

ORIGINAL ARTICLE

Pesticide contact dermatitis in agricultural workers of Himachal Pradesh (India)

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Background: Common pesticides used in the region by agricultural workers may cause contact allergy.

Methods: Thirty agricultural workers with a history of pesticide exposure and dermatitis involving the face, neck, trunk or extremities, and 20 controls comprising 2 groups of 10 subjects each, group 1 with dermatitis and no exposure to pesticides, and group 2 with neither exposure to pesticides nor dermatitis, were patch tested with 10 pesticides commonly used in the region by use of the Finn Chamber method.

Results: The 30 patients, 20 of whom were male, aged 30–77 years, had dermatitis for 1 month to 18 years, with relapses and remissions. Seasonal exacerbation was present in 18 patients. Six patients attributed aggravation of their dermatitis to pesticide exposure, and 2 of these reacted positively to propiconazole. Positive patch test reactions to pesticides occurred in 10 patients, but not in controls. Thiuram was the commonest sensitizer (4 patients). Three patients were sensitized to propiconazole, and 2 patients reacted positively to metaldehyde. Formaldehyde, mercaptobenzothiazole, cypermethrin and isoproturon gave positive reactions in 1 patient each.

Conclusion: The sensitizing potential of pesticides remains a concern. Apparently, pesticide contact dermatitis is more common than expected, but remains under-reported, as the implicated pesticides vary across regions and according to the crop patterns.

KEYWORDS

agricultural workers, cypermethrin, formaldehyde, India, isoproturon, mercaptobenzothiazole, metaldehyde, occupational dermatitis, propiconazole, thiuram

1 | INTRODUCTION

Pesticides constitute an extremely heterogeneous group of chemical compounds that are used extensively for various purposes, for example, as insecticides, herbicides, fungicides, rodenticides, nematocides, and fumigants, in agriculture, horticulture and the cultivation of vegetables (olericulture) across the world. There are >50 000 commercial formulations of pesticides in common use, with 600 active ingredients.¹ Commercial floriculture, fruit packaging, forestry and the need to increase food production, owing to population increases, have promoted the extensive use of pesticides. It is noted that developing countries account

for 20% of world pesticide usage, particularly inexpensive chemicals that are toxic and environmentally persistent.^{2,3} Pesticides are being increasingly identified as causes of occupational skin diseases, because of either exposure to the intermediate chemicals during manufacture, pesticide spraying, the sowing of pesticide-preserved seeds, weeding, the harvesting of previously sprayed crops, exposure to pesticide-contaminated soil and water during preparing for planting and cultivation, or the handling of farm produce.^{1,4–7} Pesticides are capable of causing urticaria, discolouration of the skin, hair, and nails, erythema multiforme, chloracne, porphyria cutanea tarda, toxic epidermal necrolysis and allergic and/or irritant contact dermatitis among exposed persons.⁸

The increasing use of pesticides has been implicated in the increasing incidence of diseases caused by chronic exposure, particularly of the skin, especially among those who neglect the advocated protective measures.^{6,9,10} Many pesticides used in different parts of the world also vary according to the type of crop and the usage pattern, which keeps changing over time. For instance, in Panamanian banana plantation workers, chlorothalonil, thiabendazole, imazalil and aluminium hydroxide were the commonest causes of pesticide contact dermatitis in 2002, whereas these were carbaryl, benomyl and ethoprophos in 2004.^{1,9} The most common allergens identified were pesticides (35%), rubber compounds (17%), sunscreens (9%), epoxy resin (9%), and plant materials (9%).¹¹ Inorganic compounds such as copper sulfate and the herbicides propachlor and alchlor were common irritants.¹² Various new formulations are also being introduced into the market while older ones are withdrawn, leading to the underdiagnosis of pesticide contact dermatitis. Himachal Pradesh (30°N, 70°E) is a small hill state of India in which the majority of the population are primarily engaged in agriculture and related occupations. Wheat, maize, barley, paddy and seasonal/off-seasonal vegetables and fruits are the usual crops grown in this region, which has hills and plains with semitropical climatic conditions. The patterns and number of pesticides used also vary accordingly. This prospective study was carried out between June 2016 and May 2017 to evaluate the role of commonly used pesticides in causing contact dermatitis among agricultural workers in the region.

2 | METHODS

Thirty consecutive agricultural workers with contact dermatitis presenting to the outpatient clinic were enrolled for pesticide patch testing. They had been engaged in farming and related activities for a minimum of 2 years, and had a history of exposure to pesticides. Patients aged <18 years, patients with atopic dermatitis or photodermatitis and pregnant and lactating women were excluded. Patients with acute dermatitis were enrolled after the acute episode subsided, and they had been off all treatments, including systemic or topical corticosteroids, for ≥ 1 week. The controls were 2 groups each of 10 healthy volunteer adults. Group 1 included subjects with a history of exposure to pesticides but no dermatitis, and group 2 included subjects with neither pesticide exposure nor dermatitis. All enrolled subjects were subjected to detailed medical history-taking and clinical examination. Various clinical patterns of contact dermatitis were documented (Table 1).

Table 2 lists 13 pesticides that are used in the region for commonly grown crops, vegetables, and fruits. They were patch tested along with the Indian baseline patch test series from Chemotechnique Diagnostics (Vellinge, Sweden), marketed in India by Systopic India (New Delhi, India), with Finn Chambers according to ESCD guidelines.¹³ Finn Chambers (8 mm in diameter) were applied on the upper back and left for 2 days. The readings were performed on day (D) 2 and D3, and the results were graded according to ICDRG criteria (Table S1). The positive results persisting on D3 were considered to be significant, and their relevance was determined (present, past, or unknown relevance, or definite, probable, possible, past or unknown

relevance). The entire pesticide patch test series was initially tested at 0.1%, 0.5% and 1.0% in 5 healthy adult volunteers with no dermatitis or exposure to pesticides, and 1% was finally used for patch testing in study subjects.

3 | RESULTS

The 30 patients, including 20 males, aged between 30 and 77 years (mean 56.2 years), were actively involved in agriculture, horticulture, oliculture, floriculture, and cattle rearing, primarily or during their spare time. The duration of dermatitis at the time of presentation ranged from 1 month to 18 years, with relapses and remissions. Whereas 10 patients could not identify or recall any causative or exacerbating factor, others implicated multiple factors exacerbating their dermatitis. Six patients implicated pesticides as causes and exacerbating factors for their dermatitis, but could not name these. Only 2 of them showed positive patch test reactions to propiconazole. A history of photoaggravation was present in 10 patients, whereas 5 patients implicated exposure to straw or grain dust, soil, hay dust and cattle fodder as exacerbating factors for their dermatitis. Seven patients attributed their aggravations to *Parthenium hysterophorus*. Sixteen patients had aggravation of their dermatitis during summers and rainy seasons, and in 2 patients the dermatitis was severe in winters. Acral and facial dermatitis (8 patients) and airborne contact dermatitis (5 patients) were the commonest patterns (Table 2).

Tables S1 and S2 show the results and baseline characteristics and 10 (33.3%) patients with positive pesticide results and controls. Airborne contact dermatitis was the commonest presentation (3 patients), followed by hand and acral/facial dermatitis (2 patients each), and facial dermatitis, acral dermatitis, and widespread body involvement (1 patient each). All of these patients had a history of exposure to pesticides without using protective measures. Positive reactions were observed to thiuram mix in 4 patients, propiconazole in 3 patients, and mercaptobenzothiazole and formaldehyde in 1 patient each, these haptens being the commonest fungicides, eliciting 9 positive patch test reactions in 7 patients. Concerning insecticides, metaldehyde elicited positive reactions in 2 patients and cypermethrin elicited a positive reaction in 1 patient. Isoproturon, a weedicide, elicited a positive reaction in 1 patient only. Cypermethrin elicited an irritant reaction in a 60-year-old woman who had suffered from chronic acral dermatitis for 18 years. None of them was using gloves, hats, face masks, boots, long coats or goggles for protection while spraying pesticides.

Eight of these 10 patients also had positive patch test reactions to nickel, *P. hysterophorus*, *p*-phenylenediamine, potassium dichromate, cobalt, balsam of Peru (*Myroxylon pereirae*), fragrance mix, benzocaine, epoxy resin and neomycin from the Indian baseline patch test series (Table S1). Three of these patients showed positive reactions to ≥ 2 haptens.

None of the controls from either group showed positive patch test reactions to pesticides, but positive reactions were seen to allergens from the Indian baseline series, namely, parthenium in 1 control (group 1) and nickel sulfate in 2 controls, 1 each from group 1 and group 2.

TABLE 1 Pesticides used commonly by agriculture workers in the region

Type	Name of pesticide	Uses as pesticides and types of crop	Patch test concentration used
Fungicides	Thiuram mix ^a	Protectant for seed crops from stem gall of coriander, damping off, smut of millet, or neck rot of onions	1% pet.
	Mercaptobenzothiazole ^a	Protects barley, cotton, corn and wheat from powdery mildews, mould leaf spot diseases, and rusts	2% pet.
	Thiram (tetramethylthiuram disulfide)	A component of thiuram mix. Applied directly on strawberries, peaches and after harvesting on a number of seed crops, including small and large seeded vegetables, cereal grains, coniferous seeds, cottonseeds, ornamental seeds, and soybeans, to protect from stem gall of coriander, damping off, smut of millet, or neck rot of onions	1% aq.
	Propiconazole	Protects crops (barley, corn, oats, rice, rye, and wheat), celery, peanuts, stone fruits, sugarcane and pineapple from leaf spots, rust, and powdery mildews	1% aq.
	Formaldehyde ^a	Disinfectant, fungicide, soil fumigant, and antimicrobial agent Preservative against mildew and spelt in wheat, and rot in oats. Used for destroying flies and other insects	1% aq.
Insecticides	Metalddehyde	A bait to kill slugs and snails in greenhouse crops, small-fruit plants, avocado, citrus orchards, berries, broccoli, cauliflower, lettuce, cabbage, tomatoes, and ornamentals	1% pet.
	Cypermethrin	A pyrethroid insecticide spray for cotton, cereals, vegetables, and fruits	1% aq.
	Phorate	An organophosphate that controls sucking and chewing insects, leaf hoppers, leaf miners, mites, some nematodes and rootworms in pine forests and on root and field crops (corn, cotton, coffee, and bulbs), and ornamental and herbaceous plants	1% pet.
	Imidacloprid	Controls sucking insects, including rice hoppers, aphids, thrips, whiteflies, termites, turf insects, soil insects, and beetles. Used on rice, cereal, maize, potatoes, vegetables, sugar beets, fruit, cotton, hops, and turf	1% aq.
Weedicides	Isoproturon	Pre-emergence and post-emergence control of annual meadow grass, black grass, ryegrass, silky bent grass, wild oat, broad leaf weeds used for spring and winter wheat, barley, and rye crops	1% aq.
	Atrazine	Prevents pre-emergence and post-emergence broadleaf and grassy weeds in crops such as sorghum, maize, sugarcane, pine, and eucalyptus plantations	1% aq.
	Butachlor	Controls annual grass weeds and broadleaf weeds in paddy, wheat, barley, sugar beet, cotton, peanut and cabbage crops	1% aq.
	2,4-D (2,4-dichlorophenoxyacetic acid)	Controls all broadleaf-type weeds and creepers in tea plantations, fruit orchards, and paddy and sugarcane fields	1% aq.

aq., water; pet., petrolatum. These pesticides were procured from Chaudhary Sarwan Kumar Himachal Pradesh Agricultural University, Palampur (Kangra), Himachal Pradesh, India, and the patch test series was prepared in the Institute's laboratory by selecting standard concentrations suggested by Cronin.⁸ Non-irritant concentrations were used for patch testing in all study subjects. Aqueous solutions were used for patch testing, as these pesticides are being used routinely after mixing with water, except for phorate and metalddehyde, which are water-insoluble.

^a Thiuram mix 1%, mercaptobenzothiazole 2% and formaldehyde 1% in the Indian baseline patch test series are also used as pesticides.

4 | DISCUSSION

Pesticide contact dermatitis is usually considered to be uncommon, with a prevalence varying from rare to 57% across regions and depending on pesticide usage patterns.^{14–17} Its exact prevalence in India remains unknown, and positive reactions to pesticides occurred in 36.6% of 30 farmer patients in an earlier study, whereas the prevalence was 57% among tea garden workers and 26.7% among fruit and vegetable farmers in subsequent studies.^{15–17} In comparison, 33.3% of our patients showed positive patch test reactions to pesticides. The use of pesticides, including fungicides, herbicides, insecticides, rodenticides, and soil fumigants, is high worldwide, and pesticide poisoning from occupational exposure has frequently resulted from skin contact. Pesticides can cause both irritant and allergic contact dermatitis localized to the sites of contact. The palms and dorsa of the hands, the insteps of the feet and the fronts of the legs are affected more frequently than the forearms, the backs of the legs, and the fronts of the thighs, which remain covered with clothes, manifesting as hand

dermatitis, acral, acrofacial or airborne contact dermatitis, and occasionally, as phototoxic or photoallergic reactions.^{18–21} Similar clinical presentations were found in our patients with positive patch test reactions to pesticides. This also shows that direct contact with pesticides remains the major predisposing factor for pesticide dermatitis, and protective clothing is one of the important preventive measures suggested previously.²²

In India, dithiocarbamates, thiuram, organophosphorus compounds, synthetic pyrethroids and 2,4-dichlorophenoxyacetic acid (2,4-D) were the most common sensitizers in an earlier study, as compared with captan, propargite, chlorpyrifos, tree spray oil and thiuram in a later study.^{15,16} Thiurams as included in thiuram mix are used as fungicides in the fields and for protecting seed crops. Sensitization may occur from handling seeded vegetables, cereal grains, soybeans, and coniferous, cotton and ornamental seeds. Positive reactions were observed in 13.3% of our patients. Specifically, thiram (tetramethylthiuram disulfide) may cause skin and eye irritation, and is an occasional contact sensitizer.¹⁶ However, it did not elicit any positive

TABLE 2 Clinical patterns of contact dermatitis observed

Clinical patterns	Definition	Number of patients (%) N = 30
Acro-facial dermatitis	Dermatitis predominantly affecting the face and neck (deep recesses of the face may or may not be spared) and distal extremities	8 (27)
Airborne contact dermatitis	Dermatitis involving exposed body parts, including deep creases of the face, cubital and popliteal fossae, and other body folds, caused by allergens released in the atmosphere	5 (20)
Acral dermatitis	Concurrent involvement of the hands and feet with or without involvement of the distal extremities	4 (13)
Hand dermatitis	Dermatitis predominantly involving the hands, with or without involvement of the dorsal surface	4 (13)
Facial dermatitis	Dermatitis predominantly involving the face, sparing creases and deep recesses	3 (10)
Mixed pattern	Combination of all or any of the above patterns, including widespread and involvement of multiple body sites	6 (17)

reactions in our patients. Similarly, mercaptobenzothiazole and its derivatives are contact fungicides for barley, cotton, corn, and wheat, eliciting positive reactions in 1 patient. However, non-occupational contact sensitization, both from ingredients of thiuram mix and from mercaptobenzothiazole byproducts in daily use (rubber/vinyl gloves, boots, and tyres), in studied subjects cannot be ruled out, as both are also used as additives in rubber products.²³

Propiconazole, a fungicide that is mainly used for barley, corn, oats, rice, rye, and wheat, elicited positive reactions in 10% of our patients, as compared with 3.8% and 4.2% of patients, respectively, in 2 other studies.^{1,9} A positive reaction to formaldehyde occurred in 1 patient in our study. It is mainly used as a preservative for wheat and oats. It has been reported to be associated with contact sensitization in 0.67% to 4.2% of cases as a result of degradation of synthetic resins in the inner coatings of topical medication tubes.²⁴ Metaldehyde, a bait insecticide, is used in the form of granules or sprays, or applied to the soil around plants or mixed with bran for greenhouse cultivation. It may cause skin and eye irritation on exposure. The positive patch test reactions to metaldehyde in 2 of our patients indicate that its sensitizing potential needs to be evaluated further. The pyrethroid cypermethrin is widely used as a contact insecticide spray for cotton, cereals, vegetables, and fruits. Although it is considered to be a weak sensitizer, topical contact causes cutaneous sensations and paraesthesia, and it can elicit positive patch test reactions that may or may not have clinical relevance.^{16,25,26} Similarly, it elicited both an allergic reaction and an irritant reaction in 1 each of our patients. Isoproturon is used as a weedicide, mainly in wheat, barley and rye fields. Although it is not a known contact allergen, it elicited a positive patch test reaction in our 1 of our patients. Finally, 2,4-D, butachlor and atrazine did not elicit positive reactions in any of our patients.

However, the overall variability could be attributable to differences in the types of pesticide tested or used for various crops grown at a given time in this region.

Contact sensitivity resulting from occupational exposure to weeds such as *P. hysterophorus*, agricultural chemicals or other ingredients such as *p*-phenylenediamine, compounds of the black rubber mix, metals (nickel, chromium, and cobalt), *M. pereirae*, fragrance mix, parabens mix, chlorocresol, benzocaine, epoxy resins and neomycin or nitrofurazone from multiple products in daily use (cement, rubber, leather in shoes, and cattle feed), as in our 8 patients, is not uncommon, being found in approximately two thirds of agricultural workers.^{15,27–29} Multiple sensitizations to thiuram mix and propiconazole, and to thiuram, propiconazole, and isoproturon, respectively, in 2 patients appear to represent independent sensitization, because these substances are not known to cross-react.

5 | CONCLUSION

Despite the limitations inherent to the small number of patients and pesticides tested, it can be inferred that pesticides may cause occupational contact dermatitis more often than is suspected based on the notion of a low sensitizing potential. A high clinical suspicion, a detailed occupational history and patch testing with pesticides remain important for the diagnosis and management of pesticide dermatitis. It is imperative to patch test with pesticides that are actually used at a given time and place, as the implicated pesticides may vary across regions and according to the crop patterns. Older products may be either banned, withdrawn, or replaced with newer ones, and no standard pesticide patch test series is currently available. Personal protective equipment, particularly gloves, in view of frequent hand contact with pesticides, avoiding direct skin contact while mixing, transporting, spraying or handling pesticides, maintenance of equipment and correct techniques for spraying pesticides manually will be important preventive measures, and must be emphasized in view of the frequent lack of protective measures despite the widespread use of pesticides.

ACKNOWLEDGEMENTS

The authors thank Mr Arun Vyas, District Agriculture Officer (Kangra), for identifying the pesticides used commonly in the region and procuring them from Chaudhary Sarwan Kumar Himachal Pradesh Agricultural University, Palampur (Kangra), Himachal Pradesh, India. The expert help provided by Mr Satya Bhushan, Assistant Professor (Biochemistry), from the Central Research Laboratory, Dr R. P. Government Medical College, Kangra (Tanda), Himachal Pradesh, India in preparing the precise concentrations of pesticide patch test allergens is gratefully acknowledged.

The clinical data form part of the thesis submitted to Himachal Pradesh University, Shimla (Himachal Pradesh) for the degree of MD (D.V.L.).

The study was approved by the Institutional Scientific Protocol Review Committee and Institutional Ethics Committee (Rgn no. ECR/490/Inst/HP/2013). Informed consent was obtained from all patients to be enrolled in the study. All procedures followed were in

accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Conflict of interest

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Sharma A, Mahajan VK, Mehta KS, et al. Pesticide contact dermatitis in agricultural workers of Himachal Pradesh (India). *Contact Dermatitis*. 2018;1-5. <https://doi.org/10.1111/cod.13049>

Online supplemental table-1: Pesticide contact dermatitis: Clinical patterns and Patch test results (n=10)

Age and Gender	Duration of dermatitis	Clinical patterns	Pesticides patch test allergens and grades of positive results							Sensitivity to allergens from Indian standard series (grades of positive results) ^b
			Thiuram mix 1%	Metaldehyde 1%	Propiconazole 1%	Formaldehyde 1%	Mercapto-benzothiazole 2%	Cypermethrin 1%	Isoproturon 1%	
60M	1year	Acrofacial dermatitis	1+	–	–	–	–	–	–	–
40F	1monh	Facial dermatitis	–	1+	–	–	–	–	–	Nickel So4, 5% (1+)
60M	5years	ABCD	3+	–	2+	–	–	–	–	Parthenium 1% (2+)
46M	5years	Acral dermatitis	–	–	–	2+	–	–	–	Pot. dichromate, 0.5% (2+), Cobalt So4, 1 % (2+)
77M	4years	Widespread dermatitis	–	–	–	–	1+	–	–	Pot. dichromate, 0.5% (1+), Neomycin So4, 20% (1+), Benzocaine, 5% (1+), PPD, 1% (3+), Paraben mix, 1% (1+), Epoxy resin, 1% (1+), Nitrofurazone, 1% (1+), Balsam of Peru, 25% (1+), Black rubber mix, 0.6% (1+)
60M	1years	Hand dermatitis	–	–	–	–	–	3+	–	–
62F	15years	ABCD	1+	–	–	–	–	–	–	Parthenium, 1% (3+)
48F	5years	Hand dermatitis	–	1+	–	–	–	–	–	Pot. dichromate, 0.5% (2+), Epoxy resin, 1% (1+), Fragrance mix, 8% (2+), Chlorocresol, 1% (1+)
55F ^a	12years	Acrofacial dermatitis	2+	–	1+	–	–	–	1+	Parthenium, 1% (3+)
70M ^a	1month	ABCD	–	–	1+	–	–	–	–	Parthenium, 1% (2+)

M, male; F, female; –, negative; +, positive; ABCD, airborne contact dermatitis; PPD, *p*-phenylenediamine; Pot., potassium; So4, sulfate.

^aThese two patients had attributed exacerbation of their dermatitis to pesticides.

^bThe patch test results were graded as 1+, weak positive reaction (palpable erythema, infiltration, few papules); 2+, strong positive reaction(erythema, infiltration, papules, vesicles); 3+, extreme positive reaction (intense erythema, infiltration, coalescing vesicles/bulla); IR, irritant reaction(glazed erythema, burn-like erosion, pustules, edge effect)

Online supplemental table-2: Baseline characteristics of patients with positive pesticide patch test and controls

Baseline characteristics		Number of patients	Number of Controls	
		<i>n</i> =10	Group-1 <i>n</i> =10	Group-2 <i>n</i> =10
Gender	Males (M)	6	2	2
	Females (F)	4	8	8
	M: F	1.5:1	1:4	1:4
Age in years	<50	3	8	8
	51-60	4	1	2
	61-70	2	1	-
	>70	1	-	-
	Mean (y)	57.8	42.5	43.1
Duration	1m -1y	4	-	-
	>1 -4y	1	-	-
	>4-5y	3	-	-
	>5-15y	2	-	-
	Mean (y)	4.8	-	-
Occupation	Agriculture	10	10	-
	Office goers	-	-	1
	Business	-	-	1
	House makers	4	8	8
Patch test results		As per online supplemental table-3	Parth-1 Nickel sulfate	Nickel sulfate

M, male; F, female; m, month; y, year; Parth, Parthenium; NiSo₄, Nickel sulfate. All women were house makers in addition. None of the patients or controls was on systemic corticosteroids at the time of patch testing.