CROSS REACTIONS BETWEEN SOME PESTICIDES AND THE FUNGICIDE BENOMYL IN CONTACT ALLERGY

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Abstract: To clarify the cross sensitivity between the fungicide benomyl and some other pesticides, an animal experiment and a field survey were undertaken.

1. About 20% of female farmers, who had not used benomyl, showed positive reactions to 1% benomyl in patch tests. From the results of patch tests, cross reactions between benomyl and such pesticides as Diazinon, Saturn, Daconil and Z-Bordeaux were considered to occur.

2. The results of guinea pig maximization tests suggested that cross reactions occurred between benomyl and such pesticides as Diazinon, Kitazin P, Daconil and Z-Bordeaux.

It may be concluded that the fungicide benomyl shows contact allergic cross reactions with some other pesticides.

Key words: Allergy—contact dermatitis—cross reaction—patch test—pesticide—fungicide—benomyl

INTRODUCTION

A benzimidazole compound, benomyl, is a protective and eradivative fungicide. It is generally effective on powdery mildews of a wide variety of fruits and ornamentals, and is especially useful against apple scab on fruit¹⁾. This fungicide is known to cause allergic contact dermatitis²⁻⁵⁾.

As many chemicals are known to show cross reactions, the purpose of this paper is to report on the results of our field survey of cross reactions between some pesticides and benomyl in patch tests, and to present confirmatory experimental results.

MATERIALS AND METHODS

Field survey

To study contact allergic cross reactions between the fungicide benomyl and some other pesticides, a field survey was performed on farmers in two areas of Kagoshima Prefecture, Bansei and Chiran, where many kinds of pesticides have been used. These pesticides were widely used for various vegetables in the Bansei area and for green tea

culture in the Chiran area, but in the latter area benomyl had not been used by the subjects investigated. The number of subjects and the average age of investigated farmers are shown in Table 1 with the results of patch tests.

A questionnaire and interview, and medical and biochemical examinations such as liver function tests, blood examinations and urinalysis, were carried out. Patch tests were undertaken with 1% benomyl (Benlate®) in petrolatum. The region used for patch testing was the inner side of the forearm. The patches were removed 24 hours after each application and the reaction was evaluated and recorded according to the proposals of the International Contact Dermatitis Research Group. Thereafter, all subjects were advised to observe the test sites for one week and to report the appearance of delayed reaction after 24 hours.

Animal experiments

To investigate contact sensitization cross reactions between benomyl and some other pesticides commonly used for agriculture, the allergenicity of test pesticides was evaluated using the guinea pig maximization test⁶⁾. The pesticides tested were as follows: organic phosphates (Diazinon, Kitazin P and Supracide), carbamates (Lannate and Saturn), an organochlorine compound (Kelthane), an aryl nitrile compound (Daconil), a bipyridylium compound (Grammoxon), a triazine compound (Simazine), a copper compound (Z-Bordeaux), a trichloromethylthio compound (Difolatan) and benomyl (Benlate). The pesticide preparations were diluted with distilled water to the required concentrations.

Hartley female guinea pigs, weighing about 350 g, were used for the experiments. Ten animals were used in each group. Induction and challenge were carried out according to the original method⁶⁾. The topical concentrations applied in the challenge were below the threshold values of primary irritancy for each pesticide. The concentrations of the test pesticides used for induction and challenge are shown in the tables. The results of maximization testing were evaluated by means of a statistical procedure developed by Kligman⁷⁾.

In the second experiment, the treated animals were challenged with benomyl preparation after they had been induced with test pesticides using the same procedure as adopted in the experiment mentioned above, and the cross sensitivity was evaluated. Test techniques were similar to that described above.

RESULTS

Field survey

Except for the results of patch testing with benomyl, there was no significant difference in the results of many kinds of examinations, such as liver function tests, blood examinations and urinalysis, carried out on farmers in the two areas. The incidence ratio of dermatitis due to pesticides is shown in Table 1. The causative pesticides were not the same.

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Table 1. Patch testing of farmers with the fungicide benomyl..

Area	Sex	Average age (yrs.)	Experienced dermatitis*	Patch testing**				Total number of subjects
				(-)	(±)	(+)	(++)	
Bansei	M	50.0±8.3	9(36)	20(80)	4(16)	1(4)	0(0)	25(100)
	F	47.0±9.8	5(29)	7(41)	3(18)	6(35)	1(6)	17(100)
Chiran	M	55.0±9.2	3(25)	11(92)	0(0)	1(8)	0(0)	12(100)
	F	51.0±9.4	19(23)	49(68)	9(13)	11(15)	3(4)	72(100)

Notes: 1) * No. of subjects who had experienced dermatitis due to pesticides.

** No. of subjects with each response.

2) Benomyl has not been used by farmers in the Chiran area.

3) Patch testing was carried out by application of a closed patch of 1% benomyl (Benlate®) in petrolatum for 24 h, and recorded according to the proposals of the International Contact Dermatitis Research Group.

4) The numerals inside parentheses indicate percentages of the subjects.

Table 2. Relationship between the existence of pesticides spraying and incidences of positive response in patch tests induced by benomyl.

Pesticide	Sprayer	Non-sprayer	Significance
DDVP	4/23(17)	10/49(20)	N.S.
Diazinon	3/5 (60)	11/67(16)	P<0.1
Dibrom	3/19(16)	11/53(21)	N.S.
Dipterex	5/20(25)	9/52(17)	N.S.
Kitazin P	5/18(28)	9/54(17)	N.S.
Padanbassa	4/14(14)	10/58(17)	N.S.
Supracide	4/15(27)	10/57(18)	N.S.
Lannate	9/47(19)	5/25(20)	N.S.
Saturn	4/10(40)	10/62(16)	P<0.1
Daconil	9/32(28)	5/40(13)	P<0.1
Difolatan	1/5 (20)	13/67(19)	N.S.
Grammoxon	4/12(33)	10/60(17)	N.S.
Kelthane	5/17(29)	9/55(16)	N.S.
Simazine	3/11(27)	11/61(18)	N.S.
Z-Bordeaux	4/10(40)	10/62(16)	P<0.1

Notes: 1) Seventy-two female farmers in the Chiran area were divided into two groups, i.e., sprayer and non-sprayer, depending on whether or not they had carried out spraying with the indicated pesticide, and the results of patch testing were compared.

2) Significance: chi-square test.

3) The numerals inside parentheses indicate percentages of positive reactions in patch tests with benomyl.

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The results of patch testing using 1% benomyl (Benlate®) with petrolatum are also summarized in Table 1. The highest incidence of positive reaction (41%) was found in female farmers in the Bansei area, where most of the farmers used the fungicide. In the Chiran area, about 20% of female farmers, who had not used benomyl, developed

Table 3. Sensitizing capacity of benomyl and some other pesticides predicted by the guinea pig maximization test.

Induction		Challenge	
Substance	Topical conc. (%)	Allergenicity ratings	
		24 h	48 h
Benomyl	2	V (100)	V (100)
	0.2	V (100)	V (100)
Diazinon	5	V (100)	V (100)
	0.5	III (30)	III (60)
Kitazin P	5	IV (70)	V (90)
	0.5	I (0)	II (10)
Supracide	5	V (90)	IV (80)
	0.5	III (60)	III (40)
Lannate	5	III (50)	IV (70)
	0.5	III (30)	III (40)
Saturn	5	V (90)	V (90)
	0.5	III (30)	III (40)
Daconil	5	V (90)	IV (80)
	0.5	V (90)	IV (70)
Difolatan	5	V (90)	V (90)
	0.5	III (60)	III (50)
Grammoxon	0.5	V (100)	V (100)
	0.05	IV (80)	IV (80)
Kelthane	5	IV (80)	V (90)
	0.5	III (30)	III (30)
Simazine	5	III (30)	III (40)
	0.5	II (10)	I (0)
Z-Bordeaux	5	IV (80)	III (60)
	0.5	III (60)	III (50)

- Notes: 1) Intradermal and topical concentrations of each chemical used for induction were 5% and 25%, respectively, except for Grammoxon and Lannate (1% and 5%).
- 2) Allergenicity ratings were estimated at 24 h and 48 h after removal of the patch, and are shown by grade, ranging from weak (grade I) to extreme (grade V), using a procedure developed by Kligman (1966).
- 3) The numerals inside parentheses indicate the percentages of sensitized animals.
- 4) Ten animals were used in each group.

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Table 4. Contact sensitization cross reactions between some pesticides and benomyl, using the guinea pig maximization test.

Pesticides used for induction	Benomyl concentrations used for challenge (%)	
	2	0.2
Diazinon	II (23) 0.9	I (5) 0.2
Kitazin P	II (27) 1.0	I (0) 0
Supracide	I (7) 0.2	I (0) 0
Lannate	II (10) 0.4	I (0) 0
Saturn	II (17) 0.6	I (3) 0.2
Daconil	II (23) 0.7	I (3) 0.1
Difolatan	II (13) 0.5	I (7) 0.2
Grammoxon	II (20) 0.7	I (1) 0.1
Kelthane	I (0) 0.1	I (0) 0
Simazine	I (3) 0.3	I (0) 0.1
Z-Bordeaux	III (33) 1.1	I (3) 0.1

- Notes: 1) The data indicate the grade (I to V), the percentage of sensitized animals (%) and the intensity of the reaction, in that order.
- 2) Challenge responses are given as average group scores calculated from 2, 24 and 48 h readings for reactivity after the removal of the 24 h closed patch.
- 3) Criteria for reactivity: (-)=0, no reaction; ($\pm$)=1, indistinct erythema; (+)=2, erythema; ($\#$)=3, dominant erythema and edema.

positive responses (+) and (++) with benomyl preparation, which is an interesting result. They were not always sensitive to such substances as Japanese sumac, vegetable wax, detergents and so forth. Therefore, a relationship between the positive responses with benomyl in patch tests and various kinds of pesticide used by female farmers in the Chiran area was examined. As Table 2 shows, some correlation was suggested between the results of patch testing with benomyl and the use of such pesticides as Diazinon, Saturn, Daconil and Z-Bordeaux.

Animal experiments

As shown in Table 3, a majority of the pesticides tested showed moderate to extreme sensitization potency on challenge at the concentrations indicated. The contact sensitization cross reactions between some pesticides and benomyl are similar to those seen in the field survey (Table 4). As expected from our field survey, cross reactions with mild or moderate potency were observed experimentally between benomyl and some pesticides such as Diazinon, Kitazin P, Daconil and Z-Bordeaux.

DISCUSSION

Many series of chemicals such as sulfonamides, organic color compounds (p-phenylene-diamine, azo-compounds), thiram sulfides, dithiocarbamates and so on are known to cause cross reactions to each other⁸⁻¹⁵⁾. Moreover, the authors have found cross reactions of some pesticides to others by patch testing¹⁶⁾. In view of this finding, the present study was designed to investigate the situation with benomyl.

An interesting result was obtained in our field survey; a high incidence of positive reaction in patch tests with the fungicide benomyl was observed in female farmers who had used this fungicide. Among the subjects, the occurrence of cross reactions between benomyl and some other pesticides such as Diazinon, Saturn, Daconil and Z-Bordeaux was suggested in some subjects by patch tests. However, the sex difference observed in the results of patch tests cannot be explained at present.

From the results of guinea pig maximization tests, benomyl was also found to cross react to some degree with such pesticides as Diazinon, Kitazin P, Daconil, Grammoxon, Z-Bordeaux and so forth. As is well known, the sensitization rates obtained in the guinea pig do not always reflect the risk of allergy in a population, such a risk being dependent on a number of factors related to actual usage, for example, the concentration of the substance in the product, the type of solvent or carrier used, the frequency and duration of exposure of the skin, and so on.

Benomyl is regarded as having high potency for sensitization by contact.^{2) 4) 5)} Though it has been widely used in agriculture because of its low toxicity¹⁷⁾ and ready availability, reported cases of skin disorders due to the fungicide are relatively few, probably because of its low concentration in preparations in general use.

The present study indicates that contact allergic cross reactions may occur between benomyl and some other pesticides when they are used repeatedly at high concentrations, though the theoretical basis for this remains unclear. Preventive measures seem to be desirable in using those pesticides in order to prevent such skin hazards.

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