

Allergy to Methyldibromoglutaronitrile/Phenoxyethanol (Euxyl K 400): Regulatory Issues, Epidemiology, Clinical Characteristics, and Management

Angela E. Aakhus and Erin M. Warshaw

Methyldibromoglutaronitrile/phenoxyethanol (Euxyl K 400) is a preservative found in both personal care products and industrial sources. Although Euxyl K 400 initially appeared to have low sensitizing potential, increased prevalence of contact allergy to Euxyl K 400 led to regulatory intervention. This review summarizes the history, epidemiology, and management of contact allergy to Euxyl K 400. Issues related to patch-test preparations are also discussed.

METHYLDIBROMOGLUTARONITRILE/PHENOXYETHANOL, also known as 1,2-dibromo-2,4-dicyanobutane and by the trade name Euxyl K 400 (Schülke & Mayr GmbH, Norderstedt, Germany), is a preservative used in both cosmetics and industrial products. As a 1:4 mixture of methyldibromoglutaronitrile (Fig 1) and phenoxyethanol (Fig 2), it is equally effective against bacteria, fungi, and yeast.¹ Although this preservative originally appeared to have low sensitizing potential, it has become an important source of contact allergy in the United States and Europe. The sensitizing ingredient in Euxyl K 400 is nearly always methyldibromoglutaronitrile (MDBGN); contact allergy to phenoxyethanol is rare. Under the trade name Tektamer 38 (Lanxess Corporation, Pittsburgh, PA), MDBGN was first used as an industrial biocide in products such as latex paints, metalworking fluids, and joint cement and other adhesives.² Currently, MDBGN is most commonly found in cosmetics such as Euxyl K 400. MDBGN synonyms and trade preservatives containing MDBGN are listed in Table 1 and Table 2, respectively. More than 150 mixtures contain phenoxyethanol and ingredients other than MDBGN.³

The purpose of this review is to summarize the history and epidemiology of allergy to Euxyl K 400 and its constituents, MDBGN and phenoxyethanol. Methods

included a PubMed search of the terms “methyldibromoglutaronitrile,” “phenoxyethanol,” “methyldibromoglutaronitrile phenoxyethanol,” “MDBGN/PE,” “Euxyl K 400,” “dibromodicyanobutane,” “1,2-dibromo-2,4-dicyanobutane,” and “Tektamer 38.” Hand searching of review articles was also performed. For purposes of this article, the term “Euxyl K 400” refers to the combination of MDBGN and phenoxyethanol; the individual terms “MDBGN” and “phenoxyethanol” refer to those individual ingredients specifically. Because the majority of reports state that most cases of contact allergy to Euxyl K 400 are caused by MDBGN and that relatively few are due to phenoxyethanol, the focus of this article is contact allergy to MDBGN. A brief summary of contact allergy to phenoxyethanol is also included.

Sensitization Studies

Early data from the manufacturer of Tektamer 38 showed that this preservative was a moderate skin irritant but not a sensitizer; a human repeat insult patch-test study involving 52 volunteers who applied 3,000 ppm of Tektamer 38 in corn oil 12 times daily for 3 weeks resulted in no sensitizations.² Similarly, several early animal studies conducted from 1981 to 1988 failed to demonstrate the sensitizing capacity of MDBGN⁴ (Table 3). The Ritz-Buehler method was used in seven different guinea pig studies. These studies used closed patches with concentrations of MDBGN ranging from 0.2 to 75.0% for induction and from 0.2 to 5.0% for challenge. Three other guinea pig maximization studies in this same period were performed with the Magnusson-Kligman maximization method, which involved a subdermal injection of 5 to 20%

From the Department of Dermatology, University of Minnesota School of Medicine, Minneapolis, MN, and the Minneapolis Veterans Affairs Medical Center – Center for Chronic Disease Outcomes Research, Minneapolis, MN.

Reprints not available.

DOI 10.2310/6620.2011.10081

© 2011 American Contact Dermatitis Society. All Rights Reserved.

DECKER



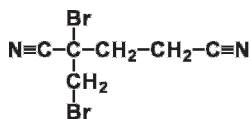


Figure 1. Chemical structure of methyldibromoglutaronitrile.

MDBGN followed 1 and 3 weeks later by 24-hour topical application of MDBGN.⁴ Finally, in 1988, a guinea pig maximization test using MDBGN at 0.5% both intradermally and topically for induction and at 0.1% topically for challenge did not show a statistically significant increase in positive reactions when the results were compared with those of controls.⁵

A later study by Hausen, however, showed that Euxyl K 400 and MDBGN were in fact weak sensitizers; these investigators used a modified Freund's complete adjuvant test. This method (considered to be more sensitive than the guinea pig maximization test previously studied by Bruze and colleagues⁵) involved sensitization via the intradermal injection of 15 mg of MDBGN into 10 guinea pigs and 30 mg of Euxyl K 400 into 20 guinea pigs. The animals were injected on days 1, 5, and 9. Challenge with open epicutaneous Euxyl K 400 (1% and 3%) and MDBGN (0.3% and 0.1%) took place on day 20; 33 to 70% of animals were sensitized with these methods⁶ (see Table 3).

A 1999 study by Wahlkvist and colleagues demonstrated the allergenic potential of Euxyl K 400 and MDBGN in two of three different animal models. The first model, the cumulative contact enhancement test (CCET), involved a dose-response protocol in guinea pigs with four consecutive topical applications of 30%, 20%, 10%, 3%, or 1% MDBGN in a mixture of acetone and arachis oil followed by challenge with 0.003%, 0.01%, 0.03%, 0.1%, 0.3%, 1%, and 3% MDBGN in olive oil. The second model, a local lymph node assay (LLNA) in mice, consisted of using 1.25%, 5%, or 20% topical MDBGN daily for 3 days followed by intravenous injection of [³H]-thymidine. The auricular lymph nodes were then collected and weighed, and the incorporation of [³H]-thymidine was calculated; a stimulation index value greater than three times that of the vehicle control indicated sensitization. The third model, the guinea pig maximization test (GMT),

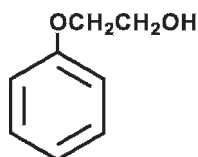


Figure 2. Chemical structure of phenoxyethanol.

Table 1. Methyldibromoglutaronitrile Synonyms

2-Bromo-2-(bromomethyl) glutaronitrile
2-Bromo-2-(bromomethyl) pentanedinitrile
1,2-Dibromo-2,4-dicyanobutane
Glutaronitrile, 2-bromo-2-(bromomethyl)

Adapted from Personal Care Products Council.⁶⁷

consisted of an intradermal injection of 0.1% MDBGN followed 1 week later by 10% topical MDBGN for induction. The animals were challenged 2 weeks later with 1%, 0.3%, and 0.1% MDBGN topically. Both the CCET and the LLNA showed a definite sensitization potential for Euxyl K 400 and MDBGN, whereas the GMT failed to do so. The authors felt that the conflicting results of the studies were a reflection of the need for various predictive test models rather than a single model. The authors also felt that multiple topical applications of the allergen may be an important and necessary step for sensitization.⁷

Regulatory History

Euxyl K 400 was first introduced in consumer products in 1985 in Europe and 5 years later in the United States. Initial and current allowable concentrations are listed in Table 4.

Europe

Euxyl K 400 was originally introduced to the European market in 1985 as a preservative in cosmetics. It was intended as a substitute for methylchloroisothiazolinone/methylisothiazolinone (also known as Kathon CG [Rohm and Haas, Philadelphia, PA]), which had been responsible for an "epidemic" of contact allergy to cosmetics in Europe.⁸ Euxyl K 400 was originally permitted in both rinse-off products (eg, soaps, shampoos) and leave-on products (eg, creams, lotions)¹ in concentrations up to 0.5% (corresponding to an MDBGN concentration of 0.1%).⁹ It was later permitted in sunscreens in concentrations up to 0.125% (0.025% MDBGN).¹⁰

Soon after its introduction, however, several reports of contact allergy to Euxyl K 400 began to surface. In 1989, two cases were reported from Germany; in both, the causative agent was MDBGN, in an antiwrinkle lotion in one case and in a massage lotion in the other.¹¹ Other case reports of allergy to MDBGN in the form of Euxyl K 400 followed; sources included a barrier cream gel,¹² cucumber eye gel,¹³ a night cleansing cream,¹⁴ moist toilet tissue, and cosmetics.¹⁵

Table 2. Trade Preservatives Containing Methyl dibromoglutaronitrile

<i>Name</i>	<i>Other Ingredients</i>	<i>Manufacturer</i>
AEC methyl dibromoglutaronitrile (and) dipropylene glycol	Dipropylene glycol	A & E Connock (Perfumery & Cosmetics) Ltd.
Chemynol K	Phenoxyethanol	Chemunion Quimica Ltda.
Euxyl K 400	Phenoxyethanol	Schülke & Mayr GmbH
Euxyl K 446	2-Bromo-2-nitropane 1-3-diol	Schülke & Mayr GmbH
Euxyl K 727	Dipropylene glycol	Schülke & Mayr GmbH
	Methylchloroisothiazolinone	
	Methylisothiazolinone	
	Phenoxyethanol	
Isocide FG	Phenoxyethanol	Biophil Chimica Fine SRL
Merguard 1105	Propylene glycol	Nalco Company
Merguard 1190	Dipropylene glycol	Nalco Company
Merguard 1200	Phenoxyethanol	Nalco Company
Microcare MCP	Methylchloroisothiazolinone	Thor Specialties Inc.
	Methylisothiazolinone	
	Phenoxyethanol	

Adapted from Personal Care Products Council.⁶⁷

Data from large European patch-test centers reported an increase in the prevalence of positive patch-test reactions to Euxyl K 400—from 0.7% in 1991 to 3.5% in 2000.¹⁶ This increase in sensitivity corresponded to the expanded use of the preservative in both rinse-off and leave-on products in Europe. These findings prompted the Scientific Committee on Consumer Products (SCCP) in 2002 to recommend that the use of MDBGN be restricted to rinse-off products and be prohibited in leave-on products until a safe concentration could be determined.¹⁷ In 2003, the European Commission completely banned the use of Euxyl K 400 in cosmetics and industrial products but continued to allow its use in rinse-off products in a maximum concentration of 0.1%.¹⁸ This was partly based on a 2000 study by Tosti and colleagues, which showed that shampoos containing up to 0.02% MDBGN could be safely used by sensitized patients.¹⁹ However, reports of contact allergy to Euxyl K 400 in rinse-off products such as soaps and shampoos continued to surface.^{9,20–22} Pedersen and colleagues hypothesized that detergents used in soaps, shampoos, and cleansing agents lower the elicitation threshold for allergy to MDBGN; therefore, a lower concentration of MDBGN could elicit contact allergy in a sensitized individual when MDBGN is combined with a detergent rather than used alone.²³

Between 2004 and 2006, Jensen and colleagues published a series of studies demonstrating the sensitizing capacity of MDBGN in rinse-off products. The first study showed that rinse-off products containing 0.1% MDBGN

(the maximum concentration allowed in Europe at the time) caused contact allergy in 7 (37%) of 19 allergic individuals.²⁴ The second study revealed that in regard to MDBGN's capacity to produce an allergic response, exposure to 0.01% MDBGN four times a day was equivalent to a single daily application of 0.04% MDBGN. This showed the potential for products with even very low concentrations of MDBGN (such as hand soaps) to cause contact allergy when used several times per day.²⁵ Finally, Jensen and colleagues demonstrated that patients sensitized to MDBGN have an augmented allergic response upon reexposure to the preservative in rinse-off products, highlighting the importance of allergen avoidance for these patients.²⁶

In 2005, Schnuch and colleagues concluded that there was no concentration of MDBGN that did not elicit contact dermatitis in sensitized individuals while still providing adequate antimicrobial activity.²⁷ These findings resulted in the 2005 recommendation by the SCCP to completely ban MDBGN in rinse-off products,²⁸ which was enacted by the European Economic Community in July 2008.

Following regulatory intervention, a significant decrease in the prevalence of contact allergy to MDBGN was noted in the United Kingdom²⁹ and in Denmark.³⁰

United States

The use of MDBGN in the United States began in industrial products in the early 1980s, in the form of

Table 3. Methyl dibromoglutaronitrile Guinea Pig Sensitization Studies

<i>Study</i>	<i>Type of Test</i>	<i>MDBGN Induction Concentration</i>	<i>No. of Guinea Pigs</i>	<i>No. of Positive Results</i>
Hill Top Research, 1981b	Ritz-Buehler method	5.0% in 80:20 ethanol/water	19	1*
Hill Top Research, 1982a	Ritz-Buehler method	5.0% in 80:20 ethanol/water	20	1*
Hill Top Research, 1982b	Ritz-Buehler method	0.2% in distilled water	40	0
Hill Top Research, 1982c	Ritz-Buehler method	0.2% in water	20	0
Hill Top Research, 1982c	Ritz-Buehler method	5.0% in 80:20 ethanol/water	Not provided	Positive reactions in both test and control groups with negative rechallenge; primary responses considered aberrant
Biosearch Incorporated, 1982a	Magnusson-Kligman maximization method	5.0% in 80:20 ethanol/water	10	0
Biosearch Incorporated, 1982b	Ritz-Buehler method	5.0% in 80:20 ethanol/water	10	0
Hill Top Biolabs, 1988	Ritz-Buehler method	75% in acetone	20	0
IBR, 1988a	Magnusson-Kligman maximization method	10% in oleum arachidis and 10% in FCA (intradermal injection) followed by 20% (dermal application)	20	0
IBR, 1988b	Magnusson-Kligman maximization method	10% in water and 10% in FCA (intradermal injections) followed by 20% (dermal application)	20	0
Bruze, 1988 ⁵	Guinea pig maximization test	0.5% in propylene glycol	48	5 [†]
Hausen, 1993 ⁶	Modified FCA method	15 mg MDBGN in saline and FCA	10	7/10 (0.3% MDBGN challenge) 3/10 (0.1% MDBGN)
		30 mg Euxyl K 400 in saline and FCA	20	9/20 (3% Euxyl K 400) 8/20 (1% Euxyl K 400)
Wahlkvist, 1999 ⁷	Cumulative contact enhancement test	30%, 20%, 10%, 3%, or 1% in acetone and arachis oil	40	26/40 (3% MDBGN challenge) 18/40 (1% MDBGN) 9/40 (0.3% MDBGN) 8/40 (0.1% MDBGN) 2/40 (0.03% MDBGN) 5/40 (0.01% MDBGN) 5/40 (0.003% MDBGN) 3/15 (1% MDBGN in olive oil) 1/15 (0.3% MDBGN in olive oil) 0/15 (0.1% MDBGN in olive oil) 1/15 (1% MDBGN in PE) 0/15 (0.3% MDBGN in PE)
	Guinea pig maximization test	0.1% (intradermal injection) followed by 10% (dermal application)	15	

Adapted from Cosmetic Ingredient Review Expert Panel.⁴

FCA = Freund's complete adjuvant; IBR = International Bio Research; MDBGN = methyl dibromoglutaronitrile; PE = phenoxyethanol.

*Primary challenge with 5.0% MDBGN in acetone.

[†]Challenge with 0.1% in ethanol.

Table 4. Initial and Current Allowable Concentrations of Euxyl K 400 and Methyl dibromoglutaronitrile in the United States and Europe

	<i>Initial Allowable Concentrations</i>		<i>Current Allowable Concentrations</i>	
	<i>Leave-On Products</i>	<i>Rinse-Off Products</i>	<i>Leave-On Products</i>	<i>Rinse-Off Products</i>
Europe	0.5% Euxyl K 400 (0.1% MDBGN)	0.5% Euxyl K 400 (0.1% MDBGN)	Banned	Banned
United States	0.125% Euxyl K 400 (0.025% MDBGN)	0.3% Euxyl K 400 (0.06% MDBGN)	0.125% Euxyl K 400 (0.025% MDBGN)	0.3% Euxyl K 400 (0.06% MDBGN)

MDBGN = methyl dibromoglutaronitrile.

Tektamer 38. As early as 1983, the first case of contact dermatitis from MDBGN was reported in a mechanic who was exposed to a paste glue used to attach labels to baby food jars.² Euxyl K 400 was introduced into cosmetic products in the United States in 1990, 5 years later than in Europe. In 1996, the Cosmetic Ingredient Review Expert Panel evaluated data on MDBGN and concluded (on the basis of data from human repeat insult patch tests) that a concentration limit of 0.0396% MDBGN would result in sensitization of 1% of the test population, whereas a 0.025% concentration would be unlikely to cause sensitization. The panel's final recommendations stated that a concentration of up to 0.025% MDBGN was safe in leave-on products and that a concentration of up to 0.06% MDBGN was safe in rinse-off products.⁴

The prevalence of positive patch-test reactions to Euxyl K 400 as documented by the North American Contact Dermatitis Group (NACDG) ranged from 1.5% (1992 to 1994) to 2% (1994 to 1996)³¹ and peaked at 7.6% (1996 to 1998).³² To date, there have been no further regulations regarding the use of Euxyl K 400 in personal care products in the United States.

Epidemiology

Since the introduction of Euxyl K 400 into cosmetic products in 1985, the prevalence of contact allergy to it has risen steadily. Interpretation of epidemiologic data is complicated by the fact that different patch-test preparations and concentrations of Euxyl K 400 and MDBGN have been used by different patch-test groups. These data (including patch-test concentrations) are summarized in Table 5.

Prevalence of contact allergy to MDBGN in Europe increased dramatically—from 0.7% in 1991 to 3.5% in 2000, exceeding that of all other preservatives.¹⁶ In Denmark, MDBGN was the third most common patch-test allergen in 2003 and had a frequency of 4.9%.³³ This percentage decreased to 2.6% in 2007 after restrictions on the use of MDBGN were instituted.³⁰ The Netherlands saw

an increase from 0.5% in 1991 to 4.0% in 1994.³⁴ Prevalence in the United Kingdom rose from 0.3% in 1993³⁵ to 2.4% in 2000 before dropping to 1.2% in 2004 to 2005²⁹ after the implementation of European Union regulations. In Italy, an increase from 1.2% between 1988 to 1990⁹ to 2.8% between 1991 to 1994¹⁰ was reported.

North America saw an increase in the prevalence of positive patch-test reactions to Euxyl K 400 from 1.5% between 1992 and 1994³¹ to a high of 7.6% between 1996 and 1998; the most recent rate (between 2005 and 2006) was 5.8%.³²

Risk Factors

Little is known about risk factors for MDBGN allergy. The overall prevalence of contact allergy to Euxyl K 400 appears to be similar in men and women. Among 2193 NACDG patients with contact allergy to a personal care product, Euxyl K 400 was the fifth most commonly identified culprit in women (8.3%) and the fourth most common in men (11.8%).³⁶ In the Netherlands, where two-thirds of all moistened toilet tissue in 1995 was preserved with Euxyl K 400,³⁷ perianal dermatitis accounted for 40 to 50% of cases of contact allergy to Euxyl K 400 and occurred mainly in men.³⁸ The NACDG found sensitivity to Euxyl K 400 in 5.8% of patch-tested patients with hand dermatitis, making Euxyl K 400 one of the three most common preservatives associated with allergic contact dermatitis (ACD) of the hands.³⁹ Common concomitant allergies include allergies to methylchloroisothiazolinone/methylisothiazolinone (Kathon CG), fragrances, formaldehyde or formaldehyde-releasers, oleamidopropyl dimethylamine, and wood alcohols.³⁸

Allergy to Euxyl K 400 from Occupational Sources

Occupation-related dermatitis often presents on the hands. The NACDG found that 11.8% of hand dermatitis cases associated with Euxyl K 400 were occupation related and

Table 5. Reported Prevalence of Positive Patch-Test Reactions to Euxyl K 400 and Methyl dibromoglutaronitrile

<i>First Author, Location</i>	<i>Year Published</i>	<i>Allergens and Concentrations</i>	<i>No. of Patients</i>	<i>% Positive Reactions (n)</i>
Europe				
Motolese, Italy ⁶⁸	1991	Euxyl K 400 (2.0% pg)	1,033	2.0 (21)
		Euxyl K 400 (0.15% pg)	1,033	1.7 (18)
Tosti, Italy ⁹	1991	Euxyl K 400 (2.5% pet)	2,057	1.2 (24)
		Euxyl K 400 (2.5% alc)	2,057	1.2 (24)
de Groot, the Netherlands ¹⁵	1991	MDBGN (0.05% pet)	1,142	0.5 (6)
Ross, UK ¹³	1992	Euxyl K 400 (1.0% aq)	> 1,800	0 (0)
Torres, Portugal ¹⁴	1992	Euxyl K 400 (1.0% aq)	400	0 (0)
Corazza, Italy ⁶⁹	1993	Euxyl K 400 (0.2% aq/alc)	889	0.6 (5)
Van Ginkel, the Netherlands ⁷⁰	1995	MDBGN (0.1% pet)	814	2.0 (16)
Tosti, Italy ¹⁰	1995	Euxyl K 400 (2.5% pet)	3,455	2.9 (99)
		Euxyl K 400 (0.5% aq)	3,022	1.8 (54)
		Euxyl K 400 (1.5% aq and pg)	729	0.7 (5)
		MDBGN (0.5% pet)	919	2.3 (21)
Jacobs, UK ³⁵	1995	MDBGN (0.1% pet)	5,167	0.3 (14)
de Groot, the Netherlands ³⁴	1996	MDBGN (0.3% pet)	2,943	4.0 (119)
Okkerse, the Netherlands ⁷¹	1996	Euxyl K 400 (0.5% pet)	1,019	2.4 (24)
		MDBGN (0.1% pet)	1,019	2.4 (24)
Schnuch, Germany ⁷²	1998	Euxyl K 400 (0.5% pet)	25,584	1.7 (444)
		MDBGN (0.1% pet)	11,052	1.8 (196)
McFadden, UK ⁷³	2000	Euxyl K 400 (0.5% pet), 1989–1997	11,379†	0–0.7
		MDBGN (0.3% pet), 1997–1999		0.4–1.6
Guimaraens, Spain ⁷⁴	2000	Euxyl K 400 (0.5% pet)	528	0.1 (3)
Geier, Germany ⁴⁹	2000	Euxyl K 400 (0.5% pet)	4,615	2.3 (105)
		Euxyl K 400 (1.0% pet)	4,615	3.5 (160)
		MDBGN (0.3% pet)	4,343	5.0 (216)
		MDBGN (0.1% pet)	988	1.4 (14)
Wilkinson, Europe ¹⁶	2002	MDBGN (0.2% pet)	48,485	3.5 (NR)
Zachariae, Denmark ²²	2003	MDBGN (0.3% pet)	807	2.9 (23)
Geier, Germany	2004	MDBGN (0.3% pet)	153	5.2 (8)
(metalworking fluid series) ⁷⁵		Euxyl K 400 (1.0% pet)	214	3.3 (7)
Zachariae, Denmark ³³	2005	MDBGN (0.3% pet)	766	5.0 (38)
Gruvberger, Europe ⁴⁶	2005	MDBGN (1.0% pet)	2,661	4.4 (NR)
		MDBGN (0.5% pet)	2,661	3.0 (NR)
		MDBGN (0.3% pet)	2,661	1.9 (NR)
		MDBGN (0.1% pet)	2,661	1.1 (NR)
Johansen, Denmark ⁷⁶	2005	MDBGN (0.3% pet)	2,146	5.1 (110)
Boyvat, Turkey ⁷⁷	2005	Euxyl K 400 (1.5% pet)	308	1.0 (3)
Hasan, Finland ⁷⁸	2005	MDBGN (0.1% pet)	5,218	1.0 (NR), 1995–1996 1.5 (NR), 2000–2002
Jong, UK ²⁹	2007	MDBGN (0.3% pet)	6,958	1.2 (NR)
ESSCA Writing Group ⁷⁹	2008	Euxyl K 400 (1.0% pet)	1,658	4.6 (76)
		MDBGN (0.3% pet)	4,733	1.6 (75)
Johansen, Denmark ³⁰	2008	MDBGN (0.3% pet)	3,849	2.6 (100)
Bordel-Gómez, Spain ⁸⁰	2009	MDBGN (0.3% pet)	1,092	1.6 (17)

Table 5. Continued

<i>First Author, Location</i>	<i>Year Published</i>	<i>Allergens and Concentrations</i>	<i>No. of Patients</i>	<i>% Positive Reactions (n)</i>
North America				
Marks, NA ⁸¹	1995	Euxyl K 400 (1.0% pet)	3,481	1.5 (NR), 1992–1994
Jackson, US ⁸²	1998	Euxyl K 400 (1.0% pet, 2.5% pet)	163	11.7 (19)
Marks, NA ³¹	1998	Euxyl K 400 (1.0% pet)	3,074	2.0 (NR), 1994–1996
		Phenoxyethanol (1.0% pet)	3,080	0 (NR), 1994–1996
Marks, NA ⁸³	2000	Euxyl K 400 (2.5% pet)	4,054	7.6 (NR), 1996–1998
		Euxyl K 400 (1.0% pet)	4,053	2.7 (NR), 1996–1998
Marks, NA ⁸⁴	2003	MDBGN (0.4% pet)	5,797	3.5 (NR), 1998–2000
		Euxyl K 400 (2.0% pet)*	5,778	6.0 (NR), 1998–2000
Pratt, NA ⁸⁵	2004	Euxyl K 400 (2.0% pet)*	4,897	5.8 (NR), 2001–2002
		MDBGN (0.4% pet)	4,897	2.7 (NR), 2001–2002
		Phenoxyethanol (1.0% pet)	4,887	0.2 (NR), 2001–2002
Warshaw, NA ⁸⁶	2008	Euxyl K 400 (2.0% pet)*	5,140	6.1 (NR), 2003–2004
Zug, NA ³²	2009	Euxyl K 400 (2.0% pet)*	4,437	5.8 (NR), 2005–2006
Other Locations				
Zoller, Israel ⁸⁷	2006	Euxyl K 400 (conc NR)	2,285	0.9 (NR), 1995–1998
				1.4 (NR), 1999–2001
				1.7 (NR), 2002–2004
Williams, Australia ⁸⁸	2007	MDBGN (0.3% pet), Euxyl K 400 (1.5% pet)	2,837	0.7 (20)

alc = in alcohol; aq = aqueous; conc = concentration; ESSCA = European Surveillance System of Contact Allergies; MDBGN = methylidibromoglutaronitrile; NA = North America; NR = not reported; pet = in petrolatum; pg = in propylene glycol; UK = United Kingdom; US = United States.

*Published concentration of 2.5% is incorrect; correct concentration of 2.0% was verified by personal communication with the North American Contact Dermatitis Group.

†Number of patients tested to specific allergens not reported separately; from 1989–1999 a total of 11,379 patients were tested.

were linked to solvents, oils, lubricants, fuels, and cosmetics.³⁹ In 2004, Geier and colleagues found the rate of allergy to MDBGN 0.3% in petrolatum (pet) to be 5.2% (8 of 153 patients) among metalworkers; allergy to Euxyl K 400 1% pet was found in 3.3% of patients (7 of 214).⁴⁰ In 2005 to 2006, 13.6% of hairdressers with ACD in Germany were sensitized to MDBGN 0.3% pet,⁴¹ likely owing to daily exposure to shampoos and other hair care products preserved with Euxyl K 400. Hospital workers may be exposed to MDBGN in work soaps.²⁰ Other reported cases of sensitization from workplace exposures are summarized in Table 6.

Allergy to Euxyl K 400 in Personal Care Products

Among 835 NACDG patients with contact allergy to a moisturizer, Euxyl K 400 was the second most commonly identified culprit.³⁶ Table 7 summarizes case reports of ACD from Euxyl K 400 or its components in personal care products. The products most commonly reported included

hand and face lotions, cosmetics, hair products, and ultrasonic gels.

Patch Testing

Several studies have shown that petrolatum is the best vehicle for patch testing with Euxyl K 400.^{10,38,42} Euxyl K 400 has limited solubility in water, restricting the maximum test concentration in an aqueous vehicle to 0.5%, an unacceptably low amount. Both ethanol and a 50% mixture of water and propylene glycol vehicles resulted in frequent irritant reactions.¹⁰ Some experts have advocated the use of an emulsifier (such as soy lecithin) for homogenous dispersion³⁷ although others have argued its utility.⁴²

While petrolatum is generally considered the best vehicle, the optimal concentration for patch testing with MDBGN and Euxyl K 400 is unclear; higher concentrations often result in doubtful or irritant reactions, whereas lower concentrations may result in false-negative results.

Table 6. Case Reports of Occupation-Related Contact Allergy to Euxyl K 400 or Its Components

<i>First Author, Year Published</i>	<i>Patient Data</i>	<i>MDBGN Concentration (Reaction)</i>	<i>PE Concentration (Reaction)</i>	<i>Euxyl K 400 Concentration (Reaction)</i>	<i>Product Test Data (Reaction)</i>
Mathias, 1983 ²	M, age 28 yr; mechanic in baby-food processing plant; hand and forearm dermatitis	—	—	0.1% pet (NR) 0.01% pet (NR) 0.001% pet (NR)	Paste glue* pet, T (+++)
Aalto-Korte, 1996 ⁸⁹	M, age 43 yr; offset printer; hand dermatitis	—	—	0.5% pet (++)	Hand cleanser 10% pet, T (?)
	F, age 60 yr; hospital cleaner; hand dermatitis	—	—	0.5% pet (++)	Liquid dishwashing detergent, T (++)
Wong, 2001 ²¹	M, age 34 yr; motor mechanic; hand and forearm dermatitis	—	—	0.5% pet (+)	Heavy-duty cleaner, NT Barrier cream 25%, T (+)
	M, age 62 yr; mechanical engineer; hand and forearm dermatitis	—	—	0.5% pet (++)	Barrier cream, T (++) Heavy-duty hand cleanser 1% aq, T (—)
	M, age 61 yr; engineer; hand and wrist dermatitis	—	—	0.5% pet (++)	Heavy-duty hand cleanser, NT After-work cream, T (++)
Diba, 2003 ²⁰	F, age 41 yr; nursing auxiliary; hand dermatitis	0.1% pet (+) 0.5% pet (+)	—	—	Hand-washing soap, NT
	M, age 38 yr; accident- and-emergency staff nurse; hand dermatitis	0.3% pet (+++)	—	—	Acaricide, NT Hand wash, NT
	F, age 27 yr; nurse; hand dermatitis	0.3% pet (+++)	—	—	Hand wash, NT
Jong, 2006 ⁵⁸	Age 53 yr; maintenance technician; hand dermatitis	NR (++)	—	—	Hand cream, T (++)
Marcano, 2007 ⁹⁰	M, age 54 yr; car glass installer; hand dermatitis	0.5% pet (NR)	—	1.5% pet (NR)	Hand degreasing toilet paper, T (NR)

F = female; M = male; MDBGN = methyldibromoglutaronitrile; NR = not reported; NT = not tested; PE = phenoxyethanol; pet = in petrolatum; T = tested; ? = doubtful reaction.

*A formulation for attaching labels to baby-food jars.

The NACDG currently tests with Euxyl K 400 2.0% pet.⁴³ In Europe, MDBGN is tested alone at a concentration of 0.5% in the European standard tray.⁴⁴

Proponents of 0.5% Concentration of MDBGN

Several studies have shown that MDBGN concentrations of less than 0.5% may result in false-negative reactions.³⁴ In 2005, Gruvberger and colleagues published a multicenter study by the European Environmental Contact Dermatitis Research Group (EECDRG) involving 2,661 patients and concluded that although MDBGN at 0.3% resulted in fewer doubtful reactions than MDBGN at 0.5%

or 1.0%, between 35% and 55% of allergies that would have been detected by the higher concentrations would have been missed by the 0.3% concentration. This was partly because many of the “doubtful” reactions (1 of 3 reactions to the 0.1% and 0.3% concentrations and 13% of those to the 0.5% concentration) were considered to be weak allergic reactions rather than irritant reactions.⁴⁵ Two other European studies with 51 and 32 patients, respectively, and using repeated open application tests (ROATs) with MDBGN, found that patch testing with 0.1% and 0.3% MDBGN missed clinically relevant allergies.^{46,47} Therefore, in 2005, the European Contact Dermatitis Society and the EECDRG recommended a test concentration

Table 7. Case Reports of Contact Allergy to Euxyl K 400 or its Components in Personal Care Products

<i>First Author, Year Published</i>	<i>Patient Data</i>	<i>MDBGN Concentration (Reaction)</i>	<i>PE Concentration (Reaction)</i>	<i>Euxyl K 400 Concentration (Reaction)</i>	<i>Product Test Data (Reaction)</i>
Senff, 1989 ¹¹	Sex NR, age 43 yr; face and neck dermatitis	0.004% (NR)	—	0.02% (NR)	Antiwrinkle lotion, T (NR)
de Groot, 1991 ¹⁵	M (3 patients), age NR; perianal dermatitis	—	—	—	Moist toilet paper, T (NR)
	F, age NR; face and hand dermatitis	0.05% pet (NR)	—	—	Several cosmetics, T (NR)
Pigatto, 1991 ¹²	F, age 13 yr; face and limb dermatitis	0.1% pet (+++)	—	—	Body gel, T (+++)
Ross, 1992 ¹³	F (2 patients), age NR; severe eyelid dermatitis	—	—	1% pet(+, +++) 0.1% pet (?, ++) 0.001% pet(–, ?)	Cucumber eye gel, T (++)
Torres, 1992 ¹⁴	F, age 41 yr; face and neck dermatitis	0.1% pet (+++) 0.01% pet (+++)	—	1% aq (+++)	Night cleansing cream, T (+)
O'Donnell, 1993 ⁹¹	F, age 24 yr; periorbital dermatitis	0.1% pet (+++) 0.01% pet (++)	2% aq (—) 1% aq (—)	0.1% pet (++)	Cucumber eye gel, T (++)
Gebhart, 1993 ⁹²	M, age 78 yr; abdominal dermatitis	—	—	0.5% pet (++)	Ultrasonic gel 10% aq, T (+), 50% aq, T (+)
Fernandez, 1995 ⁹³	F; age 27 yr; face and hand dermatitis	(NR)	(—)	—	Cleansing milk, makeup, body milk, T (NR)
Silva, 1995 ⁹⁴	F, age NR; facial dermatitis	—	—	(NR)	Antiaging cream, T (+)
Silvestre, 1996 ⁹⁵	F, age 45 yr; facial dermatitis	—	1.0% pet (—)	0.1% pet (+++)	Sunscreen cream, T (++)
Armstrong, 1999 ⁹⁶	F, age 18 yr; scalp dermatitis	0.3% pet (++)	—	—	Hair mousse, T (+)
Erdmann, 2001 ⁹⁷	M, age 62 yr; abdominal dermatitis	0.3% pet (NR)	1.0% pet (—)	1.0% pet (NR)	Ultrasonic gel, T (NR)
Hillen, 2001 ⁹⁸	F, age 44 yr; dermatitis of left axilla, trunk, limbs	—	—	NR (+++)	Deer fat cream, T (++)
Kelterer, 2002 ⁹⁹	F, age 48 yr; forehead dermatitis	—	—	1.0% pet (+++)	Protective cream,* T (+++)
Young, 2004 ¹⁰⁰	M, age 46 yr; postcoital perianal, groin dermatitis	0.3% pet(+)	—	1.5% pet (++)	Hand wash, NT (NR)
Sanchez-Perez, 2005 ¹⁰¹	F, age 22 yr; face, neck dermatitis	0.3% pet (++) 0.1% pet (++)	—	1.5% pet (++)	Makeup removal wipe, T (++)
Lujan-Rodriguez, 2006 ¹⁰²	Sex NR, age 29 yr; limb dermatitis	(+++)	—	NR (+++)	Hand cream, NT (NR)

Table 7. Continued

First Author, Year Published	Patient Data	MDBGN Concentration (Reaction)	PE Concentration (Reaction)	Euxyl K 400 Concentration (Reaction)	Product Test Data (Reaction)
Sfia, 2007 ¹⁰³	F, age 10 yr; abdominal dermatitis	NR (++)	—	—	Cosmetic products, NT (NR)
Williams, 2007 ⁸⁸	F, age 49 yr; vulvar dermatitis	—	—	1.5% pet (++)	Sanitary pad, T (NR)

aq = aqueous; MDBGN = methylidibromoglutaronitrile; NR = not reported; NT = not tested; PE = phenoxyethanol; pet = in petrolatum; T = Tested; ? = doubtful reaction.

*Used prior to a permanent-wave solution.

of 0.5% in petrolatum for the European Standard patch test series.⁴⁸

Proponents of 0.2% Concentration of MDBGN

Schnuch and colleagues compared the results of patch tests with varying concentrations of MDBGN in 40 patients and found that 70% of ROAT-positive patients were patch test positive to 0.2% MDBGN and that increasing the patch-test concentration to greater than 0.2% did not result in greater sensitivity. On the other hand, specificity decreased dramatically because of more false-positive (irritant and macular erythema) reactions, reaching a level of 12.5% with a concentration of 0.5%. These authors concluded that Euxyl K 400 1% (containing 0.2% MDBGN) was the best patch-test concentration.²⁷

Evaluating Patch-Test Preparations with Positivity Ratio and with Reaction Index

The reaction index (RI) and positivity ratio (PR) provide information on the efficiency of different patch-test formulations. The PR is defined as the percentage of weak (+) reactions among all positive reactions. The RI is another mathematical method of evaluating patch-test quality; values range from +1 (ideal patch-test preparation and no questionable or irritant reactions) to -1 (patch-test preparation that causes only irritant or questionable reactions and no true allergic reactions).⁴³

In 2000, Geier and colleagues found that MDBGN 0.3% results in a higher percentage of weak positive reactions (5%) than MDBGN/PE 1.0% (containing 0.2% MDBGN and resulting in a 3.5% rate of reactions). With MDBGN 0.1%, as compared with MDBGN 0.3%, the number of positive reactions increased from 1.4% to 3.3%

and the RI decreased from +0.33 to -0.10, corresponding with an increased number of doubtful or irritant reactions with the 0.3% concentration. Because it was felt that many of these doubtful reactions were false-positive reactions, the Dutch Contact Dermatitis Research Group opted to keep Euxyl K 400 at a concentration of 1.0% pet in its standard series.⁴⁹

Warshaw and colleagues also studied the quality of patch-test preparations of allergens in the NACDG database by using the PR and RI and found that MDBGN 0.4% and MDBGN/PE 2% and 2.5% had high PRs, indicating a high percentage of false-positive reactions. Additionally, MDBGN 0.4% had a low RI value, indicating a high number of irritant or questionable reactions. For this reason, the NACDG decreased the concentration of MDBGN/PE from 2.5% to 2.0%.⁴³

Possible MDBGN Paradox and Importance of ROATs and Late Reactions

Patch testing with MDBGN may cause false-negative results, a paradox similar to the lanolin⁵⁰ and paraben⁵¹ paradoxes. In 2008, Fischer and colleagues found that the elicitation threshold for ROATs in dose per area per application of MDBGN was significantly lower than the threshold for patch testing. This indicated that a patient could have a negative patch-test result at a certain concentration while the same patient reacted positively to this same dose (per unit area per application) in a ROAT.⁵² When in doubt, a ROAT can confirm the clinical relevance of patch-test reactions. In an unpublished meeting presentation, Javvaji and Belsito advocated patch testing with 1%, 1.5%, and 2% Euxyl K 400 as well as with 0.2%, 0.3%, and 0.4% MDBGN along with additional ROATs with 0.025% MDBGN for all patients with doubtful positive reactions.⁵³

Late reactions have also been reported. Bruze and colleagues reported a patient with clinically relevant allergy to MDBGN (1.0% concentration). Lower concentrations of MDBGN (0.5% and 0.3%) were negative on day 3; the 0.5% preparation became positive on day 7.⁵⁴

Potential Interaction of MDBGN and Phenoxyethanol

Experts have debated whether MDBGN should be tested alone or in combination with phenoxyethanol as Euxyl K 400. Tosti and colleagues found that of 99 patients who had a positive reaction to Euxyl K 400 2.5%, only 51 had a positive reaction to MDBGN 0.5% alone, and 2 had a positive reaction to phenoxyethanol (PE) 5%; the authors stated that a number of irritant and doubtful reactions resulted but specific numbers were not reported.¹⁰ Because of the possibility of cumulative irritancy, de Groot and colleagues proposed using MDBGN alone as an indicator for allergy to Euxyl K 400.³⁸ In 2005, Schnuch and colleagues reported a better RI value for Euxyl K 400 1% than for MDBGN alone at 0.3%. They recommended Euxyl K 400 at 1% or MDBGN alone at 0.2% for patch testing, maintaining that the matter of testing with the mixture or with MDBGN alone was still open for discussion.²⁷

Management of Allergy to MDBGN

Allergen avoidance is crucial to the management of ACD from MDBGN in sensitized individuals. As with other preservatives, avoidance of MDBGN-containing products may present challenges to both the patient and the clinician. Although manufacturers are required to list the ingredients on their product labels, an ingredient that does not appear on the label may occasionally be present in a product, and MDBGN is no exception.⁵⁵ This creates difficulties in both correctly diagnosing and managing contact dermatitis. Because of the length of the chemical name, patients with allergy to MDBGN have an especially difficult time with allergen identification and avoidance.⁵⁶ In addition, manufacturers sometimes change the ingredients in products that patients have used for many years.⁵⁷ Finally, despite the fact that MDBGN has been banned in Europe, old products still contain the ingredient and may still be present in slow-moving markets or in patients' homes, causing continued issues with contact allergy.⁵⁸ Computerized allergen avoidance databases³ have dramatically simplified the avoidance of antigens such as MDBGN.⁵⁹

Contact Allergy to PE

PE is a preservative with broad-spectrum antimicrobial activity and is particularly effective against *Pseudomonas aeruginosa*. PE has been in use since the 1970s in products such as cosmetics and vaccines and has only rarely been cited as a source of ACD.⁶⁰ Case reports of contact allergy to PE have included sources such as an aqueous cream,⁶⁰ a diphtheria, tetanus toxoids, and pertussis (DTP) vaccine,⁶¹ and medical gauzes.⁶² PE-induced contact urticaria has also been reported.^{63–66}

Summary

Despite the initial hope that methyldibromoglutaronitrile/phenoxyethanol (Euxyl K 400) would be a nonsensitizing and effective preservative, it has unfortunately been responsible for causing significant sensitization in humans. Prevalence of allergy has decreased likely due to regulatory interventions, including lower allowable concentrations in the United States and banned use in Europe. More studies are needed to determine the optimal concentration and composition of patch-test formulations.

Acknowledgments

Financial disclosures of authors and reviewer(s): None reported.

References

- Schülke & Mayr GmbH Company. Euxyl K 400. Product information. Available at: http://www.schuelke.com/download/pdf/cint_lint_euxyl_K_400_prod.PDF (updated, 2008; accessed May 11, 2010).
- Mathias CG. Contact dermatitis to a new biocide (Tektamer 38) used in a paste glue formulation. *Contact Dermatitis* 1983;9:418.
- American Contact Dermatitis Society. Available at: <http://www.contactderm.org> (accessed August 7, 2010).
- Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of methyldibromo glutaronitrile. *J Am Coll Toxicol* 1996;15:140–65.
- Bruze M, Gruvberger B, Agrup G. Sensitization studies in the guinea pig with the active ingredients of Euxyl K 400. *Contact Dermatitis* 1988;18:37–9.
- Hausen BM. The sensitizing potency of Euxyl K 400 and its components 1,2-dibromo-2,4-dicyanobutane and 2-phenoxyethanol. *Contact Dermatitis* 1993;28:149–53.
- Wahlkvist H, Boman A, Montelius J, Wahlberg JE. Sensitizing potential in mice, guinea pig and man of the preservative Euxyl K 400 and its ingredient methyldibromo glutaronitrile. *Contact Dermatitis* 1999;41:330–8.

8. de Groot AC, Herxheimer A. Isothiazolinone preservative: cause of a continuing epidemic of cosmetic dermatitis. *Lancet* 1989;1:314–6.
9. Tosti A, Guerra L, Bardazzi F, Gasparri F. Euxyl K 400: a new sensitizer in cosmetics. *Contact Dermatitis* 1991;25:89–93.
10. Tosti A, Vincenzi C, Trevisi P, Guerra L. Euxyl K 400: incidence of sensitization, patch test concentration and vehicle. *Contact Dermatitis* 1995;33:193–5.
11. Senff H, Exner M, Gortz J, Goos M. Allergic contact dermatitis from Euxyl K 400. *Contact Dermatitis* 1989;20:381–2.
12. Pigatto PD, Bigardi A, Legori A, et al. Allergic contact dermatitis from Tektamer 38 (dibromocyanobutane). *Contact Dermatitis* 1991;25:138–9.
13. Ross JS, Cronin E, White IR, Rycroft RJ. Contact dermatitis from Euxyl K 400 in cucumber eye gel. *Contact Dermatitis* 1992;26:60.
14. Torres V, Soares AP. Contact allergy to dibromodicyanobutane in a cosmetic cream. *Contact Dermatitis* 1992;27:114–5.
15. de Groot AC, Bruynzeel DP, Coenraads PJ, et al. Frequency of allergic reactions to methyldibromoglutaronitrile (1,2-dibromo-2,4-dicyanobutane) in The Netherlands. *Contact Dermatitis* 1991;25:270–1.
16. Wilkinson JD, Shaw S, Andersen KE, et al. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002;46:207–10.
17. Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP): intended for consumers concerning methyldibromo glutaronitrile. SCCNFP/0585/02. Proceedings of the SCCNFP 20th plenary meeting; 2002 Jun 4; Brussels, Belgium.
18. The Commission of the European Communities. Commission Directive 2003/83/EC. *Off J Eur Union* 2003;238:23–7.
19. Tosti A, Vincenzi C, Smith KA. Provocative use testing of methyldibromo glutaronitrile in a cosmetic shampoo. *Contact Dermatitis* 2000;42:64–7.
20. Diba VC, Chowdhury MM, Adishes A, Statham BN. Occupational allergic contact dermatitis in hospital workers caused by methyldibromo glutaronitrile in a work soap. *Contact Dermatitis* 2003;48:118–9.
21. Wong CS, Beck MH. Occupational contact allergy to methyldibromo glutaronitrile in abrasive cleansers and work creams. *Contact Dermatitis* 2001;44:311–2.
22. Zachariae C, Rastogi S, Devantier C, et al. Methyldibromo glutaronitrile: clinical experience and exposure-based risk assessment. *Contact Dermatitis* 2003;48:150–4.
23. Pedersen LK, Haslund P, Johansen JD, et al. Influence of a detergent on skin response to methyldibromo glutaronitrile in sensitized individuals. *Contact Dermatitis* 2004;50:1–5.
24. Jensen CD, Johansen JD, Menne T, Andersen KE. Methyldibromoglutaronitrile in rinse-off products causes allergic contact dermatitis: an experimental study. *Br J Dermatol* 2004;150:90–5.
25. Jensen CD, Johansen JD, Menne T, Andersen KE. Methyldibromo glutaronitrile contact allergy: effect of single versus repeated daily exposure. *Contact Dermatitis* 2005;52:88–92.
26. Jensen CD, Johansen JD, Menne T, Andersen KE. Increased retest reactivity by both patch and use test with methyldibromoglutaronitrile in sensitized individuals. *Acta Derm Venereol* 2006;86:8–12.
27. Schnuch A, Kelterer D, Bauer A, et al. Quantitative patch and repeated open application testing in methyldibromo glutaronitrile-sensitive patients. *Contact Dermatitis* 2005;52:197–206.
28. Scientific Committee on Consumer Products (SCCP). Opinion on methyldibromo glutaronitrile (sensitization only). SCCP/0863/05. Proceedings of the SCCP 3rd plenary meeting; 15 Mar 2005; Brussels, Belgium.
29. Jong CT, Statham BN, Green CM, et al. Contact sensitivity to preservatives in the UK, 2004–2005: results of multicentre study. *Contact Dermatitis* 2007;57:165–8.
30. Johansen JD, Veien N, Laurberg G, et al. Decreasing trends in methyldibromo glutaronitrile contact allergy—following regulatory intervention. *Contact Dermatitis* 2008;59:48–51.
31. Marks JG, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998;38:911–8.
32. Zug KA, Warshaw EM, Fowler JF Jr, et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. *Dermatitis* 2009;20:149–60.
33. Zachariae C, Johansen JD, Rastogi SC, Menne T. Allergic contact dermatitis from methyldibromo glutaronitrile—clinical cases from 2003. *Contact Dermatitis* 2005;52:6–8.
34. de Groot AC, de Cock PA, Coenraads PJ, et al. Methyldibromoglutaronitrile is an important contact allergen in The Netherlands. *Contact Dermatitis* 1996;34:118–20.
35. Jacobs MC, White IR, Rycroft RJ, Taub N. Patch testing with preservatives at St John's from 1982 to 1993. *Contact Dermatitis* 1995;33:247–54.
36. Warshaw EM, Buchholz HJ, Belsito DV, et al. Allergic patch test reactions associated with cosmetics: retrospective analysis of cross-sectional data from the North American Contact Dermatitis Group, 2001–2004. *J Am Acad Dermatol* 2009;60:23–38.
37. de Groot AC. Contact allergens—what's new? *Cosmetic dermatitis. Clin Dermatol* 1997;15:485–91.
38. de Groot AC, van Ginkel CJ, Weijland JW. Methyldibromoglutaronitrile (Euxyl K 400): an important “new” allergen in cosmetics. *J Am Acad Dermatol* 1996;35:743–7.
39. Warshaw EM, Ahmed RL, Belsito DV, et al. Contact dermatitis of the hands: cross-sectional analyses of North American Contact Dermatitis Group data, 1994–2004. *J Am Acad Dermatol* 2007;57:301–14.
40. Geier J, Lessmann H, Dickel H, et al. Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG). *Contact Dermatitis* 2004;51:118–30.
41. Uter W, Lessmann H, Geier J, Schnuch A. Contact allergy to hairdressing allergens in female hairdressers and clients—current data from the IVDK, 2003–2006. *J Dtsch Dermatol Ges* 2007;5:993–1001.
42. Gruvberger B, Bjerkemo M, Bruze M. Stability of patch test preparations of methyldibromo glutaronitrile in petrolatum. *Contact Dermatitis* 2004;51:315–6.
43. Warshaw EM, Nelsen DD, Sasseville D, et al. Positivity ratio and reaction index: patch-test quality-control metrics applied to the North American Contact Dermatitis Group database. *Dermatitis* 2010;21:91–7.
44. Maier LE, Lampel HP, Bhutani T, Jacob SE. Hand dermatitis: a focus on allergic contact dermatitis to biocides. *Dermatol Clin* 2009;27:251–64, v–vi.
45. Gruvberger B, Andersen KE, Brandao FM, et al. Patch testing with methyldibromo glutaronitrile, a multicentre study within the EECDRG. *Contact Dermatitis* 2005;52:14–8.

46. Gruvberger B, Andersen KE, Brandao FM, et al. Repeated open application test with methyldibromo glutaronitrile, a multicentre study within the EEC DRG. *Contact Dermatitis* 2005;52:19–23.
47. Isaksson M, Gruvberger B, Bruze M. Repeated open application tests with methyldibromoglutaronitrile in dermatitis patients with and without hypersensitivity to methyldibromoglutaronitrile. *Dermatitis* 2007;18:203–7.
48. Bruze M, Goossens A, Gruvberger B, et al. Recommendation to include methyldibromo glutaronitrile in the European standard patch test series. *Contact Dermatitis* 2005;52:24–8.
49. Geier J, Schnuch A, Brasch J, Gefeller O. Patch testing with methyldibromoglutaronitrile. *Am J Contact Dermat* 2000;11:207–12.
50. Lee B, Warshaw E. Lanolin allergy: history, epidemiology, responsible allergens, and management. *Dermatitis* 2008;19:63–72.
51. Cashman AL, Warshaw EM. Parabens: a review of epidemiology, structure, allergenicity, and hormonal properties. *Dermatitis* 2005;16:57–66.
52. Fischer LA, Johansen JD, Menne T. Methyldibromoglutaronitrile allergy: relationship between patch test and repeated open application test thresholds. *Br J Dermatol* 2008;159:1138–43.
53. Javvaji S, Belsito DV. Patch testing with MDBGN: are positive reactions allergic? [abstract]. Proceedings of the American Contact Dermatitis Association (ACDS) 21st Annual Meeting; 2010 Mar 4; Miami Beach, FL. Available at: www.contactderm.org (accessed August 4, 2010).
54. Bruze M, Gruvberger B, Zimerson E. A clinically relevant contact allergy to methyldibromo glutaronitrile at 1% (0.32 mg/cm) detected by a patch test. *Contact Dermatitis* 2006;54:14–7.
55. Bruze M, Gruvberger B, Goossens A, et al. Allergic contact dermatitis from methyldibromoglutaronitrile. *Dermatitis* 2005;16:80–6.
56. Noiesen E, Munk MD, Larsen K, et al. Difficulties in avoiding exposure to allergens in cosmetics. *Contact Dermatitis* 2007;57:105–9.
57. Sherertz EF. A “new” cosmetic allergen. *Am J Contact Dermat* 1997;8:257.
58. Jong CT, Statham BN. Methyldibromoglutaronitrile contact allergy—the beginning of the end? *Contact Dermatitis* 2006;54:229.
59. Yiannias JA, Miller R, Kist JM. Creation, history, and future of the Contact Allergen Replacement Database (CARD). *Dermatitis* 2009;20:322–6.
60. Lovell CR, White IR, Boyle J. Contact dermatitis from phenoxyethanol in aqueous cream BP. *Contact Dermatitis* 1984;11:187.
61. Vogt T, Landthaler M, Stolz W. Generalized eczema in an 18-month-old boy due to phenoxyethanol in DPT vaccine. *Contact Dermatitis* 1998;38:50–1.
62. Gallo R, Marro I, Sorbara S. Contact allergy from phenoxyethanol in Fitostimoline gauzes. *Contact Dermatitis* 2005;53:241.
63. Bohn S, Bircher AJ. Phenoxyethanol-induced urticaria. *Allergy* 2001;56:922–3.
64. Hernandez B, Ortiz-Frutos FJ, Garcia M, et al. Contact urticaria from 2-phenoxyethanol. *Contact Dermatitis* 2002;47:54.
65. Birnie AJ, English JS. 2-Phenoxyethanol-induced contact urticaria. *Contact Dermatitis* 2006;54:349.
66. Lujan D, Hernandez-Machin B, Penate Y, Borrego L. Contact urticaria due to phenoxyethanol in an aftershave. *Dermatitis* 2009;20:E10.
67. Personal Care Products Council. Available at: <http://www.personalcarecouncil.org/> (accessed August 7, 2010).
68. Motolese A, Seidenari S, Truzzi M, Giannetti A. Frequency of contact sensitization to Euxyl K 400. *Contact Dermatitis* 1991;25:128.
69. Corazza M, Mantovani L, Roveggio C, Virgili A. Frequency of sensitization to Euxyl K 400 in 889 cases. *Contact Dermatitis* 1993;28:298–9.
70. Van Ginkel CJ, Rundervoort GJ. Increasing incidence of contact allergy to the new preservative 1,2-dibromo-2,4-dicyanobutane (methyldibromoglutaronitrile). *Br J Dermatol* 1995;132:918–20.
71. Okkerse A, Geursen-Reitsma AM, van Joost T. Contact allergy to methyldibromoglutaronitrile and certain other preservatives. *Contact Dermatitis* 1996;34:151–2.
72. Schnuch A, Geier J, Uter W, Frosch PJ. Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. *Br J Dermatol* 1998;138:467–76.
73. McFadden JP, Ross JS, Jones AB, et al. Increased rate of patch test reactivity to methyldibromo glutaronitrile. *Contact Dermatitis* 2000;42:54–5.
74. Guimaraens D, Hernandez MI, Gonzalez MA, Conde-Salazar L. Contact allergy to Euxyl K 400 in consecutively patch-tested patients. *Contact Dermatitis* 2000;43:55–6.
75. Geier J, Lessmann H, Dickel H, et al. Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG). *Contact Dermatitis* 2004;51:118–30.
76. Johansen JD, Veien NK, Laurberg G, et al. Contact allergy to methyldibromo glutaronitrile—data from a “front line” network. *Contact Dermatitis* 2005;52:138–41.
77. Boyvat A, Akyol A, Gurgey E. Contact sensitivity to preservatives in Turkey. *Contact Dermatitis* 2005;52:329–32.
78. Hasan T, Rantanen T, Alanko K, et al. Patch test reactions to cosmetic allergens in 1995–1997 and 2000–2002 in Finland—a multicentre study. *Contact Dermatitis* 2005;53:40–5.
79. ESSCA Writing Group: The European Surveillance System of Contact Allergies (ESSCA): results of patch testing the standard series, 2004. *J Eur Acad Dermatol Venereol* 2008;22:174–81.
80. Bordel-Gómez MT, Miranda-Romero A. Contact sensitization to Euxyl K-400. *Actas Dermosifiliogr* 2009;100:201–4.
81. Marks JG Jr, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group standard tray patch test results (1992 to 1994). *Am J Contact Dermat* 1995;6:160–5.
82. Jackson JM, Fowler JF. Methyldibromoglutaronitrile (Euxyl K400): a new and important sensitizer in the United States? *J Am Acad Dermatol* 1998;38:934–7.
83. Marks JG Jr, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 1996–1998. *Arch Dermatol* 2000;136:272–3.
84. Marks JG Jr, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 1998 to 2000. *Am J Contact Dermat* 2003;14:59–62.
85. Pratt MD, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 2004;15:176–83.

86. Warshaw EM, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2003-2004 study period. *Dermatitis* 2008;19:129-36.
87. Zoller L, Bergman R, Weltfriend S. Preservatives sensitivity in Israel: a 10-year overview (1995-2004). *Contact Dermatitis* 2006; 55:227-9.
88. Williams JD, Frowen KE, Nixon RL. Allergic contact dermatitis from methylidibromo glutaronitrile in a sanitary pad and review of Australian clinic data. *Contact Dermatitis* 2007;56:164-7.
89. Aalto-Korte K, Jolanki R, Estlander T, et al. Occupational allergic contact dermatitis caused by Euxyl K 400. *Contact Dermatitis* 1996;35:193-4.
90. Marcano ME, Heras F, Conde-Salazar L. Occupational allergic contact dermatitis to methylidibromoglutaronitrile in hand degreasing toilet paper. *Contact Dermatitis* 2007;57:126-7.
91. O'Donnell BF, Foulds IS. Contact dermatitis due to dibromodicyanobutane in cucumber eye gel. *Contact Dermatitis* 1993;29: 99-100.
92. Gebhart M, Stuhler A, Knopf B. Allergic contact dermatitis due to Euxyl K 400 in an ultrasonic gel. *Contact Dermatitis* 1993;29: 272.
93. Fernandez E, Navarro JA, del Pozo L, Fernandez de Corres L. Allergic contact dermatitis due to dibromodicyanobutane in cosmetics. *Contact Dermatitis* 1995;32:109-10.
94. Silva R, Almeida LM, Brandao FM. Photoallergy to oxybenzone in cosmetic creams. *Contact Dermatitis* 1995;32:176.
95. Silvestre JF, Rodriguez-Serna M, Miquel JF, et al. Allergic contact dermatitis from Euxyl K 400 in a sunscreen cream. *Contact Dermatitis* 1996;35:315.
96. Armstrong DK, Smith HR, Rycroft RJ. Contact allergy to methylidibromo glutaronitrile presenting as severe scalp seborrhoeic eczema. *Contact Dermatitis* 1999;40:335.
97. Erdmann SM, Sachs B, Merk HF. Allergic contact dermatitis due to methylidibromo glutaronitrile in Euxyl K 400 in an ultrasonic gel. *Contact Dermatitis* 2001;44:39-40.
98. Hillen U, Franckson T, Goos M. Allergic contact dermatitis due to deer-fat cream (Hirschtalgcreme). *Contact Dermatitis* 2001;44:58.
99. Kelterer D, Kaatz M, Bauer HI, et al. Contact allergy to methylidibromo glutaronitrile in Euxyl K 400 in a cosmetic cream for protection against a permanent wave solution. *Contact Dermatitis* 2002;46:250.
100. Young HS, Beck MH. Post-coital contact dermatitis from methylidibromo glutaronitrile. *Contact Dermatitis* 2004;50:48.
101. Sanchez-Perez J, Del Rio MJ, Jimenez YD, Garcia-Diez A. Allergic contact dermatitis due to methylidibromo glutaronitrile in make-up removal wipes. *Contact Dermatitis* 2005;53:357-8.
102. Lujan-Rodriguez D, Penate-Santana Y, Hernandez-Machin B, Borrego L. Connubial allergic contact dermatitis to Euxyl K 400. *Contact Dermatitis* 2006;54:122-3.
103. Sfia M, Dhaoui MA, Doss N. Consort allergic dermatitis to cosmetic agents in a 10-year-old young girl. *Contact Dermatitis* 2007;57:56-7.