the request of the Panel, to express their views on pediculicide drug products:

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No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through December 15, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations set forth in § 330.10, the Panel reviewed OTC pediculicide drug products with respect to the following three categories:

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

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

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

The Panel reviewed 17 ingredients in pediculicide drug products and classified 2 ingredients in Category I as a combination, 13 ingredients in Category II, and no ingredients in Category III. Two ingredients were classified as inactive.

I. Submission of Data and Information

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients recognized, either through historical use or in marketed products, as parasiticide (pediculicide) active ingredients. The following inredients were identified: alkaloids of sabadilla, aqueous coconut oil soap, benzocaine, benzyl benzoate, dichlorodiphenyl trichloroethane, isobornyl thiocyanoacetate, petroleum distillate, picrotoxin, piperonyl butoxide, pyrethrins, sublimed sulfur, and thiocyanoacetate. Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC parasiticide (pediculicide) drug products.

A. Submissions

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

Firms	Marketed products
Block Drug Co., Inc., Jersey City, NJ 07302.	Dolex.
Commerce Drug Co., Farmingdale, NY 11735.	Barc.
Laboratoires Applipharm, Marseille, France.	PARA-2.
Norcliff Thayer, Inc., Tuckahoe, NY 10707.	A-200 Pyrinate.
Pfizer Pharmaceuticals, New York, NY 10017.	Rid.
Related submissions were received from:	
Fairfield America Corporation, Middleport, NY 14105.	Pediculosis control.
FMC Corporation, Middleport, NY 14105 ..	Pediculosis control.

Data were also submitted by FDA's Division of Drug Experience reporting an adverse reaction associated with the use of lindane in treating pediculosis. Because no safety and effectiveness data were submitted for lindane, and because the Panel believes that lindane should be used only under the advice and supervision of a doctor, the Panel did not consider the use of lindane in this document.

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Benzyl alcohol
Deodorized kerosene
Dioctyl sodium sulfosuccinate
Isobornyl; thiocyanoacetate
Petroleum distillate
Piperonyl butoxide
Propylene glycol
Pyrethrins

2. *Other ingredients reviewed by the Panel.*

Alkaloids of sabadilla
Aqueous coconut oil soap
Benzocaine
Benzyl benzoate
Copper oleate
Dichlorodiphenyl trichloroethane (DDT)
Picrotoxin
Sublimed sulfur
Thiocyanoacetate

C. Classification of Ingredients

1. *Active ingredients.*

Piperonyl butoxide
Pyrethrins
Isobornyl thiocyanoacetate

2. *Inactive ingredients*

Deodorized kerosene
Petroleum distillate

3. *Other ingredients.* The Panel was neither able to locate nor is it aware of any data demonstrating the safety and effectiveness of the following ingredients when used as OTC pediculicide active ingredients. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be discussed further in this document.

Alkaloids of sabadilla
Aqueous coconut oil soap
Benzocaine
Benzyl alcohol
Benzyl benzoate
Copper oleate
Dichlorodiphenyl trichloroethane (DDT)
Dioctyl sodium sulfosuccinate
Picrotoxin
Propylene glycol
Sublimed sulfur
Thiocyanoacetate

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All the information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after July 29, 1982, in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

The Panel notes that the call-for-data notices published in the **Federal Register** requested data and information on "parasiticides." The Panel believes that the term "pediculicide" is a more accurate description of the pharmacologic category of these drugs. Therefore, throughout this document, the panel will refer to these products as pediculicides.

Pediculosis is a skin infestation caused by blood-sucking lice. Three varieties of lice attact man: *Pediculus humanus capitit* (head louse), *Pediculus humanus corporis* (body louse), and *Phthirus pubis* (pubic or crab louse).

There are no recent data on the incidence or prevalence or pediculosis in the United States, although outbreaks have been reported in elementary, middle, and high schools, "hippie communities," and institutions (Ref. 1). There has been a sharp increase in the frequency of head lice and pubic lice in the United States in all socioeconomic classes. The Center for Disease Control (CDC) has found that head louse infestations are as common in children with short hair as those with long hair; however, infestation is more common among females. Blacks are infested much less ferquently (Ref. 1).

Adult and nymphal lice (a stage of development just prior to adult) are

hematophagous (blood feeding). As they feed, saliva is introduced into the site of puncture, causing an erythematous papule (small, raised, reddended area) within hours. The papules itch, and as a consequence of scratching, secondary bacterial infection may occur.

On microscopic examination, swelling, infiltration with lymphocytes, and the extravasation (discharge) of erythrocytes are found. A residual pigmentation of the skin from bleeding and scratching is characteristic of lesions from long continued infestations, particularly with crab lice.

Both the head louse and the crab louse attach their shiny, operculate (having a lid) eggs (nits) to hairs. The head louse usually attaches to head hairs, and the crab lousé usually attaches to pubic and perianal hairs, although they sometimes are found in other locations. The body louse, more often associated with people living under congested conditions, lays its eggs in the seams of clothing.

Head lice, which measure approximately 1 to 2 millimeters (mm) long, may be visible; but frequently only the nits are seen, most commonly on hair behind the ears or on the nape of the neck about one-fourth inch from the scalp (Ref. 1). One must be careful not to confuse hairspray globules or other extraneous debris with nits (Refs. 1 and 2). Intense itching of the scalp is common with head lice, and affected hairs may become lusterless and dry. Because of scratching, secondary complications of impetigo and furunculosis (a sequential occurrence of boils) are fairly common (Ref. 2). Pustular eczema may occur.

Head lice are readily spread from head to head when there is close contact, by means of hats and scarfs hung close together in schools and public places, through the fitting of headgear in stores, and the common use of hats, scarfs, combs, and brushes. When hair from a person with lice is shed, nits may be attached. Bed linen may also be a source of transmission.

Sources of head lice transmission such as scarfs, hats, coats, and bed linen should be disinfected by machine washing in hot water and drying, using the hot cycle of a dryer for at least 20 minutes. Personal articles of clothing that cannot be washed may be disinfected by dry-cleaning or by sealing them in a plastic bag for a period of about 2 weeks (Ref. 3). Personal combs and brushes may be disinfected by soaking in hot water (above 130° F) for 5 to 10 minutes. Thorough vacuuming of rooms inhabited by infected patients is recommended (Ref. 3).

Except in extreme infestations, long-haired persons with head lice need not be shorn, because modern pediculicidal preparations are efficient.

Pediculicides will not dissolve the cement that binds the nits to the hairs. Persistence of dead nits on hair shafts after treatment is common and should not be taken as evidence of infestation. Dead and empty nits will remain attached to the hairs and be unsightly as well as confusing to those who cannot distinguish between live and dead nits; therefore, it may be desirable to remove them by combing with a fine-toothed comb (Ref. 2).

The crab louse is morphologically (structurally) distinct from other species of lice and can survive away from the human host for only about 24 hours. The crab louse is about 1 mm long, is oval in shape, and has greatly enlarged second and third pairs of legs with large claws that give it a crab-like appearance (Ref. 3). Crab lice cause pale, bluish gray blotches at the site of the bites, resulting in slight discomfort to intolerable itching that may lead to scratching and secondary infections (Ref. 4). Crab lice may be spread through sexual contact, by bedding and toilet seats, and through the shared use of towels and articles of clothing. Any sexual partners of a patient with crab lice should be treated simultaneously (Refs. 4 and 5), and personal articles of clothing should be disinfected by the same procedure as outlined for head lice (Ref. 5). Unlike head lice, the occurrence of crab lice is equally common both in black and white individuals (Ref. 4).

Body lice live chiefly in the seams of clothing, particularly where there is close contact between garment and wearer, such as the waistline and armpits (Ref. 5). The lice move to the skin to feed and then return to the seams of the clothing. The bites cause general itching, reddish blotches, urticarial wheals (raised, itchy, reddened area), and excoriated papules (a solid circumscribed elevation of abraded, scratched skin) (Ref. 5). A pigmented thickening of the skin with parallel linear scratch marks from continued rubbing and scratching is often observed (Ref. 2).

Body lice can survive longer off the host (4 to 10 days) than head lice; the eggs also survive longer off the host (up to 30 days). The body louse has been found to transmit louse-borne typhus, relapsing fever, and trench fever (Ref. 3). Personal articles of clothing should be disinfected by the same procedure as outlined for head lice except that sealing clothing in a plastic bag is not recommended for body lice because the nits from these lice can remain dormant for a period of up to 30 days (Ref. 3).

References

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(4) Felman, Y. M., and J. A. Nikitas, "Sexually Transmitted Diseases; Pediculosis Pubis," *CUTIS; Cutaneous Medicine for the Practitioner,* 25:482–489, 1980.

(5) Orkin, M., E. Epstein, and H. I. Maibach, "Treatment of Today's Scabies and Pediculosis," *Journal of the American Medical Association,* 236:1136–1139, 1976.

III. Categorization of Data

A. Category I Conditions

The following are Category I conditions under which drug products used as pediculicides are generally recognized as safe and effective and are not misbranded.

1. *Category I ingredients.* The following ingredients are discussed as a combination with respect to their action as a pediculicide and not as single ingredients:

Pyrethrins with piperonyl butoxide. The Panel concludes that the combination of pyrethrins with piperonyl butoxide is safe and effective for OTC use as a pediculicide drug product.

Pyrethrins when used as a pediculicide are generally formulated with an adjuvant. An adjuvant is an active ingredient that is used to increase the pharmacologic or toxic effect of another active ingredient. The action of an adjuvant is said to be additive when the adjuvant produces its effect by acting on the same site as the active ingredient. An adjuvant is said to be a synergist when it acts through a different biological mechanism than the active ingredient. An example of a synergistic adjuvant used in toxicologic formulations is the addition of piperonyl butoxide to pyrethrins. The piperonyl butoxide will enhance the insecticidal activity of the pyrethrins (Ref. 1) by inhibiting the oxidative breakdown of the pyrethrins by the insect's detoxification system. This increases the amount of time the pyrethrins can exert their toxic effect on the insect (Refs. 2, 3, and 4).

Piperonyl butoxide, first introduced in 1947 by Wachs (Ref. 3), is a pale yellow, oily liquid. It is odorless, stable, noncorrosive, and has a slightly bitter taste. Piperonyl butoxide is soluble in organic solvents, such as petroleum oil.

The pyrethrins are fast-acting insecticides obtained from the flowers of the commercially grown plant *Chrysanthemum cinerariaefolium* (Ref. 2). The pyrethrins are esters that are formed by the combination of two acids, chrysanthemic acid and pyrethric acid, and three alcohols, pyrethrolone, cinerolone, and jasmolone. Two fractions are formed during the combination. The pyrethrins I fraction, or the esters of chrysanthemic acid, are pyrethrin I, cinerin I, and jasmolin I. The esters of pyrethric acid, known as the pyrethrins II fraction, are pyrethrin II, cinerin II, and jasmolin II (Ref. 5). The pyrethrin content ranges from 0.7 percent (flowers from Dalmatia) to as high as 3 percent (flowers from Kenya). The active constituents reach their highest concentration in mature flower heads (Ref. 6).

Pyrethrins are brown, viscous, liquid oleoresins. They have a high boiling point and are insoluble in water. Pyrethrins are rapidly oxidized, inactivated in air, and lose some of their insecticidal activity when exposed to light (Ref. 6).

Much of the pyrethrum flowers are produced in Kenya and Tanzania. The pyrethrum flowers are dried, ground, and extracted with hexane or isohexane. The crude oleoresin (mixture of resins and essential oils) is obtained when the solvent is evaporated. Rather than shipping the flowers in bulk, extraction and refining are done prior to shipment (Ref. 7).

Two methods are used in obtaining the crude oleoresin. One method, the batch system, is percolation with petroleum ether. The second method, a series of liquid-liquid extractions with petroleum ether, is a continuous flow system. In both systems, the petroleum ether is vaporized, distilled, recovered, and used again. The oleoresin containing the pyrethrins is left behind. In some areas, the crude oleoresin is separated by centrifugal force to remove some of the heavier solids. In other areas, the oleoresin is standardized with a petroleum solvent, such as deodorized kerosene, to a 25-percent solution. The pyrethrum concentrations may vary from 25 percent to 35 percent (Ref. 7).

The reduction and refinement of the crude oleoresin containing the pyrethrins produces a light-colored, relatively nonstaining extract (Ref. 7). Several methods have been formulated and patented.

Moore (Ref. 7) states that a refining process, based on a solvent system, was developed. The crude, pyrethrin-containing extract is mixed with 95 percent aqueous methyl alcohol. The aqueous alcohol layer is drawn off, and the alcohol layer is then removed by distillation at a temperature below 75° C. The residue is then suspended in a low-boiling, saturated, aliphatic hydrocarbon. The mixture is filtered, and the hydrocarbon removed by distillation. The final pyrethrin residue is dissolved in an organic solvent, such as kerosene or refined kerosene.

Moore (Ref. 7) also states that a solvent extraction process for the refinement of the pyrethrum extract or oleoresin has been patented. The oleoresin is mixed with an equal weight of anhydrous methanol. The methanol extract is cooled to a temperature below 15° C. This will cause the waxy residue to precipitate. The waxy residue is treated with methanol to recover any pyrethrins that may have been abosorbed by the wax. The dewaxed methanol solutions are decolorized with carbon, and the methanol is distilled off the solutions. Inactive solids are removed when the residue is placed in a hydrocarbon solution. The hydrocarbon solution is concentrated to the standardized form or extract by distillation.

The above two processes have a high recovery of pyrethrins, about 95 percent. Due to the low temperature used in each method, the possibility that the molecular structure of the pyrethrins will change is decreased (Ref. 7).

Moore (Ref. 7) also cites the process patented by Ward for making a refined extract directly from the pyrethrum flowers. The undried flowers are extracted with aqueous methanol (5 percent to 40 percent water, by weight) followed by a liquid-liquid partition extraction with a hydrocarbon solvent. This process works equally well with dried flowers. A light-colored, refined extract is produced. A distillation step is used to concentrate the extract to a standardized form. Recovery of the pyrethrins is about 92 percent. Other methods also exist, i.e., Cooper, Goldberg, and Haney processes, but the percent of pyrethrins recovered is not as great (Ref. 7).

a. *Safety.* Side effects from pyrethrins are uncommon. Contact dermatitis is the most frequent. In allergic individuals, asthma and rhinitis may be produced. Poisoning from pyrethrins may have several signs and symptoms. Pyrethrin insecticides when injected or inhaled are capable of causing nausea, vomiting, muscular paralysis, and even death, but severe poisoning from pyrethrins is rare. More often, the reactions are due to other ingredients in pyrethrin preparations, such as the petroleum solvent (Ref. 8).

Pyrethrin compounds are poorly absorbed through the intact skin, but once absorbed are rapidly broken down in mammals. The fatal oral dose for man has been estimated to be 50 grams (g) per 70 kilograms (kg) (Ref. 1).

Piperonyl butoxide is also poorly absorbed through the skin (Ref. 3). The oral LD_{50} for piperonyl butoxide in rabbits is 2.5 g to 5 g/kg (Ref. 8).

A study (Ref. 9) was conducted to determine the 14-day LD_{50} value of two pyrethrin-piperonyl butoxide formulations (0.33 percent pyrethrins and 4 percent piperonyl butoxide in a gel vehicle, and 0.17 percent pyrethrins and 2 percent piperonyl butoxide in a liquid vehicle). Eighty rats were divided into two groups, and each group was further divided into four subgroups. The rats were fasted for 18 hours, but were allowed to drink water prior to dosing. One group received the liquid test material, while the other group used the pyrethrin-piperonyl butoxide gel. Each subgroup received a different dose of pyrethrins and piperonyl butoxide, amounting to 3.2, 4.0, 5.0, and 6.3 g/kg, respectively. The LD_{50} value for the liquid and the gel were similar. The LD_{50} for the 0.33 percent pyrethrin and 4 percent piperonyl butoxide formulation was reported to be from 3.90 to 5.07 g/kg, while the LD_{50} for the 0.17 percent pyrethrin and 2 percent piperonyl butoxide formulation was found to be 3.69 to 5.13 g/kg. Death of more than 50 percent of the rats was seen after dosage levels of 5 g/kg and above.

The potential of a commercial product containing 0.17 percent pyrethrin and 2 percent piperonyl butoxide to produce eye irritation was studied in monkeys (Ref. 9). Six monkeys were used in the study. The procedure called for instillation of 0.1 milliliter (mL) of the test material into the right eye of each monkey. The left eye was used as the control. The eyes were examined 1, 2, 3, 4, and 7 days after application of the test material. The results showed that the right eyes had signs of redness and a discharge, although there was no effect on the iris or cornea. It was concluded from these results that the test material was slightly irritating.

Twelve albino rabbits were used to test a marketed product (0.17 percent pyrethrins and 2 percent piperonyl butoxide) against a placebo for eye irritation (Ref. 10). Both eyes of each rabbit were examined before testing to assure that the eyes were free of defects or irritation. A measured amount (0.1

mL) of the test material was placed in the right eyes of six of the rabbits, and the same quantity of the placebo was placed in the right eyes of the other six rabbits. The left eye of each rabbit served as an untreated control. The eyes were examined after 2, 4, 48, and 72 hours for any changes. Both the pyrethrins and the placebo produced some irritation. The degree of irritation was similar; a discharge and redness occurred.

Zucker (Ref. 11) studied 106 patients who were allergic to ragweed or who had shown positive intradermal (within the skin) tests to unrefined pyrethrum extracts. Of 77 patients who showed a 2+ or stronger response to ragweed on a scale of 0 to 4+, 33 of the 77 patients (43 percent) also showed cross-sensitization to pyrethrum. Skin tests with refined pyrethrins showed 4 out of 106 patients (3.8 percent) had a definite positive reaction. Fourteen patients were given inhalation tests using the complete spray, and with direct exposure, seven showed no reaction. When further tested with pyrethrins, only two patients showed side effects, such as nose or throat discomfort (itching of dryness) and eye irritation. One of those patients failed to have a reaction when the exposure was again repeated. The allergic antigen (substance that stimulates production of specific antibody) was either absent or else was present in insignificant amounts in the refined pyrethrins used in this study.

A study (Ref. 12) was done to determine whether a product containing 0.3 percent pyrethrin and 3 percent piperonyl butoxide caused sensitivity in patients with known allergies to ragweed. Fifty patients were scratch tested for sensitivity to ragweed-protein fraction and patch tested for sensitivity to the ragweed-oleoresin fraction. A response of 2+ or more on a scale of 0 to 4+ or was the criterion used for sensitivity on both tests. Twelve patients were ragweed-sensitive on the patch test alone; 36 were senstive on the scratch test alone; and 2 were sensitive to both tests. Eight patients showed sensitivity to the unrefined pyrethrins and/or chrysanthemum flowers. These 50 patients were then scratch tested and patch tested with the undiluted product. No reactions were reported. Cross-sensitization to pyrethrins was absent in patients sensitive to the protein or oleoresin fractions of ragweed.

The irritation potential of a product containing 0.17 percent pyrethrin and 2 percent piperonyl butoxide was studied in rabbits (Ref. 9). Twelve rabbit were used. Six rabbits received two applications of a test material, while the other six rabbits had two applications of 0.33 percent pyrethrin and 4 percent piperonly butoxide. One application was done on intact skin, and the second application was done to an area in which the top layer had been rubbed off or abraded. A sample of 0.5 mL of test material was used with each application. Each area was covered by surgical gauze held in place by a plastic wrap, which prevented loss of the sample. The test material remained on the skin for 24 hours; then the plastic and gauze were removed and the area was cleaned.

Observations were made at 24 and 72 hours after the application of the test material. Slight redness and swelling were seen on both the intact and abraded skin areas 24 hours after the application of the pyrethrin. The skin sites appeared normal 48 hours later. The two pyrethrin and piperonyl butoxide formulations tested were not considered primary irritants.

A primary skin irritation study was performed on six closely clipped albino rabbits using a combination of 0.3 percent pyrethrin and 3.0 piperonyl butoxide (Ref. 13). There were two test sites for each rabbit, one on intact and one on abraded skin. The abrasions were minor cuts through the upper layer of skin, and 0.5 mL of test material was placed beneath a surgical gauze square. To keep the gauze in place, the animals were then wrapped with plastic sheeting secured with adhesive tape. The tape, plastic, and gauze were removed after 24 hours.

Signs of skin irritation were recorded at 24 and 72 hours after application. After 24 hours, results showed that on the abraded skin, four out of six rabbit had a slight redness and only two out of six showed signs of swelling. Observations of the intact skin revealed that two out of six rabbits exhibited a slight swelling and/or redness. No swelling or redness was present 72 hours after application of the pyrethrin to either intact or abraded skin.

Twenty children infested with head lice were selected for a study designed to determine the safety of a pyrethrin formulation (Ref. 14). The children ranged in age from 6 to 14 years. Children with ragweed allergies or skin problems were excluded. Each patient received three 10-minute applications of 0.3 percent pyrethrin formulated with 0.3 percent piperonyl butoxide. The time between each application was 1 week. Two ounces of the test material was left applied to each child's head. The test material was rubbed in so as to wet the hair and was left on for 10 minutes. The hair was washed with a mild shampoo and combed after each application.

Nine of 20 patients had side effects of swelling or redness of the skin. Four of nine had these signs prior to treatment, but the severity of the swelling and redness did not increase after application of the pyrethrin formulation. The swelling and redness disappeared after 3 days. In the other five children, the swelling and redness of the skin lasted only 30 to 75 minutes and were barely perceptible. All adult lice and nits were gone by the second application of the pyrethrin-piperonyl butoxide formulation. The side effects that were reported were mild and lasted a short time.

Two pyrethrin-piperonyl butoxide formulations, one a liquid containing 0.17 percent pyrethrin and 2 percent piperonyl butoxide and the other a gel containing 0.33 percent pyrethrin and 4 percent piperonyl butoxide, were studied in a group of 102 white females, with an age range of 20 to 50 years, to determine sensitization potential of the drug (Ref. 9). The back of each individual was thoroughly cleaned with 70 percent aqueous isopropyl alcohol. Next, a ½-inch square of white blotting paper completely soaked with the pyrethrin material was applied to the back and covered with an adhesive. The patch remained in contract with the skin for 48 hours. After the patch was removed, observations were made for any reactions. The procedure was repeated 10 times. Before each application, the skin was examined for any delayed responses.

Two weeks after the tenth application, a final patch was placed on the back of each individual. The patch remained in contact with the skin for 48 hours, at which time the skin was observed for irritation. A total of 1,116 patch applications of the liquid and 1,116 patch applications of the gel were made to the skin of 102 individuals (a total of 2,232 patches of both of the test materials) (Ref. 9). No immediate or delayed skin reactions were seen in any subject.

The Panel has reviewed conflicting reports on the allergenicity of ragweed-sensitive individuals to pyrethrin formulations. Because there is no standard extraction method of refining pyrethrins, the sensitive component may be present in one formulation and absent in another. Therefore, the Panel recommends the following warning for pediculicides containing pyrethrins: "Use with caution on persons allergic to ragweed."

b. *Effectiveness.* The insecticidal action of pyrethrins has not been

associated with the inhibition of any specific enzyme system or the disruption of a particular biochemical pathway. Neuropharmacological studies indicate that the primary mode of action probably involves the disruption of ion transport at nerve membranes (Ref. 2). Piperonyl butoxide enhances the effectiveness of pyrethrin by inhibiting enzymatic destruction in the insect.

Several in vitro studies were performed to determine the efficacy of two pyrethrin formulations with respect to time (Ref. 15). One study utilized a modified patch test in which square patches of dark corduroy were covered with 0.5 g of test material (either 0.17 percent pyrethrin and 2 percent piperonyl butoxide or 0.33 percent pyrethrin and 4 percent piperonyl butoxide). The lice were transferred to clean dark cotton corduroy patches, placed in clean 250 mL beakers, and incubated for 48 hours (at 82° F, relative humidity 80 percent). Death counts were taken, and lice were classified as dead, moribund (unable to crawl one body length), or alive. Moribund counts were added to dead counts.

When the study was conducted using 0.17 percent pyrethrin and 2 percent piperonyl butoxide, a 4-minute rinse (using water applied by a wash bottle) was done. Five trials and one control were done. The control patch was treated with 0.5 g of water and a 4-minute rinse. Death counts were taken at 24 and 48 hours.

For the 0.33 percent pyrethrin and 4 percent piperonyl butoxide formulation, six trials were run. In these trials, the lice were dipped in the test material and shaken every 10 seconds for a 2-minute period. Death counts were taken at 10 and 20 minutes, and 2, 24, and 48 hours after exposure. The lice in the other three trials were not rinsed before they were incubated. Death counts were taken at 10 and 30 minutes, and 2, 24, and 48 hours after exposure.

One test, a modified dip test, was done using the 0.17-percent pyrethrin and 2-percent piperonyl butoxide. Three different schedules were used. For each schedule, five male and five female lice was placed in a vial with a screen on the open end. The ends were placed into the pyrethrin liquid for a varied amount of time. For the first trial, the immersion time was 30 minutes with no rinse. The second trial had a 30-minute immersion time with a 2-minute rinse. During the third trial, the vials were submerged for 10 minutes with a 2-minute rinse. All the death counts were taken immediately and repeated after 30 minutes, and 2, 5, and 15 hours after exposure. The control lice were submerged in water for 10 minutes, rinsed for 2 minutes, and placed on corduroy patches.

The results illustrate in vitro efficacy of pyrethrins with piperonyl butoxide against lice. The 10-minute exposure followed by the 2-minute rinse killed 90 percent of the lice, while the 10-minute exposure followed by a 30-minute rinse killed all the lice.

The exposure of lice to 0.33 percent pyrethrin and 4 percent piperonyl butoxide for the 10-minute period effected a 97- to 100-percent mortality rate, and the 10-minute exposure with 2-minute rinse killed from 92 to 100 percent of the lice. The death rate of the control ranged from 5 to 10 percent.

Two formulations of a material, a liquid and a gel, were tested against human body lice (Ref. 9). The gel contained 0.33 percent pyrethrin and 4 percent piperonyl butoxide, while the liquid contained 0.17 percent pyrethrin and 2 percent piperonyl butoxide (Ref. 9). Ten dark cotton corduroy patches were used for the test. On five patches, 0.5 g of the gel was applied and on the other five patches, 0.5 g of the liquid material was applied. The patches were placed in clean 250 mL beakers. Ten male and 10 female lice were placed on top of each patch. The beakers were put into an incubator (at 80° F, relative humidity 80 percent) for 24 hours. Each beaker was then examined. The lice were classified as dead, moribund, or alive. The controls were corduroy patches treated with 0.5 g of water.

The results showed that both pyrethrin formulations were effective. All the adult lice were either dead or moribund after treatment with pyrethrin. No adult lice were found dead or moribund on the control patches.

Two similar studies were done to determine the safety and efficacy of a single application of 0.3 percent pyrethrin and 3.0 percent piperonyl butoxide (Refs. 16 and 17). Thirty adults infested with public lice were used for each study. None of the patients in either study were sensitive to ragweed or had any other skin problems. Prior to application of any test material, the number of adult or nymphal lice and nits were recorded. The degree of redness, swelling, and itching also was noted.

In both studies, 2 ounces (oz) of the test material was applied to dry pubic hair, rubbed in to thoroughly wet the hair and the skin, and left on for 10 minutes. The pubic area was then washed with a gentle soap.

Lindane was used as the positive control in both studies. One study used lindane lotion, which was rubbed in and left on for 12 hours. The second study used lindane shampoo. After application of the shampoo to dry pubic hair, the hair was wet with warm water and rubbed to produce a lather, which was left on for 4 minutes. In both studies, the pubic area was washed with a gentle soap.

In both studies, a fine-toothed comb was run through the patient's hair. The patient's hair and skin were inspected again for any lice or nits that remained. Any redness or swelling of the skin also was recorded. The patients returned 1 week later for a follow-up examination. At this time, the presence or absence of lice, nymphs, or nits, was recorded. The occurrence of any side effects was also recorded.

One study reported four patients (two pyrethrin-treated patients and two lindane shampoo-treated patients) with slight redness. The duration of redness was 5 to 15 minutes. No side effects were reported in the other study. The patients with swelling and/or redness prior to treatment did not report any increase in severity.

The results of each study were similar. One week after treatment, all lice seen prior to treatment were gone. In one study, three nits were found, but were not viable. In the other study, all nits were gone. All itching that had been reported earlier had stopped.

Twenty-six children, both male and female, were infested with head lice and were selected for a study designed to determine the safety and efficacy of a pyrethrin formulation (Ref. 18). None of the children were known to be sensitive to ragweed or have any other skin problems. Each child received treatment once a week for 3 weeks. The hair and scalp were inspected prior to treatment to count the number of adult lice, nymphs, and nits.

Thirteen children were treated with 2 oz of 0.3 percent pyrethrin and 3.0 percent piperonyl butoxide. The formulation was rubbed in to wet the hair and scalp and was left on for 10 minutes. Then the hair was washed with a mild shampoo. The other 13 children used 2 ounces of lindane shampoo. It was rubbed in to a rich lather, left on for 4 minutes, and then washed out. A fine-toothed comb was used on each patient's hair. The patient's hair and scalp were inspected again to see if any lice or nits still remained and if there were any side effects, such as redness or swelling.

The patients returned 1 week later for a second application of either pyrethrin or lindane. The patients then returned a week later for the third and final application.

One child in the pyrethrin group had a very slight swelling following treatment.

Four children in the lindane group also had a very slight swelling following treatment. In the lindane group, two had mildly abraded skin prior to treatment and two had no skin abrasions prior to treatment. The swelling experienced in both the pyrethrin and the lindane group was mild and transitory. There were three additional children in the pyrethrin group and five in the lindane group who showed swelling and/or redness following treatment. However, because the severity of swelling and/or redness after treatment was the same as that before treatment, these symptoms following treatment were not considered side effects.

Out of 26 children, 19 completed the study. After the first application of the pyrethrin compound, and before the second application, 4 out of 10 children were not infested with lice compared with 0 out of 9 children who were treated with lindane. After the second application and, before the third application, 8 out of 10 children treated with the pyrethrin compound were not infested with lice, whereas 3 out of 9 children using lindane did not have lice. Immediately following the third treatment, all children in the pyrethrin group were free of lice, and eight out of nine children using lindane were free from lice.

A study was conducted to determine the effectiveness of 0.3 percent pyrethrin and 3.0 percent piperonyl butoxide (Ref. 19). For this study, the public health nurse visited the homes of all children with reported cases of head lice infestation. The cases were verified, and the families were provided with the pyrethrin compound along with information on how to disinfect their belongings and decrease the transmission of lice. Each patient received a second visit from the nurse. A total of 248 children ranging in age from 6 months to 12 years participated in the study and were treated. The average time from diagnosis and return to school was 2.9 days. The symptoms associated with lice infections were redness and itching, which disappeared in a majority of the cases following the pyrethrin-piperonyl butoxide treatment. Only six children reported any side effects, which included itching and redness. All lice were killed.

However, the Panel could find no conclusive clinical evidence that the combination of pyrethrins and piperonyl butoxide is completely effective in exterminating all viable forms of lice (i.e., adult lice, nymphs, and nits) in one application. One in vitro study (Ref. 10) designed to show ovicidal (capable of killing eggs) effectiveness of different pyrethrin-piperonyl butoxide products reported a range between 19.6 to 33.6 percent nits killed (Refs. 10 and 20). The Panel, therefore, recommends that labeling state that a second treatment must be made in 7 to 10 days to kill any newly hatched lice.

c. *Dosage.* Based on the available data, the Panel concludes that a combination of pyrethrin (0.17 to 0.33 percent) with piperonyl butoxide (2 to 4 percent) is safe and effective for use as an OTC pediculicide.

d. *Labeling.* The Panel recommends Category I labeling for pediculicide active ingredients. (See part III. paragraph A.2. below—*Category I labeling.)*

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(19) Billstein, S., and P. Laone, "Demographic Study of Head Lice Infestations in Sacramento County School Children," *International Journal of Dermatology,* 18:301–304, 1979.

(20) OTC Volume 16JPAI, section 1.7.

2. *Category I labeling.* The Panel recommends the following Category I labeling for OTC pediculicide drug products:

a. *Indications.* "For the treatment of head, pubic (crab), and body lice."

b. *Directions.* "Apply to affected area until hair is thoroughtly wet with product. Allow product to remain on area for 10 minutes but no longer. Wash area thoroughtly with warm water and soap or shampoo. A fine-toothed comb may be used to help remove dead lice or their eggs (nits from hair. A second treatment must be made in 7 to 10 days to kill any newly hatched lice."

c. *Other required statements*—(1) *"HEAD LICE:* Head lice live on the scalp and lay small white eggs (nits) on the hair shaft close to the scalp. The nits are most easily found on the nape of the neck or behind the ears. All personal headgear, scarfs, coats, and bed linen should be disinfected by machine washing in hot water and drying, using the hot cycle of a dryer for at least 20 minutes. Personal articles of clothing or bedding that cannot be washed may be dry-cleaned or sealed in a plastic bag for a period of about 2 weeks. Personal combs and brushes may be disinfected by soaking in hot water (above 130° F) for 5 to 10 minutes. Thorough vacuuming of rooms inhabited by infested patients is recommended."

(2) *"PUBIC (CRAB) LICE:* Pubic lice may be transmitted by sexual contact; therefore, sexual partners should be treated simultaneously to avoid reinfestation. The lice are very small and look almost like brown or grey dots on the skin. Pubic lice usually cause intense itching and lay small white eggs (nits) on the hair shaft generally close to the skin surface. In hairy individuals, pubic lice may be present on the short hairs of the thighs and trunks, underarms, and occasionally on the beard and mustache. Underwear should be disinfected by machine washing in hot water; than drying, using the hot cycle for at least 29 minutes."

(3) "BODY LICE: Body lice and their eggs are generally found in the seams of clothing, particularly in the waistline and armpit area. They move to the skin to feed, then return to the seams of the clothing where they lay their eggs. Clothing worn and not laundered before

treatment should be disinfected by the same procedure as outlined for head lice, except that sealing clothing in a plastic bag is not recommended for body lice because the nits (eggs) from these lice can remain dormant for a period of up to 30 days."

d. *Warnings.* (1) "Use with caution on persons allergic to ragweed."

(2) "Do not use near eyes or permit contact with mucous membranes. If product should get into the eyes, immediately flush with water."

(3) "If skin irritation or infection is present or develops, discontinue use and consult a doctor."

B. Category II Conditions

These are conditions under which active ingredients used as pediculicides are not generally recognized as safe and effective or are misbranded.

1. *Category II ingredient—Isobornyl thiocyanoacetate.* The Panel concludes that isobornyl thiocyanoacetate is not safe becaue there are no human data available to demonstrate safety when used as an OTC pediculicide. The Panel further concludes that there is insufficient evidence to prove it is effective as a pediculicide.

Isobornyl thiocyanoacetate is a yellow, oily liquid with a terpene-like odor and a molecular weight of 253.36 (Refs. 1 and 2). It is very soluble in alcohol, benzene, chloroform, and ether, but practically insoluble in water. It is used as the technical grade, which contains 82 percent or more of isobornyl thiocyanoacetate with other terpenes (Ref. 2). It is a primary irritant and should not be applied near the eyes or on mucous membranes (Refs. 1, 2, and 3).

Isobornyl thiocyanoacetate has been used as an OTC pediculicide to eradicate crab, head, and body lice. It is available as a 4.1-percent liquid and cream (Ref. 4). Treatment involves external application of approximately 30 to 60 mL or g worked into a lather and allowed to remain on for 10 minutes before a subsequent wash with soap and water.

a. *Safety.* A chronic animal toxicity study showed that white rats tolerated up to 0.6 mg/kg daily for 6 months (Ref. 2). Studies involving oral toxicity in rats (LD_{50}), rabbit eye irritation, rabbit skin irritation, and guinea pig sensitization potential were stated to be in progress in January 1974, but have not been submitted (Ref. 4). No human safety data were submitted.

b. *Effectiveness.* Liquid preparations of 4.1 percent isobornyl thiocyanoacetate have been compared with a combination product of 0.165 percent pyrethrins and 2.0 percent piperonyl butoxide in the knockdown (rendering the lice unable to crawl) of lice. The 4.1-percent isobornyl thiocyanoacetate was effective under the test conditions, although not as effective as the comparison preparation (Ref. 4). The tests against adult lice were conducted using a modified patch/beaker test (Ref. 4). This test method uses dark cotton corduroy cloth cut into 4-centimeter (cm) square pieces.

The compounds are then applied to each patch at the rate of 0.5 g per patch. The liquid is applied with a dropping pipette to ensure even distribution of the compound over the 16-cm square area. The patches are then placed individually into clean 250 mL beakers. Into each beaker, 20 adult lice are introduced on top of the patch. The beakers containing the lice are then transferred to an incubator set at 27° C. After 1 hour of exposure, the lice in each beaker are examined for mortality. At the end of 24 hours, the lice in each beaker are again examined for mortality. The lice are classified as dead, moribund, or alive. Moribund lice are added to the dead counts when calculating the percent mortality.

Each treatment consisted of 4 replicates. Each replicate contained 20 adult lice. In addition, two replicates were run as controls using patches treated with 0.5 g of water. Another two replicates were run with dry, untreated patches.

The isobornyl thiocyanoacetate liquid produced a 76.25-percent knockdown after 1 hour of exposure and complete mortality after 24 hours of exposure. The pyrethrins with piperonyl butoxide produced complete knockdown after 1 hour and complete mortality after 24 hours of exposure (Ref. 4).

c. *Evaluation.* The Panel concludes that isobornyl thiocyanoacetate cannot be generally recognized as safe and effective for OTC use as a pediculicide due to a lack of data and classifies this ingredient as Category II.

References

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(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 673, 1976.

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(4) OTC Volume 160011.

2. *Category II labeling.* The Panel has examined the submitted labeling claims for OTC pediculicide drug products and has classified the following claims as Category II:

a. Unqualified claims that the product is "ovicidal." Available data report the ovicidal activity of pyrethrin formulations to range from 19.6 to 33.6 percent nits killed, which is insufficient to warrant use of an ovacidal claim (Refs. 1 and 2).

b. Claims stating that the product may be reapplied in less than 7 days. Data demonstrated that pyrethrin formulations kill lice upon application, but have low ovicidal activity (Ref. 1). The unaffected ova (nits) will hatch in 7 to 10 days at which time a second application of the product is warranted.

References

(1) OTC Volume 160400.

(2) OTC Volume 16MPAI, section 1.9.

C. Category III Conditions

None.

List of Subjects in 21 CFR Part 358

OTC drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p) 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 358, new Subpart G, to read as follows:

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

Subpart G—Pediculicide Drug Products

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart G—Pediculicide Drug Products

§ 358.6601 Scope.

(a) An over-the-counter pediculicide drug product in a form suitable for topical application is generally

recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1.

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

§ 358.603 Definitions.

As used in this subpart:

Pediculicide drug product. A drug product for the treatment of head, pubic (crab), and/or body lice.

§ 358.610 Pediculicide active ingredients.

The active ingredients of the product consist of the combination of pyrethrins (0.17 to 0.33 percent) with piperonyl butoxide (2 to 4 percent) in a nonaerosol dosage formulation.

§ 358.650 Labeling of pediculicide drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "pediculicide."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "For the treatment of head, pubic (crab), and body lice."

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

(1) "Use with caution on persons allergic to ragweed."

(2) "Do not use near eyes or permit contact with mucous membrances. If product should get into the eyes, immediately flush with water."

(3) "If skin irritation or infection is present of develops, discontinue use and consult a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

"Apply to affected area until hair is thorougly wet with product. Allow product to remain on area for 10 minutes but no longer. Wash area thoroughly with warm water and soap or shampoo. A fine-toothed comb may be used to help remove dead lice or their eggs (nits) from hair. A second treatment must be made in 7 to 10 days to kill any newly hatched lice."

(e) *Other required statements*—(1) *"HEAD LICE:* Head lice live on the scalp and lay small white eggs (nits) on the hair shaft close to the scalp. The nits are most easily found on the nape of the neck or behind the ears. All personal headgear, scarfs, coats, and bed linen should be disinfected by machine washing in hot water and drying, using the hot cycle of a dryer for at least 20 minutes. Personal articles of clothing or bedding that cannot be washed may be dry-cleaned or sealed in a plastic bag for a period of about 2 weeks. Personal combs and brushes may be disinfected by soaking in hot water (above 130° F) for 5 to 10 minutes. Thorough vacuuming of rooms inhabitated by infested patients is recommended.

(2) *"PUBIC (CRAB) LICE:* Pubic lice may be transmitted by sexual contact; therefore sexual partners should be treated simultaneously to avoid reinfestation. The lice are very small and look almost like brown or grey dots on the skin. Pubic lice usually cause intense itching and lay small white eggs (nits) on the hair shaft generally close to the skin surface. In hairy individuals, pubic lice may be present on the short hairs of the thighs and trunk, underarms, and occasionally on the beard and mustache. Underwear should be disinfected by machine washing in hot water; then drying, using the hot cycle for at least 20 minutes."

(3) *BODY LICE:* Body lice and their eggs are generally found in the seams of clothing, particularly in the wastline and armpit area. They move to the skin to feed, then return to the seams of the clothing where they lay their eggs. Clothing worn and not laundered before treatment should be disinfected by the same procedure as outlined for head lice, except that sealing clothing in a plastic bag is not recommended for body lice because the nits (eggs) from these lice can remain dormant for a period of up to 30 days.

(Interested persons may, on or before September 27, 1982, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before October 27, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: May 14, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: June 21, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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