceutical necessity.

(3) Evaluation. The Panel concludes that chloroform should be restricted to use as a flavoring agent (pharmaceutical necessity) in amounts not to exceed 0.4 percent by volume in an OTC CCABA product.

REFERENCES

(1) "The United States Dispensatory," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 291, 1972.

(2) "Clinical Toxicology of Commercial Products, Acute Poisoning," 3d Ed., Edited by Gleason, M. N., R. E. Gosselin, H. C. Hodge and R. P. Smith, Williams & Wilkins Co., Baltimore, p. 36, 1969.

(3) Schroeder, H. G., "Acute and Delayed Chloroform Poisoning. A Case Report," British Journal of Anaesthesiology, 37:972-975, 1965.

(4) Schneck, J. M., "Chloroform Inhalation," Journal of the American Medical Association, 226:465, 1973.

(5) Harris, R. H., "The Implications of Cancer Causing Substances in Mississippi River Water," The Environmental Defense Fund, Washington, D.C., 1974.

(6) OTC Volume 040338.

(7) Kimura, E. T., D. M. Ebert and P. W. Dodge, "Acute Toxicity and Limits of Solvent Residue for Sixteen Organic Solvents," Toxicology and Applied Pharmacology, 19:699-704, 1971.

(8) Summary Minutes of the OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Advisory Panel is included in OTC Volume 040298.

(9) "Assessment of Health Risk from Organics in Drinking Water," Ad Hoc Study Group to the Hazardous Materials Advisory Committee, Environmental Protection Agency, 1975.

(10) Richerson, H. B., "Expectorants," Journal of the Iowa Medical Society, 58:875-876, 1968.

(11) "Remington's Practice of Pharmacy," 12th Ed., Edited by Martin, E. W. et al., Mack Publishing Co., Easton, PA, p. 1322, 1961.

c. Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide). The Panel concludes that the iodides are neither safe nor effective for OTC use as expectorants.

(1) Safety. At a dosage that may be effective, iodides are not considered safe as OTC preparations.

The action and toxic effects of these compounds are due to the iodide content. The iodides are readily absorbed from the gastrointestinal tract and concentrated primarily in the secretions of the respiratory tract. The Panel is unaware of any animal studies on the safety of the iodides. There are no controlled studies on short-term use of iodides as expectorants. The incidence of side effects and toxicities are directly proportional to the dose and duration of therapy, and practically all persons continually treated with high doses will manifest symptoms of iodism which may simulate the symptoms of the "common cold". Some individuals, though not frequently, are highly sensitive to iodides and will react to the first few doses with serious consequences (Ref. 1). The clinical experience with iodides has been mostly in the treatment of chronic

diseases, such as bronchial asthma, chronic bronchitis, bronchiectasis and emphysema; therefore, most of the toxicity has been related to chronic administration. The effective dose is 900 mg daily in divided doses (Refs. 2 and 3). Leonardy (Ref. 4) estimates the optimal dose at 25 to 35 mg/kg daily in divided doses. At these doses, there is a high incidence of toxic effects varying in seriousness from mild iodism to generalized papulovescicular eruptions, hypothyroidism, edema of the glottis, submandibular adenitis (Ref. 1), and iodide fever (Ref. 5).

Murray and Stewart (Ref. 6) reported two cases of iodide goiter and found at least 170 cases in the literature as well as several other cases through personal communications. Carswell, Kerr and Hutchison (Ref. 7) reported iodide-induced goiters in the fetuses of pregnant women. Two cases of neonatal death apparently due to congenital goiter caused by iodides compressing the trachea are reported by Galina, Avnet and Einhorn (Ref. 8). Continued heavy use in children and adults may produce goiter and/or hypothyroidism (Refs. 9 and 10). The Medical Letter (Ref. 11) discusses the hazards of drug-induced goiters and cites iodides as the most frequent cause. The blood levels needed to induce goiter

could not be established. Falliers et al. (Ref. 2), in a double-blind crossover study of 52 asthmatic children, found a high incidence of adverse effects. One child could not complete the study because of the development of a severe generalized papulovesicular eruption. Sixteen adolescents developed acne-form lesions. Eighteen showed thyroid enlargement but no evidence of suppressed thyroid functions. Leonardy (Ref. 4), in discussing the use of iodides in the treatment of bronchial asthma, cites a review by Peacock and Davison (Ref. 12) of 500 cases in which 13.5 percent of patients receiving iodides had sufficient side effects to warrant discontinuing the drug.

There is a wide variety of diseases which contra-indicate the use of iodides or require caution that the consumer does not have the expertise to determine, such as hypersensitivity to iodides, thyroid disease, psoriasis (Refs. 3 and 13) and various types of dermatoses.

Because of the high incidence of untoward effects and the potential for toxicity, iodides should be used only under the advice and supervision of a physician.

(2) Effectiveness. Iodides may be effective as an expectorant when given in adequate doses in some chronic respiratory disease. There is no evidence that they are efficacious in acute upper respiratory infections.

Animal studies have demonstrated the presence of iodides in the respiratory tract fluid (RTF) and an increase in the amount of RTF or a decrease in its viscosity (Refs. 14 and 15). Numerous investigators have reported observations on the expectorant action of iodides (Ref. 14). Many cite the rapid appearance of iodides in the RTF after the administration (Refs. 16, 17, and 18). The mechanism of the action of iodides as expectorants is not clear. Their presence in the RTF does not necessarily indicate increased amounts of RTF or decreased viscosity. It has been suggested by Lieberman and Kurnick (Ref. 19) that the iodides may liquefy purulent sputum by inducing the enzymatic hydrolysis of proteins. In asthmatics, no consistent change in viscosity resulting from iodides was reported by Leonardy (Ref. 4), citing as evidence a number of studies. Hirsh et al. (Ref. 20), using a new technique to measure viscosity, have been able to obtain

consistent and reproducible results, but no final answer is yet available.

Falliers et al. (Ref. 2), in a 3-year double-blind study of 52 children with chronic asthma, demonstrated a statistically significant improvement in the children receiving potassium iodide 300 mg 3 times daily. The population receiving iodides improved but there was a wide variability in the response of the individuals in the study, and there is no answer as to why. It may be due to some other property than that of its expectorant property.

While the iodides are possibly expectorants, there are insufficient studies to confirm this. This would suggest the need for more controlled studies and better techniques for evaluation of the action of iodides.

(3) Evaluation. The Panel concludes that iodides are not safe for OTC use. Because of the wide variety of diseases which contraindicate their use and because of the potential for toxicity and untoward effects, iodides should be used only under the advice and supervision of a physician.

REFERENCES

(1) Harden, R. McG., "Submandibular Adenitis Due to Iodide Administration," British Medical Journal, 1:160-161, 1968.

(2) Falliers, C. J. et al., "Controlled Study of Iodotherapy for Childhood Asthma," Journal of Allergy, 38:183-192, 1966.

(3) Shelley, W. B., "Generalized Pustular Psoriasis Induced by Potassium Iodide," Journal of the American Medical Association, 201:1009-1014, 1967.

(4) Leonardy, J. G., "The Use of Iodides in Bronchial Asthma," Southern Medical Journal, 61:959-962, 1968.

(5) Steffen, G. E., "Iodide Fever," Journal of the American Medical Association, 192:571-572, 1965.

(6) Murray, I. P. C. and R. D. H. Stewart, "Iodide Goitre," The Lancet, 1:922-926, 1967.

(7) Carswell, F., M. M. Kerr and J. H. Hutchison, "Congenital Goitre and Hypothyroidism Produced by Maternal Ingestion of Iodides," The Lancet, 1:1241-1243, 1970.

(8) Galina, M. P., N. L. Avnet and A. Einhorn, "Iodides During Pregnancy," The New England Journal of Medicine, 267:1124-1127, 1962.

(9) Chapman, R. S. and R. A. Main, "Diffuse Thinning of Hair in Iodide-Induced Hypothyroidism," British Journal of Dermatology, 79:103-105, 1967.

(10) Begg, T. B. and R. Hall, "Iodide Goitre and Hypothyroidism," Quarterly Journal of Medicine, 32:351-362, 1963.

(11) Anon., "Drug-Induced Goiters in the Fetus and in Children and Adults," The Medical Letter on Drugs and Therapeutics, 12:61-62, 1970.

(12) Peacock, L. B. and H. M. Davison, "Observations on Iodide Sensitivity," Annals of Allergy, 15:158-164, 1957.

(13) "Drill's Pharmacology in Medicine," 4th Ed., Edited by DiPalma, J. R., McGraw-Hill Book Co., New York, 1971.

(14) Boyd, E. M., "Expectorants and Respiratory Tract Fluid," Pharmacological Reviews, 6:521-542, 1954.

(15) Boyd, E. M. et al., "The Effect of Inorganic and Organic Iodides Upon the Output of Respiratory Tract Fluid," Canadian Journal of Research, 23:195-205, 1945.

(16) Tuft, L. and N. M. Levin, "Studies of the Expectorant Action of Iodides," American Journal of the Medical Sciences, 203:717-722, 1942.

(17) Baker, J. M., L. C. Roettig and G. M. Curtis, "The Prevention and Treatment of Atelectasis by the Control of Bronchial Secretions," Annals of Surgery, 134:641-652, 1951.

(18) Lopez-Belo, M., W. J. Henderson, M. Mansueto and P. H. Holinger, "The Concentration of I^{131} in the Bronchial Tree after Oral Administration of Tagged CaI_2 and KI," Diseases of the Chest, 39:158-161, 1961.

(19) Lieberman, J. and N. B. Kurnick, "The Induction of Proteolysis in Purulent Sputum by Iodides," Journal of Clinical Investigation, 43:1892-1904, 1964.

(20) Hirsch, S. R. et al., "Evaluation of Changes in Sputum Consistency with a New Instrument," American Review of Respiratory Diseases, 94:784-789, 1966.

d. Ipecac fluidextract. The Panel concludes that ipecac fluidextract is not safe for OTC use as an expectorant.

(1) Safety. Based on its long history of use, it is generally accepted that syrup of ipecac is safe although no studies can be found to substantiate this belief (Ref. 1). The fluidextract of ipecac, however, is 14 times more potent than the syrup (Ref. 2) possessing a 2 percent total alkaloidal content. The chief alkaloids of ipecac are emetine and cephaeline varying in ratio from equal parts to a fourfold preponderance of emetine. These alkaloids are responsible for its therapeutic and toxic manifestations (Ref. 3).

Toxic, even fatal doses may occur in man at 2 oz of the fluidextract. A dose of 10 ml produced death in a 4-year-old child (Ref. 4). Death from the ingestion of the syrup has not been reported. However, it is believed that many cases of overdosage result from mistaking the fluidextract for the syrup. Toxic manifestations of overdosage include nausea, bloody stools and vomitus, cramping, and abdominal pain. Myocardial manifestations have also been reported (Ref. 3).

The Panel is aware of a reference to an expectorant dose of the fluidextract of 0.2 to 0.5 ml (Ref. 5), however the Panel feels that the syrup possesses a superior benefit-to-risk ratio and that ipecac fluidextract should not be available for OTC use as an expectorant.

(2) Effectiveness. Ipecac fluidextract has both local and central effects; however, there are no acceptable clinical studies to substantiate its use as an expectorant.

(3) Evaluation. The Panel is unable to determine a safe dose for ipecac fluidextract for use as an expectorant. Because of its documented toxicity and since there is no evidence to support effectiveness, the Panel concludes that ipecac fluidextract is not safe for use as an expectorant.

REFERENCES

(1) Rollo, I. M., "Drugs Used in Chemotherapy of Amebiasis," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, pp. 1128-1129, 1970.

(2) "The Pharmacopeia of the United States of America," 19th Rev., The United States Pharmacopeial Convention, Inc., Bethesda, Md., p. 268, 1975.

(3) "Clinical Toxicology of Commercial Products: Acute Poisoning," 3d Ed., Edited by Gleason, M. N. et al., Williams and Wilkins, Baltimore, Md., pp. 128-129, 1969.

(4) Bates, T. and E. Grunwaldt, "Ipecac Poisoning. A Report of Two Cases of Ingestion of Fluidextract of Ipecac," American Journal of Diseases of Children, 103:169-173, 1962.

(5) Blumgarten, A. S., "Textbook of Materia Medica, Pharmacology and Therapeutics," 7th Ed., The Macmillan Co., New York, p. 307, 1941.

e. Squill preparations (squill, squill extract). The Panel concludes that squill preparations are not safe or effective for OTC use as expectorants.

(1) Safety. Squill is a toxic substance capable of causing nausea, vomiting, and violent purging. It contains scillarin A and scillarin B, glycosides that may be toxic to the heart. The powdered drug and extracts from it have been used as rat poison. As a rat poison, red squill is usually preferred but all squill preparations have the same general properties (Ref. 1). Although the market experience would indicate that squill is probably safe, the doses used are small and there are no data available to relate this dose to effectiveness or to the lower limits of toxic doses (Ref. 2). Available information relates to sources and methods for preparation. The lowest toxic dose is currently estimated at 50 mg/kg (Ref. 3).

(2) Effectiveness. Squill is an irritant to the gastric mucosa and produces a reflex expectorant action. In larger doses it is an emetic (Refs. 1, 4, and 5). There are no available data to relate these effects to dose. Squill is practically always given as one of several drugs in various preparations and there are no data to indicate whether

it does or does not contribute to the expectorant action of the preparation.

3. Evaluation. Because of its known toxicity and historical use as a rat poison, and since there are no data available to relate marketed doses as an expectorant to the lower limits of toxic doses, the Panel is of the opinion that the risks outweigh whatever benefit might occur. Therefore, the Panel concludes that squill preparations are not safe or effective for OTC use.

REFERENCES

(1) "Martindale. The Extra Pharmacopoeia," 26th Ed., Edited by Blacow, N.W., The Pharmaceutical Press, London, pp. 716-717, 1972.

(2) OTC Volume 040159.

(3) "Clinical Toxicology of Commercial Products. Acute Poisoning," 3d Ed., Edited by Gleason, M. N. et al., The Williams and Wilkins Co., Baltimore, Md., p. 134, 1969.

(4) Lloyd, J. U., "Origin and History of All the Pharmacopeial Vegetable Drugs, Chemicals and Preparations," Vol. I, Vegetable Drugs, The Caxton Press, Cincinnati, Oh., p. 298, 1921.

(5) Bastedo, W. A., "Materia Medica, Pharmacology, Therapeutics and Prescription Writing," 3d Ed., W. B. Saunders Co., Philadelphia, pp. 244-247, 1932.

f. Turpentine oil (spirits of turpentine) (oral). The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as an expectorant.

(1) Safety. Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically and by inhalation.

In doses of 15 ml in children and 150 ml in adults fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain, renal irritation, bloody stools and hyperemia of all abdominal organs. Continued oral use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as an expectorant, the Panel concludes that turpentine oil should not be available for oral OTC use as an expectorant. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied

topically or used as an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an expectorant. (See part IV. paragraph B.3.n. below--Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) Effectiveness. Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as an expectorant when taken orally.

(3) Evaluation. The Panel is unable to determine a safe oral dose for turpentine oil for use as an expectorant. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as an expectorant.

REFERENCES

(1) "Emetics and Expectorants," in "The Pharmacological Basis of Therapeutics," 1st Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan Co., New York, pp. 819-820, 1941.

(2) McGuigan, H. A., "A Textbook of Pharmacology and Therapeutics," W. B. Saunders and Co., Philadelphia, pp. 309-320, 1928.

(3) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, J. B. Lippincott Co., Philadelphia, pp. 1465-1466, 1960.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above--CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the following claims are misleading and are unacceptable for preparations used as expectorants. These and similar claims are unsupported by scientific data. The term "congestion", which may be interpreted by the target population to denote a discomfort of the chest, may result from a variety of causes, several of which may be of a most serious nature and require professional attention. Other terms and phrases are descriptive, but vague, and cannot be scientifically evaluated. Statements or phrases which allude to greater potency or suggest superiority of a product are not acceptable.

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable, e.g., "specially formulated", "improved", "selected", "natural", "extra strength", "teamed components", "superior to ordinary", "modern", and "superior".

Claims implying a physiological effect that has no foundation or meaning or will be meaningless to the public are unacceptable; such as "antiallergic", "gets at the roots of", "fights", "wakes up", "recommended by doctors", "multiaction", and "travels through the blood stream", "works internally", and "actively moistens".

Claims for relief where time is indeterminate and not supported by scientific data are unacceptable, such as "fast" and "prompt". Using the above criteria the Panel feels that the following specific claims are unacceptable:

a. Unacceptable claims because of vagueness and the inability to evaluate them scientifically. (1) "Temporarily relieves cough congestion by working internally to break up phlegm".

(2) "Help decongest bronchial passage".

(3) "To help clear congestion".

(4) "Frees secretions along lower respiratory tract".

(5) "Helps loosen congestion so you can cough it up and get it off your chest".

(6) "Works internally".

(7) "Actively moistens the bronchial lining".

(8) "Soothes tired throats".

(9) "Promotes free breathing".

(10) "Restores free breathing".

(11) "Eases breathing".

b. Unacceptable because the claims allude to greater potency or suggest superiority of a product which is not supported by scientific data. (1) "Full expectorant".

(2) "Combines modern expectorant".

(3) "Superior expectorant".

3. Category III conditions for which the available data are insufficient to permit final classification at this time. The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed conditions listed below. Because of the lack of suitable objective criteria for evaluating expectorant activity and the need to rely on subjective assessment of highly variable symptoms, the Panel believes it reasonable to provide 5 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 5 years, however, the conditions listed in this category should no longer be marketed as over-the-counter products.

Category III Active Ingredients

The Panel has concluded that the available data are insufficient to permit final classification of the following claimed expectorant active ingredients:

Ammonium chloride

Beechwood creosote

Benzoin preparations (inhalant)

Compound tincture of benzoin

Tincture of benzoin

Camphor (topical/inhalant)

Eucalyptol/eucalyptus oil (topical/inhalant)

Glyceryl guaiacolate

Ipecac syrup

Menthol/peppermint oil (topical/inhalant)

Pine tar preparations

Extract white pine compound

Pine tar

Syrup of pine tar

Compound white pine syrup

White pine

Potassium guaiacolsulfonate

Sodium citrate

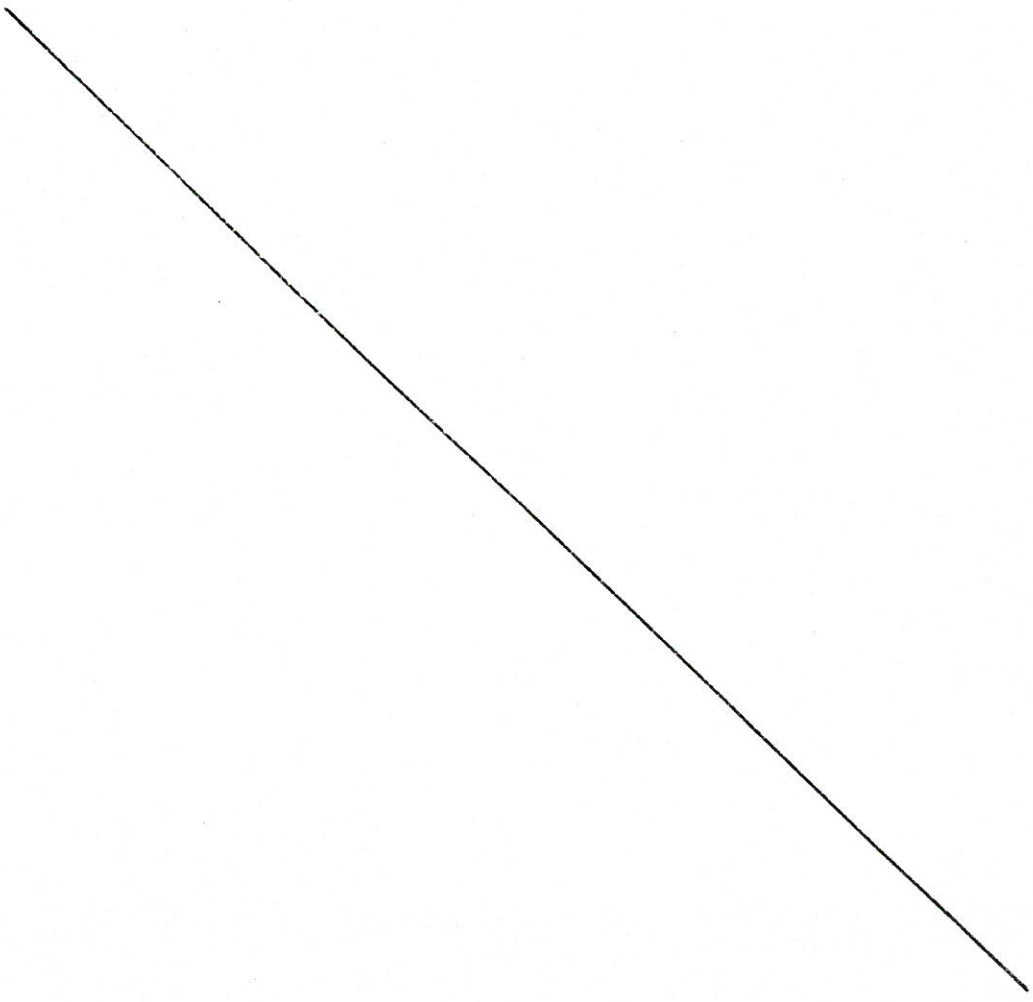
Terpin hydrate preparations

- Terpin hydrate
- Terpin hydrate elixir

Tolu preparations

- Tolu
- Tolu balsam
- Tolu balsam tincture

Turpentine oil (spirits of turpentine) (topical/inhalant)



a. Ammonium chloride. The Panel concludes that ammonium chloride is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that ammonium chloride is safe in the dosage ranges used as an expectorant.

Several studies have documented the occurrence of severe acidosis, especially in patients with renal or hepatic dysfunction (Refs. 1 through 3). Most of these occurred with doses in excess of 6 to 8 gm per day where it was being used as a diuretic. Relman, Shelburne and Talman (Ref. 4) reported two near fatal cases following ingestion of huge amounts, 82 gm taken in a 48 hour period; while Ticktin, Fazekas and Evans (Ref. 5) described a case report of hepatic coma precipitated by 6 gm in a patient with congestive heart failure. At the dose ranges of 250 to 500 mg 4 to 6 times daily, which is the customary dose as an expectorant, the major adverse reaction has been nausea and emesis (Ref. 6).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of ammonium chloride as an expectorant. No objective evaluations have been reported. Partially controlled subjective

studies (Ref. 7) showed no significant change in either sputum volume or viscosity. Several investigators (Refs. 8 through 10) felt that sputum was more fluid and easier to raise when given at doses 0.3 gm every 2 hours, and Basch, Holinger and Poncher (Ref. 11) reported a decrease in viscosity and pH (acidity) in patients with damaged bronchial tubes and infection.

(3) Proposed dosage. Adult oral dosage is 300 mg every 2 to 4 hours. Children 6 to under 12 years oral dosage is 150 mg every 2 to 4 hours. Children 2 to under 6 years oral dosage is 75 mg every 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above--Category I Labeling.) In addition, the Panel recommends the following specific labeling: Warnings. (i) "Caution: This product must be taken with adequate amounts (1/2 to 1 glass) of fluids with each dose".

(ii) "Do not take this product if you have heart trouble or chronic kidney or lung disease except under the advice and supervision of a physician".

(5) Evaluation. Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) Anon, "Dangers of Acidifying Salt Therapy in Urologic Cases," (abstract), Journal of the American Medical Association, 104:864, 1935.

(2) Sievers, M. L. and J. B. Vander, "Toxic Effects of Ammonium Chloride in Cardiac, Renal and Hepatic Disease," Journal of the American Medical Association, 161:410-415, 1956.

(3) Sleisenger, M. H. and A. S. Freedberg, "Ammonium Chloride Acidosis. A Report of Six Cases," Circulation, 3:837-845, 1951.

(4) Relman, A. S., P. F. Shelburne and A. Talman, "Profound Acidosis Resulting from Excessive Ammonium Chloride in Previously Healthy Subjects," The New England Journal of Medicine, 264:848-852, 1961.

(5) Ticktin, H. E., J. F. Fazekas and J. M. Evans, "Ammonia Intoxication in a Patient with Congestive Heart Failure Receiving Ammonium Chloride Orally," The New England Journal of Medicine, 255:905-907, 1956.

(6) Cass, L. J and W. S. Frederik, "Comparative Clinical Effectiveness of Cough Medication," American Practitioner, 2:844-851, 1951.

(7) Simon, S. W. and G. A. Harmon, "A Comparison of Various Expectorant Drugs Employing a New Method for Determining Sputum Viscosity," Journal of Allergy, 32:493-500, 1961.

(8) Brown, C. L., "The Use of Expectorants," Journal of the American Medical Association, 109:268-271, 1937.

(9) Prickman, L. E., "Therapeutic Aspects of Asthma, Emphasizing the Role and Control of Cough," Hawaii Medical Journal, 23:23-31, 1963.

(10) Boyd, E. M., "Expectorants and Respiratory Tract Fluid," Pharmacological Reviews, 6:521-542, 1954.

(11) Basch, F. P., P. Holinger and H. G. Poncher, "Physical and Chemical Properties of Sputum. II. Influence of Drugs, Steam, Carbon Dioxide and Oxygen," American Journal of Diseases in Children, 62:1149-1171, 1941.

b. Beechwood creosote. The Panel concludes that beechwood creosote is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that beechwood creosote in the usual dosages contained in lozenges or cough mixtures for expectorant activity is safe.

Creosote is a distillate of wood tar and has a smokey color and a pungent taste. Dosages in excess of 4 gm 3 times daily produces giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of beechwood creosote as an expectorant. No controlled or partially controlled studies were submitted to the Panel documenting its effectiveness as an expectorant.

Only one reference (Ref. 3) was found that reported some increase of respiratory tract fluid (RTF) in animals given high dosages but the authors expressed doubt as to the applicability of these data to man. According to the standard compendia (Refs. 1 and 4), an average dose of beechwood creosote is 250 mg 3 or 4 times a day. In the two submissions to the Panel listing creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Ref. 5). This 40 to 80-fold difference in dosage (3.29 mg/lozenge, 8 dosages daily) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) Proposed dosage. Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1,500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above--Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., Edited by Osol, A., R. Pratt and M. D. Atschule, J. B. Lippincott Co., Philadelphia, p. 341, 1967.

(2) "Drill's Pharmacology in Medicine," 2d Ed., Edited by DiPalma, J. R., McGraw-Hill Co., New York, p. 690, 1958.

(3) Stevens, M. E., A. K. Ronan, T. S. Sourkes and E. M. Boyd, "On the Expectorant Action of Creosote and the Guaiacols," Canadian Medical Association Journal, 48:124-127, 1943.

(4) "The National Formulary," 7th Ed., American Pharmaceutical Association, Washington, D.C., pp. 105-106, 1942.

(5) OTC Volume 040208 and 040235.

c. Benzoin preparations (compound benzoin tincture, tincture of benzoin) (inhalant). The Panel concludes that tincture of benzoin and compound benzoin tincture are safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that benzoin tincture and compound benzoin tincture are safe in the dosage ranges used in boiling water as a steam inhalant for expectorant purposes.

Benzoin is the balsamic resin obtained from Styrax benzoin Dryander or Styrax paralleloneurus Perkins, known in commerce as Sumatra Benzoin or from Styrax tonkinensis (Pierre) Craib ex Hartwich, or other species of the Section Anthostyrax of the genus Styrax, known in commerce as Siam benzoin (San. Styraceae) (Ref. 1).

Benzoin is used in preparing official preparations, e.g., compound benzoin tincture, United States Pharmacopeia XIX (Ref. 1) and benzoin tincture, National Formulary XI (Ref. 2). Compound benzoin tincture contains 74 to 80 percent alcohol and is prepared by a maceration process incorporating benzoin,

aloe, storax and tolu balsam using alcohol as a menstruum (Ref. 1). Benzoin tincture contains 75 to 83 percent alcohol and is also prepared by macerating benzoin, the final product being a 20 percent solution of benzoin (Ref. 2). These preparations are used topically as a protectant and antiseptic and by steam inhalation as an expectorant (Refs. 3 and 4). It is generally recognized as safe when administered by steam inhalation in accordance with recommended concentrations. The alcohol content would be responsible for the major toxic signs and symptoms arising from oral administration of the tincture (Ref. 5).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of tincture of benzoin and compound benzoin tincture as an expectorant.

Although compound benzoin tincture and benzoin tincture have been advocated and used for generations as a component of steam inhalations to promote an expectorant action, no studies demonstrating this effect have been found in the literature or OTC submissions.

3. Proposed dosage. Dosage for adults and children 2 to under 12 years of age is as follows: Add 1 teaspoonful of compound benzoin tincture or benzoin tincture to a pint of water in a hot steam vaporizer, bowl or washbasin. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

4. Labeling. The Panel recommends the Category I labeling for expectorant active ingredients (See part IV. paragraph B.1. above--Category I Labeling.) In addition, the Panel recommends the following specific labeling: Warning: "For use by steam inhalation only. Do not take by mouth".

5. Evaluation. Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) "The Pharmacopeia of the United States of America," 19th Rev., The United States Pharmacopeial Convention, Inc., Rockville, Md., pp. 50-51, 1974.

(2) "The National Formulary," 11th Ed., Mack Printing Co., Easton, Pa., p. 48, 1960.

(3) "The United States Dispensatory," 26th Ed., Edited by Osol A., R. Pratt and M. D. Altschule, J. B. Lippincott, Philadelphia, pp. 195-196, 1967.

(4) Sollman, T., "A Manual of Pharmacology," 3d Ed., W. B. Saunders Co., Philadelphia, p. 170, 1957.

(5) "Clinical Toxicology of Commercial Products: Acute Toxicology," Edited by Gleason, M. N., R. E. Gosselin, H. C. Hodge and R. P. Smith, Williams and Wilkins Co., Baltimore, Md., p. 27, 1969.

d. Camphor (topical/inhalant). The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficent data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarily on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor equivalent to a teaspoonful of linament of camphor or camphorated oil that contains 20 percent camphor has been fatal to a child. Commercially

available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with recovery (Ref. 2).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

A standard text indicates that camphor may have a slight expectorant action (Ref. 1). Well-controlled specific studies to document this effect have not been found in the literature.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing

should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repated 3 times daily.

(iii) For topical use as a lozenge 0.02 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above--Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth".

(5) Evaluation. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, the Macmillan Co., New York, p. 993, 1970.

(2) Thienes, C. H. and T. J. Haley, "Clinical Toxicology of Commercial Products," 3d Ed., Lea and Febiger, Philadelphia, pp. 24-25, 1955.

e. Eucalyptol/eucalyptus oil (topical/inhalant). The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, was applied for 48 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of ten subjects who received application of an ointment containing several volatile substances including eucalyptus oil 1.3 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by

another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils, including eucalyptus oil 1.3 percent, applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5). In another study, the vapors were produced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation. Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects (Refs. 8 through 11). Lozenges containing up to 5.5 mg eucalyptus oil

were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. Incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently recalled from the market due to potential hazards of this substance (Ref. 13).

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of eucalyptol/eucalyptus oil (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Eucalyptus oil is traditionally assumed to have an expectorant action by virtue of direct stimulation of bronchial secretory cells following inhalation (Ref. 14). In one study, eucalyptus oil was administered via steam inhalation to rabbits and respiratory tract fluid collected (Ref. 15). At normal doses eucalyptus oil did not increase the volume or decrease the specific gravity of the collected fluids. Larger doses were required for eucalyptus oil to produce this effect, and these doses led to local inflammation and several animal deaths (Ref. 15). In a later study, this group administered eucalyptol by stomach tube to anesthetized animals. Eucalyptol was shown to be an expectorant in rats, guinea pigs, rabbits, cats, and dogs. The effect was not influenced by section of the afferent gastric nerves. From this observation the authors concluded that eucalyptol does not act by a reflex mechanism in the stomach but directly upon the secretory cells of the respiratory tract (Ref. 16). Conclusive studies to confirm this expectorant property in humans are lacking.

(3) Proposed dosage. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every 1/2 to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above--Category I Labeling.). In addition, the Panel recommends the following specific labeling: (i) For

topical ointment use: Warning: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth".

(5) Evaluation. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) "Clinical Toxicology of Commercial Products, Acute Poisoning," 3d Ed., Edited by Gleason, W. N., R. E. Gosselin, H. C. Hodge and R. P. Smith, Williams and Wilkins Co., Baltimore, Md., p. 65, 1969.

(2) "Martindale. The Extra Pharmacopoeia," 25th Ed., Edited by Todd, R. G., The Pharmaceutical Press, London, p. 854, 1967.

(3) Thomas, W. S., "A Study of the Effects of Vick's Vapo-rub upon Human Skin," Draft of unpublished data is included in OTC Volume 040298.

(4) Kligman, A. M., "Trunk Rub Study (V331-34)," Draft of Unpublished Data is Included in OTC Volume 040298.

(5) Larkin, V. P. and J. C. Castellano, "Laryngoscopic Findings in Acute Respiratory Infections Treated With and Without a Mentholated Rub," in "Menthol and Menthol-Containing External Remedies," Edited by Dost, F. H. and B. Leiber, Georg Thieme Verlag, Stuttgart, Germany, pp. 108-119, 1967.

(6) Shapiro, M., "Steam Alone vs. Vaposteam in Steam," Draft of Unpublished Data is Included in OTC Volume 040298.

(7) Larkin, V. P., "Vaposteam (Commercial Package)," Draft of Unpublished Data is Included in OTC Volume 040298.

(8) Glassman, S. and E. W. Packman, "Menthol-Eucalyptus Cough Drops (Victors), Safety: Exaggerated Use," Draft of Unpublished Data is Included in OTC Volume 040298.

(9) Glassman, S. and E. W. Packman, "Cherry Victors," Draft of Unpublished Data is Included in OTC Volume 040298.

(10) Glassman, S. and E. W. Packman, "Menthol-Eucalyptus Cough Drop," Draft of Unpublished Data is Included in OTC Volume 040298.

(11) Glassman, S. and E. W. Packman, "Menthol-Eucalyptus Cough Drops (Victors). Safety Screening," Draft of Unpublished Data is Included in OTC Volume 040298.

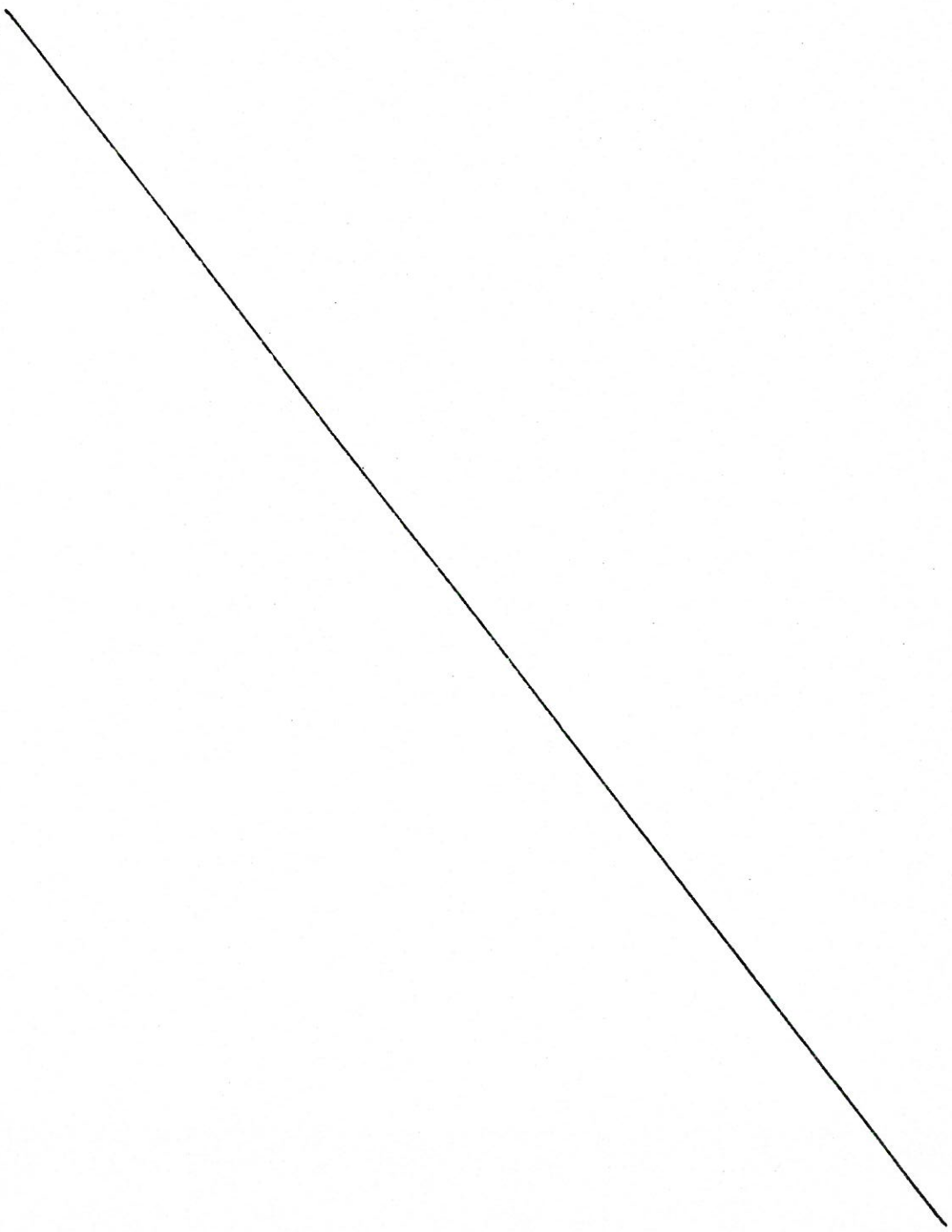
(12) Summary of Human Safety Data is Included in OTC Volume 040298.

(13) "HEW News," U. S. Department of Health, Education, and Welfare, (Food and Drug Administration), 73-29, July 2, 1973.

(14) "Drill's Pharmacology in Medicine," 2d Ed., Edited by DiPalma, J. R., McGraw-Hill, New York, p.688, 1958.

(15) Boyd, E. M. and L. P. Sheppard, "The Effect of Steam Inhalation of Volatile Oils on the Output and Composition of Respiratory Tract Fluid," The Journal of Pharmacology and Experimental Therapeutics, 163:250-256, 1968.

(16) Boyd, E. M. and G. C. Pearson, "On the Expectorant Action of Volatile Oils," American Journal of Medical Science, 211:602-610, 1946.



f. Glyceryl guaiacolate. The Panel concludes that glyceryl guaiacolate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) Safety. Clinical experience has confirmed that glyceryl guaiacolate is safe in the dosage ranges used as an expectorant.

Acute and chronic toxicity studies in animals demonstrated no adverse pathologic findings (Ref. 1). A number of studies in humans also demonstrates the safety of glyceryl guaiacolate over a wide range of dosages (Refs. 2, 3, and 4). Carter (Ref. 5) administered 100 mg/lb of body weight to 18 children with cerebral palsy for periods of 1 month. One child complained of loss of appetite and two exhibited nausea and vomiting. All laboratory data remained within normal limits (blood chemistry, complete blood count, and urine). An epidemiological study (Ref. 6) indicates that glyceryl guaiacolate is one of the most widely used medications with few reported adverse reactions.

Inhibition of in vitro platelet aggregation in the blood with prolongation of coagulation time of activated plasma has been described (Refs. 7 and 8) but appears to

have no clinical significance (Refs. 9 and 10). Glyceryl guaiacolate may interfere with certain laboratory tests, such as 5-hydroxyindoleacetic acid and vanillyl mandelic acid (Refs. 11 and 12) which are employed as screening tests for carcinoid (hormone secreting) tumors and pheochromocytoma.

(2) Effectiveness. There are no well-controlled studies documenting the effectiveness of glyceryl guaiacolate as an expectorant.

Earlier animal studies, in which glycerol guaiacolate was reported as increasing respiratory tract fluid (Refs. 13 and 14) were subsequently revised to indicate that the expectorant activity of glyceryl guaiacolate occurred only at extremely high doses (Ref. 15).

There have been a large number of clinical studies in man. Even in the early studies, the lack of acceptable standard techniques for evaluation was recognized. These studies can be subdivided into subjective uncontrolled reports (Refs. 16, 17, and 18) claiming effectiveness in the management of cough and good patient acceptance; subjective controlled or semicontrolled studies (Refs. 19 and 20) claiming superiority of glyceryl guaiacolate

(100 to 200 mg 4 times daily) over placebo with respect to ease of raising sputum, and ameliorating the unproductive cough and objective controlled studies in which the flow properties of sputum were measured or the clearance rates of inhaled radioactive tracer particles were determined. Hirsch et al. (Ref. 2) and Hirsch, Viernes and Kory (Ref. 21) found glyceryl guaiacolate at dosages of 800 to 1,600 mg daily to be no more effective than placebo in lowering sputum consistency, increasing sputum volume or improving ventilatory function. The subjective ease of expectoration was also no different than with placebo. Chodosh (Ref. 22) and Chodosh, Medici and Enslein (Ref. 23), on the other hand, dispute these findings and in a letter to the editor of Chest, Chodosh and Medici (Ref. 24) claim improvement in subjective symptoms, pulmonary function tests, and sputum stickiness (adhesiveness) with 2.4 gm glyceryl guaiacolate daily. Perhaps the most striking point in his discussion is that even at 2.4 gm daily the most significant changes were noted only after 10 days although trends could be detected at 7 days. The report by Thomson, Pavia and McNicol (Ref. 25) showing a significantly faster clearance of inhaled radioactive particles

over the first 5 hours with glyceryl guaiacolate in single doses of 200 mg as compared to placebo in bronchitic patients in a double-blind crossover study is of special interest both in the evaluation of glyceryl guaiacolate and as an objective type of assessment for expectorant drugs. This is a new approach to the study of expectorants and is objective in design. If results can be confirmed, it may represent a "breakthrough" in methodology.

If glyceryl guaiacolate requires 7 to 10 days to begin to demonstrate a significant expectorant effect, it is obviously not suited for OTC use where rapid relief of symptoms in a self-limited illness of relatively short duration is desired. It should be emphasized that the study by Thomson, Pavia and McNicol (Ref. 25) suggesting drug activity is a single study that has not been confirmed by any other investigator. Hirsch et al (Ref. 2) and Hirsch, Viernes and Kory (Ref. 21), employing another objective controlled method of study, were unable to demonstrate effectiveness. It would appear that the contradictory results of these two studies cancel each other out in a manner of speaking.

A recent subjective double-blind study was submitted in which there were 121 patients in a placebo group and 118 who received 200 mg every 6 hours for a period of 72 hours (Ref. 26).

Statistical analysis of the data was reported as showing a significant reduction in cough frequency and intensity in the patients on glyceryl guaiacolate. However, this conclusion by a subjective method of evaluation is unacceptable as a claim for suppression of cough frequency or intensity in keeping with the Panel's statement that effectiveness of a drug with respect to antitussive activity must be assessed by objective techniques, such as cough-counting methods as described in the section under evaluation of antitussives. (See part III. paragraph C. below--Data Required for Evaluation.)

In addition, this study reported that glyceryl guaiacolate administration was associated with the production of a significantly thinner sputum and was effective in increasing sputum volume and facilitating the raising of secretions in patients with a productive cough. In examining the data, it was noted that one investigator in this multidisciplinary study submitted two separate studies with a total of 76 subjects which accounted for approximately one-third of the total subject population. Another investigator presented data that showed no significant difference from placebo and a third investigator showed a significant trend in favor of glyceryl guaiacolate. Because of the conflicting results of the different investigators on this study and the likelihood that the data from the single investigator referred to above would bias the results of the study when all the information is pooled, serious questions are raised as to the validity of the study. Retrospective

analysis of the data with respect to smoking showed that there was no bias introduced by the incidence of smoking of the subjects (Ref. 27).

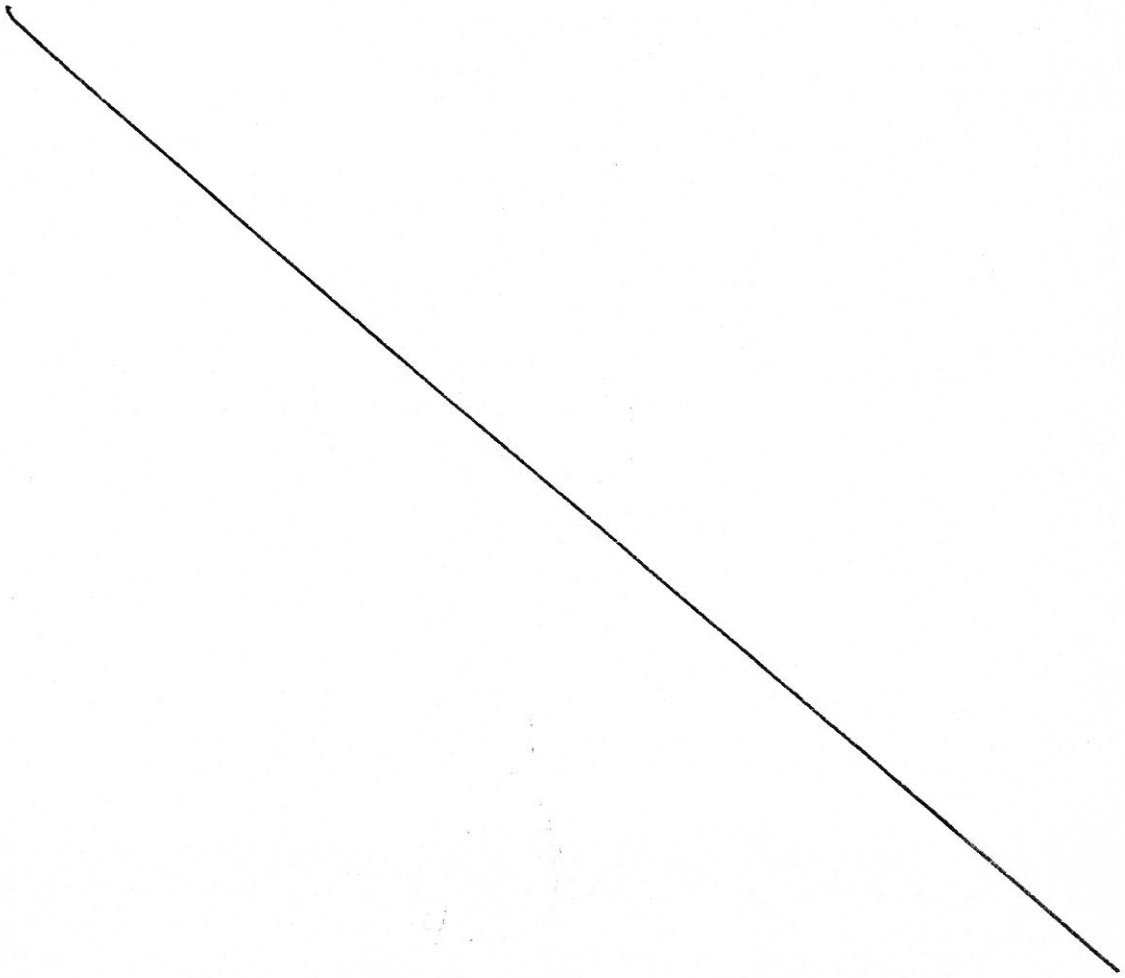
There are a number of controlled, objective studies with combinations of theophylline and glyceryl guaiacolate in reversible airway obstruction studies but these were not relevant to its expectorant activity.

There is considerable dispute as to the effective dosage. From the more recent reports in the literature it would appear to be 2 to 4 times higher than the customary dose of 100 mg.

(3) Proposed dosage. Adult oral dosage is 200 to 400 mg every 4 hours not to exceed 2400 mg in 24 hours. Children 6 to under 12 years oral dosage is 100 to 200 mg every 4 hours not to exceed 1200 mg in 24 hours. Children 2 to under 6 years oral dosage is 50 to 100 mg every 4 hours not to exceed 600 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above--Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. Effectiveness to be established by only one additional controlled study which in view of the difficulty in obtaining objective criteria for such evaluations, could be a well-designed subjective study. (See part IV. paragraph C. below--Data Required for Evaluation.)



REFERENCES

(1) OTC Volume 040026.

(2) Hirsch, S. R. et al., "The Expectorant Effect of Glyceryl Guaiacolate: A Controlled in vitro and in vivo Study," Journal of Allergy, 45:115-116, 1970.

(3) Heisen, A. J., "Treatment of Bronchial and Pulmonary Parenchymal Disorders," The Journal of the Medical Society of New Jersey, 61:104-106, 1964.

(4) Puls, R. J., "Clinical Study with Oxtriphylline-Glyceryl Guaiacolate Tablets in Chronic Pulmonary Disease: A Double-blind Crossover Study," Current Therapeutic Research, 6:353-356, 1964.

(5) Carter, C. H., "Muscle Relaxant Properties of Glyceryl Guaiacolate," Western Medicine, 7:206-211, 1966.

(6) Jick, H. et al., "Comprehensive Drug Surveillance," Journal of the American Medical Association, 213:1455-1460, 1970.

(7) Eastham, R. D. and E. P. Griffiths, "Reduction of Platelet Adhesiveness and Prolongation of Coagulation-time of Activated Plasma by Glyceryl Guaiacolate," The Lancet, 1:795-796, 1966.

(8) Silverman, J. L. and H. A. Wurzel, "The Comparative Effects of Glyceryl Guaiacolate and Adenosine on the Inhibition of ADP-Induced Platelet Aggregation," American Journal of the Medical Sciences, 254:491-498, 1967.

(9) Silverman, J. L. and H. A. Wurzel, "The Effect of Glyceryl Guaiacolate on Platelet Function and Other Coagulation Factors In Vivo," The American Journal of Clinical Pathology, 51:35-40, 1969.

(10) Duval, D. L. et al., "Effects of Monoamine Oxidase Inhibitors, Glyceryl Guaiacolate and Ethanol on Experimental Arterial Thrombosis," Mayo Clinic Proceedings, 45:579-585, 1970.

(11) Sjoerdsma, A., "Clinical and Laboratory Features of Malignant Carcincoid," A.M.A. Archives of Internal Medicine, 102:936-938, 1958.

(12) Maloof, F. et al., "Case 28-1963. Presentation of a Case," New England Journal of Medicine, 268;894-898, 1963.

(13) Perry, W. F. and E. M. Boyd, "A Method for Studying Expectorant Action in Animals by Direct Measurement of the Output of Respiratory Tract Fluids," Journal of Pharmacology and Experimental Therapeutics, 73:65-77, 1941.

(14) Stevens, M. E. et al., "On the Expectorant Action of Creosote and Guaiacols," Canadian Medical Association Journal, 48:124-127, 1943.

(15) Boyd, E. M., "A Review of Studies on the Pharmacology of the Expectorants and Inhalants," International Journal of Clinical Pharmacology, Therapy and Toxicology, 3:55-60, 1970.

(16) Blanchard, K. and R. A. Ford, "Effective Antitussive Agent in the Treatment of Cough in Childhood," The Journal-Lancet, 74:443-446, 1954.

(17) Hayes, E. W. and L. S. Jacobs, "A Clinical Evaluation of the Effectiveness of Robitussin in Chronic Cough," Diseases of the Chest, 30:441-447, 1956.

(18) Schwartz, E. et al., "The Use of Antitussives in the Management of Bronchial Asthma," American Practitioner and Digest of Treatment, 7:585-588, 1956.

(19) Cass, L. J. and W. S. Frederik, "Comparative Clinical Effectiveness of Cough Medication," American Practitioner and Digest of Treatment, 2:844-851, 1951.

(20) OTC Volume 040026.