

PYRETHRUM ALLERGIC CONTACT DERMATITIS IN HUMANS—REAL?, COMMON?, OR NOT DOCUMENTED?: AN EVIDENCE-BASED APPROACH

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Pyrethrum has been reported to produce allergic contact dermatitis in humans. Moreover, it has been speculated that cross reactions occur in ragweed-sensitized people. This review presents the botany, contemporary chemistry, and case reports of alleged allergic contact dermatitis. Our interpretation suggests that the evidence presented in literature does not show that allergic contact dermatitis results from exposure to pyrethrum. Similarly, the data do not suggest cross reactions in ragweed-sensitized people. Changes in the chemical composition of the refined pyrethrins suggest the putative sensitizer is present at a lower level in today's refined extracts than in ground pyrethrum flowers or the extracts used earlier.

Keywords: Allergic contact dermatitis; Compositae; Cross sensitivity; Insecticide; Pesticide; Pyrethrin; Pyrethrosin; Pyrethrum; Sesquiterpene lactones; Type IV hypersensitivity

INTRODUCTION

Pyrethrum, used as an insecticide for centuries, is derived from dried and ground flowers of *Chrysanthemum cinerariifolium*, which is a member of the Compositae family. It is presently used in insecticide products for the control of crawling and flying insects in the home, food handling establishments, to a limited degree in agriculture, and in medicine to control lice on man. Pyrethrins are the six insectically active ingredients in pyrethrum extract. They are categorized into two groups: pyrethrins I (pyrethrin 1, cinerin 1, and jasmolin 1) and pyrethrins II (pyrethrin 2, cinerin 2, and jasmolin 2). "Pyrethrins" is the term used on most current product labels to describe pyrethrin I and pyrethrin II collectively, also known as total pyrethrins. Although we endorse this nomenclature and will use it when possible, the use of the terms *pyrethrum* and *pyrethrins* vary from author to author. Thus, even when referencing the original literature, uncertainty often arises about what specifically

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the authors were attempting to identify. Given this, unless a clear distinction is made in the context of a given literature reference, the terms pyrethrum and pyrethrin(s) should be considered to be relatively synonymous.

Incidences of dermal reactions to pyrethrum have been reported sporadically over the last 100 years or so. Most compendia of toxicological information as well as standard dermatology textbooks state that pyrethrum may itself produce allergic contact dermatitis or cross reactions in some individuals believed to have Type IV hypersensitivity (allergic contact dermatitis) to certain plants from the Compositae family (1). U.S. Food and Drug Administration (FDA)-guided package labeling of pediculicide uses of pyrethrins in the United States also mentions this potential interaction.

This document investigates the veracity of the assertions that pyrethrum is a dermal sensitizer in humans. Although reports pertaining to pyrethrum and immediate hypersensitivity (Type I or contact urticaria) are important to the overall clinical understanding of pyrethrum, these will be addressed specifically in a later publication. Our assessment of the likelihood that pyrethrum is a sensitizer is based primarily on a critical review of the human clinical reports suggesting sensitization. We used an evidence-based approach to review the reported cases of Type IV hypersensitivity reactions to pyrethrum and pyrethrum-based products from the late 19th century to the present. Moreover, we briefly discuss how improved refining of pyrethrum may have resulted in a decrease in the putative sensitizer present in the extracts used for pyrethrum-based products. To correctly evaluate the pertinence of reported reactions we detail the botany, chemistry, and refining procedure.

BOTANY

Pyrethrum is the name for the dried and ground flowers of *Chrysanthemum cinerariifolium* or *C. coccineum*. Although the genus *Chrysanthemum* (a.k.a. *Tanacetum*) has more than 100 species, few of the species are toxic to insects. Both *C. cinerariifolium* and *C. coccineum* have insecticidal properties. *Chrysanthemum cinerariifolium*, also known as Dalmatian pyrethrum, has greater insecticidal properties than *C. coccineum* (2,3). Therefore, although both species had insecticidal uses throughout history, *C. cinerariifolium* is the only commercially important species cultivated and used in production of today's pyrethrum-based insecticides (Fig. 1).

To the casual observer, most *Chrysanthemum* species resemble field daisies (Fig. 2). *C. cinerariifolium* is an herbaceous perennial plant with several hundred flowers per plant. It has many shoots that branch from the crown and terminate into a white daisy-like flower head. The shoots are slightly hairy and grow approximately 75 cm high (2,4). The taxonomy for some species differs due to variations in morphology and flower color. This is the case for *C. Coccineum* (Persian pyrethrum), which recognizes *C. roseum*, *C. marschalli*, *C. carneum*, *Pyrethrum roseum*, and *P. carneum* all as names for this particular species (4).

HARVEST, EXTRACTION, AND REFINEMENT

Over recent decades, as the commercialization of pyrethrum increased, an industry standard has been followed in terms of extraction and purification. Figure 3 outlines the current procedures discussed below.

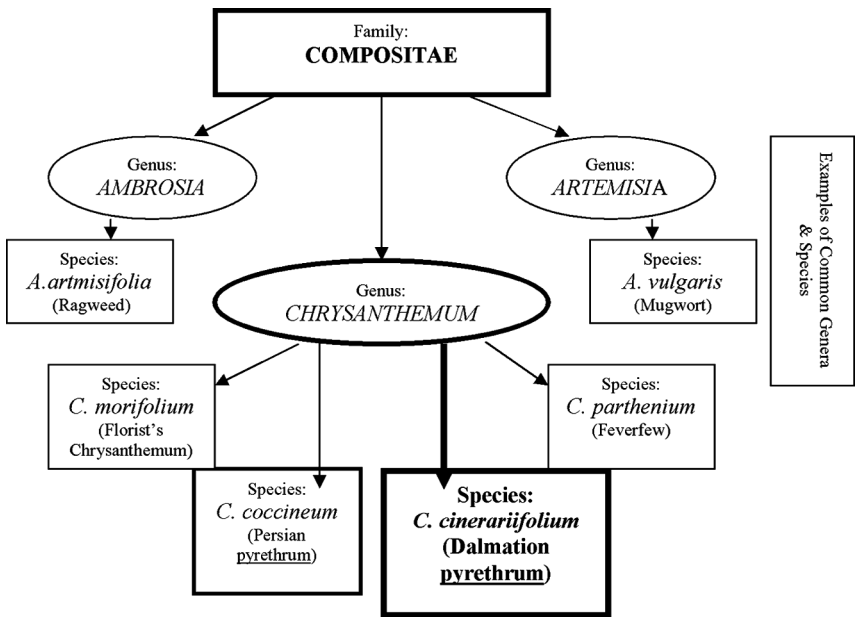


Figure 1 Some representative genera and species of the Compositae family that have been shown to be associated with dermatological reactions.

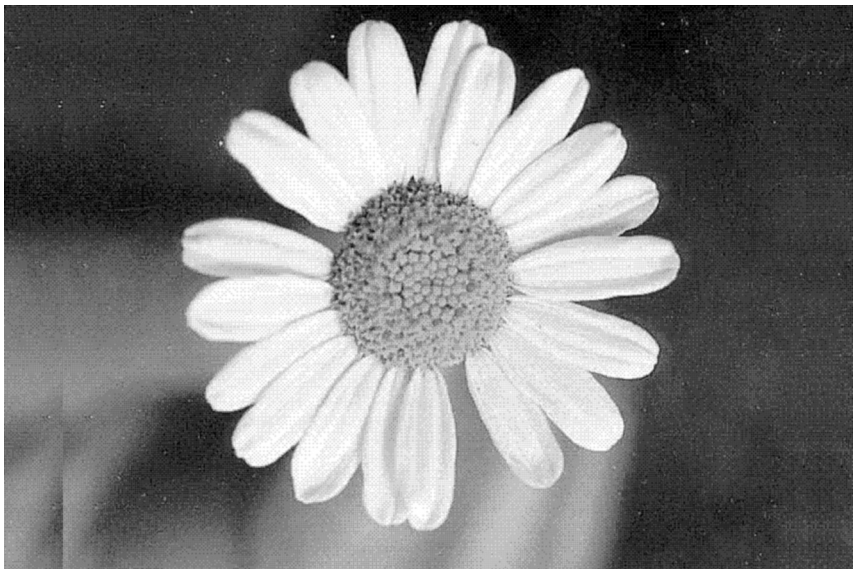


Figure 2 Flower head of pyrethrum plant. Photograph by D.R. Maciver.

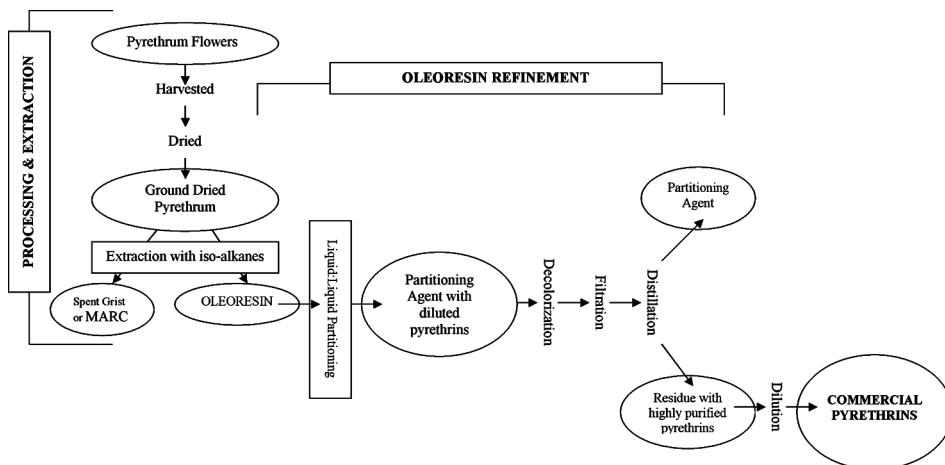


Figure 3 Harvesting, preparation and refinement of commercial pyrethrum as of 1967.

Flower Harvesting

Pyrethrins are extracted from *Chrysanthemum* flowers, *C. cinerariifolium*, grown as a crop mainly in East Africa (Kenya, Tanzania, and Rwanda) and Tasmania, Australia. African pyrethrum harvesting is dictated by the flowering pattern of their plants, which is asynchronous—buds and immature flowers are all present along with mature blooms. Thus, it calls for hand selection and harvesting. The harvested flowers are collected and dried in the sun. In contrast, Australian flowering pattern is synchronous—all flowers mature at the same time. This permits for mechanical harvesting. The flowers are then also field dried.

Crude Extract Preparation

Dried flowers are coarsely ground and the grist is extracted by percolation with low boiling iso-alkanes (hexanes). The resulting solution or miscela is filtered and iso-alkanes removed by distillation to leave a viscous dark greenish-brown liquid oleoresin or “brut.” The spent extracted grist, warmed to remove hexanes, is sold as “marc” for cattle food. The oleoresin is the remaining insecticidally active portion, which is further refined to produce the commercial product (5).

Oleoresin (Brut) Refining

This oleoresin is then refined to a pale yellow liquid. The refining stage substantially removes triglycerides, high molecular weight plant waxes, plant pigments, and polymers that could clog the spray nozzles of aerosols or stain light colored fabrics or surfaces (5).

Commercial refining currently takes place in East Africa, China, Australia, and North America, and although the techniques vary somewhat, a similar product is produced from each location. These processes evolved throughout the 1950s and 1960s and by 1967 all of the refiners were using processes that resulted in a highly

refined extract fundamentally different from that produced in the first half of the 20th century.

The oleoresin is partitioned by liquid:liquid partitioning into a polar low boiling agent such as methanol (East African technique) or subcritical liquid carbon dioxide (Australian technique). The partitioning agent containing diluted pyrethrins is decolorized with active carbon and filtered. The partitioning agent is then removed by distillation. The residue containing highly purified pyrethrins is adjusted to a determined approved concentration by diluting with a hydrocarbon diluent such as a commercially available iso-alkane. It is then suitable for formulating, for example, as a water emulsifiable concentrate by adding inert emulsifiers and wetting agents to produce a commercial product. The food approved antioxidant butylated hydroxyl toluene (BHT) is typically added (5).

CHEMISTRY OF COMMERCIALY AVAILABLE PYRETHRINS

Commercially available pyrethrins have three principal components (Fig. 4) active ingredients, plant extracts, and additives/diluents. Although investigators have reported on the pyrethrins chemistry, the most definitive analysis of pyrethrins currently used in commerce comes from the work of the Pyrethrin Joint Venture (PJV). (The PJV is a consortium of pyrethrins growers, refiners, and end-use product marketers that was formed to address the data requirements for reregistration of pyrethrins with the USEPA.) (5). As with most natural products, pyrethrins have a variable composition. Thus, a composite sample of products from the leading producers was made in 1986 (referred to as FEK-99) and used for toxicology, chemistry, and environmental fate studies. The chemistry discussed in this section relate specifically to the analysis conducted by the PJV of the FEK-99 sample (5). Similar refinement techniques are in place today and it is expected that FEK-99 is generally representative of the refined pyrethrins being produced today.

Active Ingredients

Pyrethrum contains six biologically active esters. They are grouped as Pyrethrins I (Pyrethrin 1, cinerin 1, and jasmolin 1) and pyrethrins II (Pyrethrin 2, cinerin 2, and jasmolin 2). Together, they are referred to as the total pyrethrins. Generally, the

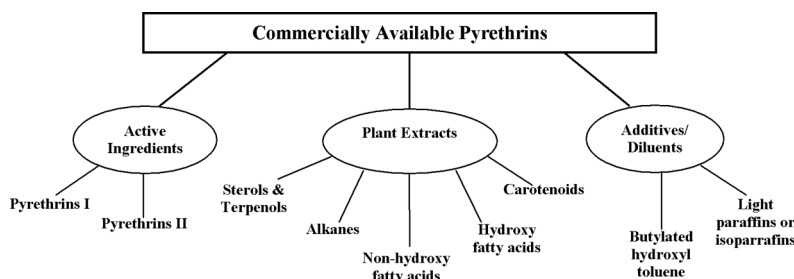


Figure 4 Basic components of commercially refined pyrethrins.

concentrations of Pyrethrins I and Pyrethrins II are expressed in the form of a ratio, known as the PI/PII ratio. The ratio varies from differences in geographic growing location and stages of flower maturity (5). A typical sample of refined pyrethrum concentrate such as FEK-99 can contain 50–57% total pyrethrins. There are other commercial pyrethrum products that are further diluted with solvent such as iso-octane that contain 20–25% pyrethrins.

Plant Extracts

A typical sample of refined pyrethrum concentrate will also contain other ingredients of vegetable origin, including the following: 1) nonhydroxy fatty acids (often as glycerides), 12%; 2) hydroxy fatty acids (often as glycerides), 8%; 3) alkanes (waxes), 0.4%; 4) carotenoids (as free xanthopylls), 0.04%; 5) sterols and terpenols, 3%. Traces of diterpenes such as murolene and alpha and delta cadinene and the alycyclic beta-fasnesene have been detected while sesquiterpenoids have also been detected at low levels in refined pyrethrum extract.

Additives/Diluents

The following solvents and preservatives are typically added to refined pyrethrum concentrate: 1) Light paraffins or isoparaffins (food grade,) 15-20%; 2) Butylated hydroxyl toluene (BHT, food grade), 4-5%. Literature reports cases of allergic contact dermatitis to BHT [6,7]. The hydrocarbons may also include 5,6-dimethyldecane, 4-methylundecane, and n-dodecane.

Terpenoids: Triterpenols and Sesquiterpene Lactones

Terpenoids are present in low concentrations in commercially refined pyrethrins. The predominant terpenoid in the FEK-99 sample is taraxasterol (0.39%). Lesser contributions of beta-amyrin (0.11%) and pyrethrosin (0.15%) are also present. Taraxasterol and beta-amyrin are pentacyclic triterpenols (5). Pyrethrosin (structurally unrelated to the pyrethrins, also known as chrysanthin) is a sesquiterpene lactone (Fig. 5). Sesquiterpene lactones, as a class, are of particular interest because of the high proportion of members that are considered to be potential dermal sensitization hazards (8). Pyrethrosin was first isolated from pyrethrum extract by Rose and Haller (9) and chemically identified between 1957 and 1960 (10). Pyrethrosin has low solubility in paraffinic and isoparaffinic solvents and can precipitate when primary extracts from crushed flowers are concentrated (5). This limits the likelihood that it will be found in significant amounts in the pyrethrum oleoresin that ultimately goes to produce insecticide products. Studies (discussed below) have suggested that pyrethrosin is a putative dermal sensitizer present in pyrethrum flowers.

SESQUITERPENE LACTONES AND CROSS-SENSITIVITY

As noted above, sesquiterpene lactones are Compositae components responsible for “contact allergy” (11–15). Lipophilic sesquiterpene lactones are found in

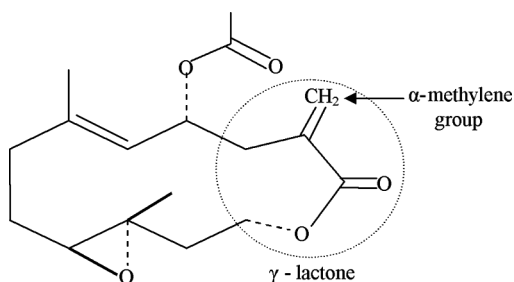


Figure 5 Structural formula for pyrethrosin. Putative pyrethrum allergen also known as chrysanthin. The α -methylene group exocyclic to the γ -lactone elicits contact allergy. Systematic names for pyrethrosin include: 1) Germacra-4, 11(13)-dien-12-oic acid, 1-beta, 10-epoxy-6-alpha, 8-alpha-dihydroxy-, 12,8-lactone, acetate, (E)-; 2) Germacra-4,11(13)-dien-12-oic acid, 1-alpha, 10-alpha-epoxy-6,8-beta-dihydroxy-, 12,8-lactone, acetate (8CI); 3) Oxireno(8,9)cyclodeca(1,2-b)furan-8(2H)-one, 6-(acetyloxy)-1a,3,6,6a,7,9a,10,10a-octahydro-4,10a-dimethyl-7-methylene-, (1aR-[1aR*,4E,6R*,6aR*,9aS*,10aR*]).

the plant oleoresins (8,16). More than 1350 different sesquiterpene lactones have been identified in weeds and plants from the Compositae family and approximately half are potential contact allergens (8). Sesquiterpene lactones belong to 6 main structural groups with differing sesquiterpene skeletons. Some, but not all, sesquiterpene lactones with a α -methylene group are contact allergens in humans (10). For entities that are allergens, it is the α -methylene group exocyclic to the γ -lactone that enables the elicitation of contact allergy (Fig. 5).

Cross-reactivity between the various types of sesquiterpene lactones may occur (12,17). However, Mitchell et al. (17) ascertained that cross sensitization among sesquiterpene lactones depend on the nature of the hapten and the "immunological specificity of the patient test." Baer (18) stated that

each and every patient develops his or her own pattern of cross-sensitization which is as characteristic for him as his finger prints.

Therefore, sensitivity to one species of Compositae is not always indicative to sensitization to others.

In a 1952 article, Fisher (19) speculated there to be cross-reactivity between pyrethrum (of the time) and turpentine from the results of an investigation on decreased patch test reactivity to an amount of oleoresin as a measure of oral hyposensitization (20). However, Mitchell et al. (21) found that subjects sensitive to the sesquiterpene lactones derived from pyrethrum and ragweed showed negative patch test reactions to turpentine. The most frequently cited study on the topic of pyrethrum cross-sensitivity is Zucker (22), which stated that up to 40% of ragweed-sensitive individuals may have a positive reaction to pyrethrum powder. Since Zucker's publication, much research has been presented to the contrary.

Fisher studied 14 subjects with either ragweed dermatitis or allergic rhinitis (immediate sensitivity) and all had negative patch tests with modern, refined pyrethrum extract (23). This information suggested that Compositae-sensitive individuals can safely use pyrethrins containing products without experiencing negative reactions (20). Thus, the occurrence of dermatitis in ragweed-sensitive individuals

upon pyrethrum exposure speculated in earlier literature (1,22,24) was likely caused by impurities not present in current commercial preparations of pyrethrins (25).

When evaluating literature reporting cross-sensitivity between Compositae species it is also important to consider the challenge testing procedure. False-positive reactions (excited skin syndrome or angry back) can occur when patch tests are performed on subjects with active dermatitis. For example, in a study by Goncalo (26) investigating cross-sensitivity between lichens and Compositae, the presence of active lesions of dermatitis to sesquiterpene lactones of a specific species (not associated with pyrethrum) may have facilitated additional sensitization to other compounds, in this case lichens.

PYRETHRUM AS A SENSITIZER

The statement, often referenced in secondary literature, that pyrethrum is a “moderately potent sensitizer” was first made by McCord, Kilker, and Minster (27) in 1921. In ascertaining the veracity of the above statement today, it is crucial that one understands how advancements in pyrethrum extraction and refinement alone make today’s commercial pyrethrum/pyrethrins quite different than that of the early 20th century. As established, pyrethrosin is the putative sensitizer in pyrethrum.

Improvements in refining during the 1950s through the 1960s make it reasonable to assume that as early as 1970 the levels of pyrethrosin being present in commercially refined extracts were quite low. Mitchell et al. (21) recognized this as well in 1972:

...it is highly unlikely, if not impossible, that pyrethrosin should be present in commercial refined pyrethrum extracts. Moreover, such extracts for agricultural or household use contain smaller quantities of pyrethrins than we have used for patch testing.

Additionally, it is known that pyrethrins themselves are not allergenic. In an experimental study on the identification of chrysanthemum allergens Hausen and Schultz (28) state:

The pyrethrins, i.e. constituents with strong insecticidal activity, derived from certain chrysanthemum species and often suspected to be the causative agents, were shown to play no role in chrysanthemum dermatitis.

When interpreting the clinical significance of the literature, it is important to consider that Mitchell’s observation in 1972 that the concentration of pyrethrum used in commercial products is much lower than is used in diagnostic patch tests still holds today (21).

Concentrations of pyrethrum extracts as high as 25% were used in some of the reported challenges (29). In interpreting these studies, caution must be used in determining the relevance of the results to likely exposure scenarios, particularly for refined pyrethrum extracts that are typically used at less than 0.5% in insecticide formulations (30). Thus, the risk of sensitization is slight, regardless of the chemical

Table 1 Pyrethrins concentration associated with residential exposure and patch testing with 2% pyrethrum in petrolatum

Scenario	During or post application	Estimated skin concentration ($\mu\text{g}/\text{cm}^2$)	Ratio of patch test concentration/residential exposure concentration
Crack & crevice aerosol (CIK)	Post	0.011	1.23×10^5
Indoor total release poggier	Post	0.008	1.68×10^5
Carpet and room aerosol	Post	0.021	6.43×10^4
Pet care (shampoo)	During	0.124	1.9×10^4
Patch testing (2% pyrethrum in pet)	—	1350 ^{*†‡}	—

The residential exposure scenario based on data from *Pyrethrins: Non-Dietary (Residential) Risk Assessment* (31) with the exception of the pet care scenario data, which was based on a Non-Dietary Exposure Task Force (NDETF) pet cases shampoo study (32).

*Assumed 300 μL pyrethrum challenge.

†Assumed patch test area = 2.54 cm^2 (33).

‡Assumed pyrethrum contains 57% pyrethrins by weight.

potentially responsible for the effect. Table 1 presents estimates of human dermal exposure following several consumer product use scenarios (31). Compared to the applied dose used in a typical patch test of pyrethrum at 2% in petrolatum ($1300 \mu\text{g}/\text{cm}^2$), real-life human dermal exposure following consumer use of pyrethrins-containing products is at least 10,000 times lower. Thus, the clinical relevance of positive patch tests using concentrations as low as 2% pyrethrum in petrolatum is doubtful.

MATERIALS AND METHODS

To obtain relevant literature on pyrethrum and allergic contact dermatitis, we reviewed databases including Toxnet (multidatabase system), PubMed (1950–present), Embase (1974 present), Agricola (1970–present), Web of Science (1974–present), Scopus (1996–present)/Science Direct (variable), Online Computer Library Center (OCLC) PubChem and the Index Catalogue of the Surgeon General (1700s to 1945), and Science Citation Index (1974–present). We also used internet sources, including Google, Google Scholar, the British Museum, and the Research Libraries Group databases. In addition to reviewing more than 500 abstracts and reading more than 250 papers in seven languages dating from the late 1800s to the present, we hand searched textbooks in dermatology, dermato-allergy, and occupational dermatology in English, French, Italian, and German.

We set out to review the quality of the publications using the methodology outlined by Benezra et al. (34). The central aspect of their approach is a Degree of Confidence rating that indicates how well the data demonstrate whether a chemical does or does not induce allergic contact dermatitis. A six-point scale is used: a zero is assigned if the study shows no clear relationship of the case report to allergic contact dermatitis, and five implies total confidence that the study demonstrates allergic contact dermatitis in humans. The Degree of Confidence is assigned to study/test results based on whether or not certain criteria are met including: 1) presence of a

Table 2 Summarized data from possible clinical cases and patch test screening

Study year (ref. No.)	No. of + responses/ no. of subjects	Sex/ age (y)	Type of exposure	Prior dermal condition	Symptoms
1921 (27)	18/85 —26/85 1/85 1/85	—	Occupational Insecticide manufacturing plant	—	Dermatitis Erythema venenatum Vesicular dermatitis/dermatitis bullosa Intense anaphylaxis
1930 (35)	1/1	F/33	Occupational: housekeeper Black Flag insect powder (contains pyrethrum)	—	Vesicular, erythematous and popular eruption Urticarial wheals
1931 (36)	1/1	M	Occupational: zoologist (insecticide used on lab animals)	—	Dermatitis (face, neck, dorsa of hands & forearms) Diffuse erythematous scaling eruption Slight edema of the eyelids Erythematous papules of the forearms Intense itching and burning of the face (2 hr) Generalized eruption Within 2 days: eyes swelled significantly & face became covered with eczema
1934 (37)	5/18	M&F/28–74		Ragweed dermatitis	Dermatitis Redness and edema Pruritus
1934 (24)	104/225 1/114	—	—	Sensitive to ragweed pollen asthma and hayfever	
1934 (38)	1/1	M/43	Occupational: worker in insecticide and fly repellant plant	—	Dermatitis: erythematous, vesicular, scaly, crusting eruptions: fingers and hand spread to arm face and legs Severe itching and burning Dermatitis
	1/1	—	Occupational: worker in insecticide and fly repellant plant		
1935 (39)	1/618 3/618	—	Use of pyrethrum ointment for treatment of scabies	Scabies	Sensitivity Diagnosed contact dermatitis
1936 (40)	1	—	Occupational: pyrethrum grower (worked for long time before manifested)	—	Sensitivity Generalized eruption Large blebs formed on forehead Intense itching, lacrimation and coryza Short outbreaks of urticaria Sun exacerbated the symptoms

Challenge/patch test	Concentration	Results	Comment(s)
—	—	—	No diagnostic patch testing to confirm causation
Black Flag insect powder	—	Positive	Human clinical relevance not defined Concentration of commercial product unknown
Black Flag insecticide (contains pyrethrum)	—	Positive	Human clinical relevance not defined
J-O insecticide (contains pyrethrum)	—	Positive	Relevance to current commercial pyrethrins unknown
Intradermal test of pyrethrum	—	Delayed positive	Concentration of commercial products unknown
Intradermal test of timothy	—	Delayed positive	
Scratch test to pyrethrum	—	Negative	
J-O insecticide (contains pyrethrum)	—	Positive	
Percutaneous test to J-O	—	Delayed positive	
Intradermal test to pyrethrum	—	Negative	
p-Phenylenediamine	—	Positive	
Intradermal staphylococcus toxin	—	Positive	
Other epidermal, contact and foods	—	Negative	
Pyrethrum	—	Positive (1, 1+; 1, 2+; 1, 3+; 2, 4+)	Human clinical relevance not defined Concentration of challenge substances unknown Unclear how readings were performed Relevance to today's commercial pyrethrin unknown
Commercial pyrethrum extract (1930's)	—	Cutaneous reactions ++	Human clinical relevance not defined
Insecticide	—	72 h, erythema, edema & vesicles	Human clinical relevance not defined
Cattle spray	—	72 h, erythema, edema & vesicles	
Alcotate	—	48 h, erythema	Concentration of challenge substances unknown
Kerosene	—	48 h, erythema	
Methyl-salicylate	—	Erythema, edema and	Unclear how readings were performed
Antifreeze	—	vesiculation markedly	
Components of insecticide and cattle spray: Japanese insect	—	hypersensitive	
flower, oil of sassafrassy,	—	Mildly hypersensitive	
isopropyl alcohol, heavy	—	Negative	
petroleum distillate, di-ethyl-	—	Negative	
phthalate	—	Negative	
Components of insecticide:	—	Negative	
Japanese insect flower, oil of	—	Negative	
sassafrassy, isopropyl	—		
alcohol, heavy petroleum	—		
distillate, di-ethyl-phthalate	—		
Pyrethrum ointment	0.5–0.75% pyrethrin	Positive	Human clinical relevance not defined
Pyrethrum ointment	0.5–0.75% pyrethrin	Negative	Relevance to today's commercial pyrethrin unknown
—	—	—	No diagnostic patch testing to confirm causation

(Continued)

Table 2 Continued

Study year (ref. No.)	No. of + responses/ no. of subjects	Sex/ age (y)	Type of exposure	Prior dermal condition	Symptoms
1936 (41)	1/595 5/1213	—	Use of pyrethrum ointment for treatment of scabies	Scabies Scabies	Dermatitis Sensitive
1941 (42)	1/1	—		—	—
1947 (43)	6/62	M	Daily anointment behind ear w/cream (40% concentrate of pyrethrum)	—	Various reactions, including: Visible reactions Erythema after continued use followed by papular eruptions Sting sensation
1970 (17)	1/5	—	—	Patients with allergic eczematous contact dermatitis to Frullania	—
1972 (21)	1/1	M	—	—	—
1973 (44)	—17/540	—	—	Almost all patients with history of skin disease; the majority suspected of having eczematous dermatitis	—
1973 (45)	1/1	M/76	—		Lichenified dermatitis of exposed areas
	1/1	?/60	—	Five years of recurrent rashes	Confined to exposed areas except for papular dermatitis of the lower abdomen
	1/1	M/76	—	20 years of recurrent generalized dermatitis	
	1/1	M/64	—	Recurrent dermatitis for 16 years	Lichenified dermatitis of exposed areas
	1/1	M/69	—	Persistent dermatitis for 8 years	Lichenified dermatitis of exposed areas
	1/1	M/43	—		Acute bullous contact dermatitis of hands a forearms scattered vesicular rashes on trunk
	1/1	M/63	Use of fly spray containing pyrthins	4 year recurrent dermatitis from contact with chrysanthemums	Dermatitis on forearms
1973 (46)	2/50	—	—	—	—

Challenge/patch test	Concentration	Results	Comment(s)
Pyrethrum ointment	0.75% pyrethrin	Positive	Human clinical relevance not defined No details as to when and how the test was read Relevance to today's pyrethrin unknown
Pyrethrum extract in mineral oil (right forearm)	— 1% (total pyrethrin)	— + (48 h)	Human clinical relevance not determined
Pyrethrum extract in mineral oil (trunk, near iliac crest)	— 1% (total pyrethrin)	— + (48 h)	Relevance to current commercial pyrethrin unknown
Pyrethrin concentrate (upper left forearm)	93% pyrethrins	— +? (27 h)	Possibly ACD No diagnostic patch testing to confirm causation Relevance to current commercial pyrethrin unknown
Pyrethrum (<i>C. Coccineum</i>)	10% pet	++ +	Human clinical relevance not determined Relevance to current commercial pyrethrin unknown Patch test concentration appears high
Pyrethrosin (80% aq ethanol)	1.0% aq ethanol	++	Human clinical relevance not defined
Dried pyrethrum flower heads	0.1% aq ethanol	++ +	Relevance to current commercial pyrethrin unknown
Pyrethrum powder	2% pet	++	
Pyrethrum "marc"	2% pet	++ +	
Pyrethrum oleoresin (30% pyrethrins)	2% pet	++	
Fully dewaxed pyrethrum extract	2% pet	++	
Refined pyrethrin extract	2% pet	++	
Pyrethrin II	2% aq ethanol	+	
Pyrethrum flowers	—	Positive (7, 1 +; 7, 2 +; 2, 3 +; 4, 1 +)	Human clinical relevance not defined Composition of test substance uncertain Relevance to current commercial pyrethrin unknown
Pyrethrins	—	Positive	Human clinical relevance not defined
Pyrethrins	—	Positive	Relevance to current commercial pyrethrin unknown
Pyrethrins (photopatch test)	—	Positive	
Pyrethrins	—	Positive	
Pyrethrins	—	Positive	
Pyrethrins	—	Positive	
Pyrethrins	—	Positive	
Pyrethrum	100%	Positive	Human clinical relevance not defined Patch test concentration appears high

(Continued)

Table 2 Continued

Study year (ref. No.)	No. of + responses/ no. of subjects	Sex/ age (y)	Type of exposure	Prior dermal condition	Symptoms
1974 (47)	3/45	—	—	—	—
—1975 (23)	0/14	M&F/8–80		Sensitivity to ragweed	2+ response to scratch and/or patch test to ragweed protein and/or oleoresin
1975 (48)	0/5	—	—	Chrysanthemum ACD	—
	0/20	—	—	Nonsensitized controls	—
1976 (13)	1/6	—	—	Elicited positive reactions to an extract of chrysanthemum of florists	—
	1/13	—	—		—
	0/6	—	—	Experimental control elicited positive reactions to an extract of chrysanthemum of florists	—
1980 (29)	1/1	40	Occupational: vineyard worker	Recurring eczematous skin condition for the past 1.5 years	Itching and burning first on back of hands then spreading to lower arms and face diagnosed with typical ACD
1981 (49)	1	F/2 wks	Crib sprayed w/pyrethum- based insecticide	—	12 h: elevated temperature and generalized 36 h: symmetrical maculopapular rash (abdomen, back, limbs) facial erythema lesions 0.5 to 2 cm with a erthyematous elevated periphery and clean center; erythema multiforme
1986 (50)	2	—	Use of shampoo: (0.165% pyrethrins 2.0% piperyonl butoxide, 5.3% deoderized kerosene, 92.8% inerts, 6% oleoresin parsley seed, (Triton X-100 40%, fragrance, propylene glycol)	—	Corneal abrasions Irritation
1987 (51)	0/389	M&F/11–84	—	Either contact dermatitis on hands or nonallergenic skin disorders	—
1990 (52)	1/1	F/40	Occupational worked seasonally in a tobacco plantation (3 yr)	—	Highly pruriginous eczematous lesions on exposed areas
1993 (53)	1/1	—	—	Either prior positive patch test reaction to SL mix or suspected of having Compositae dermatitis: showed clinical features and suspicions of exacerbations on sun exposure	—
1995 (54)	1/1	M/41	Occupational farmer (pyrethrin & endosulfan use)	—	Facial pruritus, nausea Biopsy: lymphohistiocytic

Challenge/patch test	Concentration	Results	Comment(s)
Pyrethrum	—	Positive	Human clinical relevance not defined
Commercial RID	0.3% pyrethrins 3% piperonyl butoxide 1.2% petroleum distillate	All negative	Human clinical relevance not defined
Pyrethrins	1% mixture	All negative	Human clinical relevance not defined
Pyrethrins	1% mixture	All negative	Relevance to current commercial pyrethrin unknown
Pyrethrum	5% ethanolic sol	Positive	Human clinical relevance not defined
Pyrethrum	6% ethanolic sol	Positive	
Pyrethrins II	5% ethanolic sol	All negative	
Pyrethrum	25% olive oil	Positive (+, day 1; ++ days 2 and 3)	Clinical history intriguing, possible relevance Relevance to current commercial pyrethrin unknown Patch test concentration appears high
—	—	—	Human clinical relevance not defined No diagnostic patch testing
—	—	—	Not tied specifically to pyrethrum Possibly due surfactants in shampoo
pyrethrum	2% pet	All negative	Human clinical relevance not defined
Pyrethrum	2% pet	+++ (48 & 1.96 h)	Human clinical relevance not defined
Pyrethrosin	0.1% pet	Negative	Human clinical relevance not defined
Pyrethrum	2% pet	++ (D2)	Not diagnostic of ACD Tests were not repeated to rule out excited skin erthematous

(Continued)

Table 2 Continued

Study year (ref. No.)	No. of + responses/ no. of subjects	Sex/ age (y)	Type of exposure	Prior dermal condition	Symptoms
					perivascular infiltrate necrotic basal keratinocytes
1996 (55)	1/1	F/66	Occupational horticulturalist	10 yr of eczema outbreaks on areas that were in direct contact with <i>Dendranthema</i> <i>morifolium</i> (Ramat)	Acute eczema on exposed areas 2 days after Ramat
1998 (56)	0/9	—	—	Chronic actinic dermatitis	—
1998 (57)	1/1	M/65	Gardening (and fertilizer use)	Chronic eczema on the face and hands	Presence of erythematous squamous (6 months clinical lesion relapses
2000 (58)	1/11	M	Occupational fishermen	—	Erythema, edema, scaling, or lichenificat□
2001 (59)	4/12	—	—	Compositae-sensitive individuals	—
	9/28	—	—	—	—

These eight decades of publications span vast differences in patch test techniques and interpretation of clinical relevance. Most patches performed with samples not as refined as current commercial products (see text for details).

Challenge/patch test	Concentration	Results	Comment(s)
			multiforme like eruption
Pyrethrum	2% pet	++ (D4) ++	Human clinical relevance not defined
pyrethrum	2% pet	All negative	Author hypothesizes about possible cross reactions to other SLs Human clinical relevance not defined
Pyrethrum	2% pet	++ + (day 2 & 3)	Human clinical relevance not defined
Pyrethrin	—	Hypersensitivity	Human clinical relevance not defined Author does not suggest clinical relevance
Pyrethrum	1% pet	Positive	Human clinical relevance not defined
Pyrethrosin	0.1% pet	Positive	

vehicle-treated or untreated control; 2) use of a concentration of test substance judged sufficient to elicit a response; 3) use of an appropriate vehicle; 4) use of a sufficient purity of the substance tested to ensure that the response obtained is for the chemical under consideration, and; 5) use of a sufficient number of cases evaluated to ensure a meaningful response.

RESULTS

Table 2 represents our best interpretation of the data in original publications relevant to pyrethrum and allergic contact dermatitis (Type IV hypersensitivity). Many references evaluated here date to the early 20th century, when the details of chemistry then known and the criteria for the diagnosis of allergic contact dermatitis were much less developed than today. Note, the literature pertaining to pyrethrum and immediate hypersensitivity reactions (Type I or contact urticaria) are not covered in this review. These will be addressed in a later publication.

The results of our evaluation of the literature are presented in Table 2. Although we attempted to rigorously apply the approach of Benezera et al. (34) to our evaluation, because the reports relating to pyrethrum are severely limited in detail and rigor of method, this was not possible. However, the principles he outlined guided our evaluation. All of the studies evaluated in this review would classify as either a zero or a one, implying they failed all the criteria (listed previously in the Methods section), the former, or they failed several of the criteria and the results are not considered reliable, the latter.

For example, the subjects in many of the earlier studies reviewed (pre-1970) were patch tested with actual pyrethrins containing products, hence, failing criterion No. 4 requiring the use of a well-defined test article. Moreover, none of the reports detailed their selection of an appropriate vehicle and concentration of test substance to elicit a response. Additionally, much of the literature reviewed were case studies involving patch testing only one or a small number of subjects. Therefore, there were not a sufficient number of cases evaluated to ensure that the responses were meaningful.

Further, in considering the implications of these reports, it is useful to refer to Marrakchi and Maibach (60), who provide details of the evidence-based method for determining clinical relevance of a response for a given subject. This operational definition with several steps aids separating a diagnostic test—a bioassay (patch test)—from defined causation of Type IV hypersensitivity—clinical allergic contact dermatitis.

Fundamentally, many subjects can have false-positive patch tests or even a patch test that indicates true Type IV hypersensitivity, yet do not have clinical manifestations of allergic contact dermatitis. Examples of frequent false positives are to materials patch tested at the threshold of irritation, including some metal salts and some quaternary ammonium compounds. Examples of contact allergy (i.e., legitimate and documented Type IV hypersensitivity) demonstrated in patch tests that only infrequently have demonstrated clinical skin manifestations are gold and gold salts.

In reviewing these older cases, as well as some of those more recent, we failed to identify subjects that we could ascertain that had clinical allergic contact dermatitis. The number of positive patch tests screened over the century appears minimal. Most

reports (Table 2) document testing of many subjects as a part of routine screening of dermatitis in which the investigators wished to identify an unknown allergen. Relatively few studies report results of testing in individuals clinically suspected of having pyrethrum allergic contact dermatitis. None document whether the patch test was demonstrated to be of clinical relevance and, if so, the criteria used for this determination.

DISCUSSION

No literature interpretation with regard to pyrethrum is complete without appreciation of the botany, chemistry, and refinement of the botanical extracts. Many of the early investigations on pyrethrum were performed with crude preparations and without chemical characterization. Modern refinement procedures and chemical analysis permit the production and characterization of a much more refined extract. Attempting to understand whether clinical pyrethrum allergic contact dermatitis exists we suggest it is appropriate to separate the earlier literature (1893–1967) from the more recent literature (post-1967) based on the approximate time at which “modern pyrethrum” was being produced globally.

Critical to any determination of causation of allergic contact dermatitis is the knowledge of the chemistry of the test article. Despite the advances in the commercial refinement of pyrethrum for use in products, samples of such refined materials have seldom been used by investigators and no commercial source has been available. The Pyrethrin Joint Venture (PJV) is working to make such samples available for future diagnostic studies.

Although extensive patch testing has been done with pyrethrum extracts, most studies were done before the current refined commercial material was available (pre-1967). Thus, it is possible, if not likely, that some of the subjects in the older studies were patched with irritating levels of pyrethrins (possibly associated with unknown impurities), leading to a false-positive reaction. In the future, it is essential that, before patching, investigators test normal controls with serial dilution of the current commercial refined material to verify the nonirritating level and to select the diluent. Recent literature suggests the 2% pyrethrins extract in petrolatum may fulfill these criteria; however, no documentation of this occurs in the literature. Moreover, when faced with a suspected sensitization case in the future, clinical relevance should be ascertained by relating the clinical morphology, the clinical history, and subsequent follow-up. Details of this algorithm for determining clinical relevance are provided by Ale and Maibach (61). Presently, we know of no cases where such clinical relevance has been examined or established with regard to pyrethrum. Should such detailed data on future suspected cases become available, it will then be possible to more clearly ascertain whether primary sensitization or cross reaction in ragweed-sensitive individuals is occurring as proposed by Fisher (1). Although this is a theoretical possibility, our evidence-based review of the literature (using the current level of diagnostic standards) and consideration of the current chemistry suggests that allergic contact dermatitis does not occur in response to pyrethrum at a significant incidence in either ragweed-sensitive individuals or otherwise.

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