

Fentichlor Photocontact Dermatitis: A Persistent Enigma

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Background: Fentichlor elicits high rates of positive photopatch test reactions despite its currently unknown clinical relevance.

Objectives: The aims of this study were to provide a comprehensive review of fentichlor, to investigate the characteristics of patients with photosensitivity to fentichlor, and to explore the current uses of fentichlor.

Methods: A review of photopatch test studies involving fentichlor was performed. A retrospective chart review was conducted in patients with positive photopatch test reactions to fentichlor at our institution. Product inquiries were placed to manufacturers of fentichlor to elicit the current uses of fentichlor.

Results: In selected photopatch test studies, positive reactions to fentichlor occurred in 0.0% to 11.8% of subjects. We found that 25 companies distribute or manufacture fentichlor worldwide, which includes 2 companies that sell 25-kg drums of fentichlor. The most common current uses of fentichlor are in research, in high throughput screening, and in antibacterial and antifungal creams.

Conclusions: Our review of selected photopatch test studies demonstrates that fentichlor remains a potent photosensitizing allergen worldwide. The bulk quantities of fentichlor available for sale and the current uses of fentichlor suggest that fentichlor may be currently incorporated into consumer products. We recommend that fentichlor remain in the standard series of photopatch test allergens.

FENTICHLOR (2,2'-THIOBIS[4-CHLOROPHENOL] or *bis* [2-hydroxy-5-chlorophenyl]sulfide) is a halogenated phenolic chemical that historically has caused high rates of positive photopatch tests. This observation remains perplexing to the clinician because of its currently unknown clinical relevance. This comprehensive review of fentichlor seeks to elucidate the clinical relevance of fentichlor through discussion of its case reports, mechanisms of photoallergy, photopatch test series, and cross-reactivities. In addition, we present new information on the current uses of fentichlor and a retrospective chart review of patients with photosensitivity to fentichlor at our institution. At the summary of this review, we discuss the current clinical relevance of fentichlor that includes the question of whether to include fentichlor in the standard series of allergens in photopatch tests.

HISTORICAL USE AND REGULATION OF FENTICHLOR

The antifungal and antibacterial properties of fentichlor were discovered in the 1950s and 1960s.¹⁻³ The mechanism of action of

these properties was later found to involve the inhibition of active transport through an energy-uncoupling mechanism.⁴ As a result of these findings, the pharmaceutical importance of including fentichlor in various products rose appreciably in the 1960s. The products containing fentichlor that were manufactured and distributed worldwide included antibacterial and antifungal creams and ointments, hair creams, cosmetics, and hand soaps; however, these products were never extensively used in the United States.⁵ The past use of fentichlor as a biocide in water treatment facilities was more common in the United States. The last known products that contained fentichlor in the United States were 2 biocides that were used in water treatment facilities and that were both discontinued in 1993.

Associated with the increase of products containing fentichlor, case reports of photoallergic contact dermatitis after exposure to the chemical began to appear in the literature in the late 1960s. These case reports led to the removal of products that contained fentichlor from purchase by their manufacturers. The United States Food and Drug Administration (FDA) prohibited the use of bithionol and halogenated salicylanilides in cosmetics in 1968 and 1975, respectively. Similarly, the FDA has restricted the use of hexachlorophene in cosmetics. The European Medicines Agency (EMA) also has prohibited the use of bithionol, halogenated salicylanilides, and hexachlorophene in cosmetics. Despite the regulations on these related chemicals by the FDA and EMA, no such prohibition or restriction of the use of fentichlor in cosmetics or other products exists in the United States.

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CASE REPORTS

Case reports of photoallergic reactions to products that contained fentichlor began to appear in the literature after the discovery of the antibacterial and antifungal properties of fentichlor in the 1950s and 1960s. In 1967, Burry described 3 patients in southern Australia that developed photoallergic contact dermatitis after application of fentichlor cream to sun-exposed areas.⁶ All 3 patients had positive photopatch test reactions to fentichlor. Cross-reactivity to bithionol and hexachlorophene was demonstrated in 1 patient each. In 1968, Burry described 2 more patients who developed photoallergic contact dermatitis in sun-exposed areas after application of fentichlor-containing products to the back or perineum.⁷ Both patients had positive photopatch test reactions to fentichlor and cross-reactivity to bithionol. The photoallergic reactions resolved in all 5 of the previously mentioned patients through avoidance of sunlight and glucocorticoid application.^{6,7}

In 1976, Clayton⁸ reported a case of fentichlor photosensitivity that developed into actinic reticuloid. The patient, who was an industrial chemist, developed a photoallergy to fentichlor after occupational exposure. The patient subsequently developed clinical characteristics that resembled actinic reticuloid. The patient had positive patch test and positive photopatch test reactions to fentichlor.

In 1979, Ramsay⁹ described 4 patients in England who developed photoallergic contact dermatitis after exposure to fentichlor. Three of the patients used a hair cream that contained fentichlor, and the other patient was an industrial chemist who had occupational exposure to fentichlor. All 4 patients had positive photopatch test reactions to fentichlor, and 1 patient had cross-

reactivity to bithionol. In addition, 2 patients had positive patch test reactions to fentichlor. Another case of photoallergic contact dermatitis from industrial exposure to a water cooling system biocide composed of a 40% solution of fentichlor was reported by Norris et al¹⁰ in 1988 in England. After exposure, the patient had positive patch test and positive photopatch test reactions to fentichlor.

In 1992, Jeanmougin et al¹¹ reported a case of photoallergic contact dermatitis in a patient in France that resulted from hand washing with a commercial hygienic soap containing 0.1% fentichlor. The patient had positive photopatch test reactions to fentichlor, bithionol, and the hygienic soap containing fentichlor. Although fentichlor was not permitted in cosmetic products at that time in France, the authors stated that legislation involving professional hygiene products was not strict.

MECHANISMS OF PHOTOALLERGY

Fentichlor absorbs UV radiation in a pH-dependent manner.⁹ At pH 4.0, fentichlor absorbs UV radiation between 310 to 325 nm. At pH 7.0 and pH 9.2, fentichlor absorbs UV radiation between 275 to 350 nm.

Fentichlor covalently binds to human serum albumin, human γ -globulin, and bovine insulin when irradiated with UV light and demonstrates the ability to form photoadducts with proteins in the dermis and epidermis.¹² The postulated mechanism of the photochemical reaction between fentichlor and proteins involves the loss of 1 or both of its chlorine atoms. UV irradiation of fentichlor results in the formation of aryl, hydroxyl, and semiquinone radicals, which provides evidence for the photodechlorination of

TABLE 1. Photosensitivity to Fentichlor in Photopatch Test Studies From 1980 to the Present

Study	Period	Location	No. Subjects	Positive Photopatch Test Reactions to Fentichlor, n (%)
Menz et al ¹⁸	1980–1985	Rochester, Minnesota	70	5 (7.1)
Thune et al ³²	1980–1985	Scandinavia	1993	25 (1.3)
DeLeo et al ³³	1985–1990	New York, New York	11	1 (9.1)
Hölzle et al ²⁰	1985–1990	Austria, Germany, Switzerland	1129	—(11.1)*
Gritiyarangsarn ¹⁷	1987–1989	Thailand	274	9 (3.3)
Bakkum et al ³⁴	1989–1994	Netherlands	44	0 (0.0)
Neumann et al ²¹	1991–1997	Austria, Germany, Switzerland	1261	—(9.9)†
Leonard et al ³⁵	1991–2001	France	2067	4 (0.2)
Victor et al ²²	1993–2006	New York, New York	76	9 (11.8)
Scalf et al ¹⁹	2000–2005	Arizona, Florida, Minnesota	177	17 (9.6)
Cardoso et al ³⁶	2003–2007	Portugal	83	1 (1.2)
de la Cuadra-Oyanguren et al ²⁸	2004–2005	Spain	224	8 (3.6)
Pigatto et al ³⁷	2004–2006	Italy	1082	16 (1.5)

Positive photopatch test reactions include photoallergic, phototoxic, photoaggravated, photoirritant, and unclassified photo-induced reactions.

*This number represents the summation of the frequencies of phototoxic, photoallergic, and unclassifiable photo-induced reactions to fentichlor reported in the study. The number of positive photopatch test reactions to fentichlor was not reported.

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fentichlor.^{13,14} The binding between fentichlor and human serum albumin after UV irradiation was further shown to be partly oxygen dependent, which indicated a role for semiquinone radicals in the binding mechanism.¹⁵ In addition, the related chemical tetrachlorosalicylanilide cross-links erythrocyte membrane proteins after irradiation with UV light, which suggests that fentichlor could function as a protein cross-linker owing to its symmetrical structure.¹⁶

PREVALENCE OF FENTICHLOR PHOTOSENSITIVITY IN SELECTED CASE SERIES

The prevalence of photosensitivity to fentichlor in photopatch test studies in the United States, Europe, and Asia from 1980 to the present ranges from 0.0% to 11.8% (Table 1). In the United States, positive photopatch test reactions occurred in 7.1% to 11.8% of subjects. In Europe, positive photopatch test reactions occurred in 0.0% to 11.1% of subjects. In 1 available study from Asia, positive photopatch tests occurred in 3.3% of subjects.¹⁷ No evident temporal or geographical relationship can be determined from the photopatch test series. However, at institutions that provided data from distinct periods, the prevalence of photosensitivity to fentichlor remains relatively consistent. Evidence of this relationship is observed at the Mayo Clinic in Rochester, Minnesota (7.1%–9.6%)^{18,19} and institutions in the German, Austrian, and Swiss Photopatch Test Group (9.9%–11.1%).^{20,21} Through analysis of the reported photopatch studies, it is evident that fentichlor

presently remains as a potent photosensitizing allergen despite its disputed current clinical relevance.

REVIEW OF PATIENTS WITH PHOTOSENSITIVITY TO FENTICHLOR AT OUR INSTITUTION

A retrospective chart review of patients who underwent photopatch testing at the New York University Skin and Cancer Unit between 1994 and 2008 disclosed 9 patients with positive photopatch test reactions to fentichlor. All 9 patients presented with a photo-distributed eruption of varying duration. Photopatch tests were performed in these patients because of clinical suspicion of photoallergy. A more thorough examination of the patients' demographic data and photopatch test results is presented in Table 2.

CROSS-REACTIVITY BETWEEN FENTICHLOR AND OTHER ALLERGENS

The cross-reactivity between fentichlor and other chemicals has been widely reported. Cross-reactivity between the structurally related molecules fentichlor and bithionol (2,2'-thiobis[4,6-dichlorophenol]) has been well-established. The postulated mechanism of cross-reactivity involves the UV radiation-induced loss of chlorine atoms from bithionol.^{7,12} Despite the number of photopatch test studies that included fentichlor and bithionol, limited data exist that examine the rates of concomitant positive photopatch test reactions with fentichlor and bithionol. In 1968, Burry reported

TABLE 2. Demographic Data and Photopatch Test Results of Patients With Photosensitivity to Fentichlor at the New York University Skin and Cancer Unit

Mean age, y	44.6
Age range, y	11–74
Sex	Male (6), female (3)
Patients with skin types I-II	6
Patients with skin types III-IV	2
Patients with skin types V-VI	1
Allergies	Penicillin (2), sulfa drugs (1), thiazides (1), codeine (1), morphine (1)
Medications	Atenolol (2), oral contraceptives (2), aspirin (2), levothyroxine, methotrexate, lisinopril, gemfibrozil, lovastatin, pentoxifylline, cetirizine, indapamide, PUVA
Known occupational exposure	None
Fentichlor PPT+	9
Bithionol PPT+	2
PPT+ reactions to sulfur-containing allergens	Promethazine (2), chlorpromazine, sulfanilamide, captan, captafol, folpet, mercaptobenzothiazole, mercapto mix
PPT+ reactions to other allergens	Oxybenzone (2), musk ambrette, PABA, butyl methoxydibenzolymethane, trichlorocarbaniide, 1-(4-isopropylphenyl-3-phenyl-1,3-propanedione (Eusolex 8020)), taraxacum officinale, lichen acid mix, benzocaine, dichlorophen, photoplex sunscreen, Ti-Screen sunscreen

The mean age and age range categories report the age in years at the time of photopatch testing.

PABA, para-aminobenzoic acid; PPT+, positive photopatch test; PUVA, psoralen and UVA light therapy.

that, in 7 patients with positive photopatch test reactions to fentichlor, all 7 had concomitant positive reactions to bithionol.⁷ A study by Victor et al reported 9 patients with positive photopatch test reactions to fentichlor and 3 patients with positive photopatch test reactions to bithionol in 70 patients.²² However, only 1 patient had concomitant reactions to both fentichlor and bithionol.²²

Recently, high rates of positive photopatch test reactions to fentichlor have been reported in patients who are photosensitized to ketoprofen, which is an agent that belongs to the propionic acid class of nonsteroidal anti-inflammatory drugs (Table 3). In several studies in Europe, 54.1% of patients who had positive photopatch test reactions to ketoprofen also had positive photopatch test reactions to fentichlor (range, 10.5%–81.8%).^{23–27} Computerized conformational analysis has shown that no structural similarities exist between fentichlor and ketoprofen, which suggests that coreactivity, rather than cross-reactivity, explains the concomitant positive photopatch test reactions.²⁷

CURRENT USES OF FENTICHLOR

An extensive review of the World Wide Web and other resources showed no current products that listed fentichlor as an ingredient; however, this review yielded 25 companies worldwide that advertised the manufacture of fentichlor. Product inquiries regarding the price, availability, and uses of fentichlor were placed at all 25 companies. Twelve companies offered price quotations in response to the product inquiry that ranged from \$2.88 to \$300 (USD) per gram for 1 to 100 g. This price per gram range excludes 2 companies that only offer 25-mg bottles of fentichlor for \$500. Two companies in China offered bulk 25-kg drums of fentichlor for industrial use. Of the 6 companies that responded to the question regarding past sales, 4 companies stated that they regularly sell fentichlor. Of the 5 companies that responded to the question regarding the current uses of fentichlor, the most common use is in research (4), followed by use in high-throughput screening and in antibacterial or antifungal creams. Despite the absence of known products that contain fentichlor, the ability to easily obtain bulk pharmaceutical or industrial quantities of fentichlor suggests that companies worldwide may be still using the chemical in unknown products.

CURRENT RELEVANCE OF FENTICHLOR IN PHOTOPATCH TEST SERIES

The high rates of photosensitization to fentichlor from 1980 to the present in numerous photopatch test studies demonstrate that fentichlor remains a potent photosensitizing allergen worldwide (Table 1). To date, at least 95 patients have been photosensitized to fentichlor (Table 1). However, the lack of known products that contain fentichlor has caused several clinicians to question the current clinical relevance of fentichlor in photoallergic contact dermatitis and suggest the removal of the chemical from their standard photopatch test series.^{19,28–31} Although fentichlor is unlikely to be present in products that are manufactured in the United States, our patients were instructed that fentichlor potentially could be present in our cosmetic products and pharmaceutical preparations produced elsewhere. Lists of ingredients should be thoroughly reviewed before the use of any products.

In our retrospective chart review of patients with photosensitivity to fentichlor, the main conclusion that can be drawn is that fentichlor is not likely the result of cross-reactivity to other photoallergens (Table 2). Concomitant positive photopatch test reactions to fentichlor and bithionol were observed in only 2 of the 9 patients with fentichlor photosensitivity. As a result, cross-reactivity to bithionol cannot explain the photosensitivity to fentichlor in most of our patients. Although ketoprofen is not included in our current series of photopatch test allergens, cross-reactivity between fentichlor and ketoprofen is not likely because of their different structures in computerized conformational analysis and the infrequent use of topical nonsteroidal inflammatory agents in the United States.²⁷ However, the possibility of cross-reactivity between fentichlor and an unknown allergen cannot be entirely excluded.

Through our investigation into the current uses of fentichlor, we recommend that fentichlor should remain in the standard series of allergens used in photopatch testing. Our findings that fentichlor is used in research, in high-throughput screening, and in unnamed antibacterial and antifungal creams demonstrate that the chemical is still being used in several applications. Our ability to elicit price quotations from 12 companies that manufacture fentichlor suggests that unknown companies are purchasing this product. More importantly, our findings that 2 companies offered

TABLE 3. Fentichlor Photosensitivity in Patients With Positive Photopatch Test Reactions to Ketoprofen

Study	Period	Location	No. Subjects	Positive Photopatch Test Reactions to Ketoprofen	Positive Photopatch Test Reactions to Fentichlor	Positive Photopatch Test Reactions to Both, %
Durieu et al ²³	1994–1999	France	19	19	2	10.5
Vigan et al ²⁴	1998–2001	France	11	11	9	81.8
Durbize et al ²⁵	1998–2002	France	18	18	12	66.7
Hindsén et al ²⁶	2003–2005	Sweden	35	35	26	74.3
Foti et al ²⁷	2006–2007	Italy	15	15	4	26.7

A positive photopatch test reaction includes photoallergic, phototoxic, photoaggravated, photoirritant, and unclassified photo-induced reactions.

bulk 25-kg drums of fentichlor suggest that companies can easily obtain industrial quantities for unknown uses.

The incorporation of harmful ingredients into consumer products has been widely reported in the media since 2007. These reports include the inclusion of melamine into infant formula from China, diethylene glycol into toothpaste from China, and formaldehyde into baby shampoos from the United States. The fact that the FDA and EMA do not specifically prohibit or restrict the incorporation of fentichlor into cosmetics or other products suggests the real possibility that patients could still be exposed to fentichlor in unknown products. Short of enforcing truthful labeling of products, it is unclear whether further regulation is needed for fentichlor. Therefore, fentichlor remains a clinically relevant photoallergen, and clinicians should remain vigilant in their search for products that contain fentichlor in their photosensitized patients.

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