

ALLERGEN Focus



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Focus on: NACD Allergen Methyldibromoglutaronitrile

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In 1997 the Food and Drug Administration granted an indication for the use of the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test (which includes panels 1.1 and 2.1) as a valuable, first-line screening tool in the diagnosis of allergic contact dermatitis (ACD). Many dermatologists utilize this standard tool in their practice and refer to Contact Dermatitis Referral Centers when the T.R.U.E test fails to identify a relevant allergen. Specifically, the T.R.U.E. Test screens for 46 distinct allergens and the balsam of Peru mixture. The test is thought to adequately *identify an allergen in approximately 24.5%* of patients with allergic contact dermatitis.¹ This being said,

many relevant allergens are not detected by use of this screening tool alone and, for this reason, the “Allergen Focus” column has been expanded to cover the notorious Allergens of the Year and the up-and-coming T.R.U.E. Test panel 3² and North American Contact Dermatitis standard allergens.

“Allergen Focus” is a column designed to concentrate on common allergens and is intended to answer some of the most frequent questions relating to their origin and most common uses.

This month, we focus on methyldibromoglutaronitrile (MDGN), a preservative commonly used in toilet paper and some other personal hygiene products. In addition, MDGN will be one of seven new allergens included in the T.R.U.E. test panel 3 in the near future.

CONTACT DERMATIDES

The contact dermatides include, *irritant contact dermatitis, contact urticaria, and allergic contact dermatitis.*

Irritant contact dermatitis, the most common form, accounts for approximately 80% of environmental-occupational based dermatoses.

Contact urticaria (wheal and flare reaction) represents an IgE and mast cell-mediated immediate-type hypersensitivity reaction that can lead to anaphylaxis, the foremost example of this would be latex protein hypersensitivity. While this is beyond the scope of this column, we acknowledge this form of hypersensitivity due to the severity of the potential reactions and direct the reader to key sources.^{3,4}

Allergic Contact dermatitis (ACD) is an important disease with high impact both in terms of patient morbidity and economics. ACD represents a T-helper cell Type 1 [Th1]-dependent delayed-type (Type IV) hypersensitivity reaction. The instigating exogenous antigens are primarily small lipophilic chemicals

TABLE 1

COMMON PRODUCTS CONTAINING METHYLDIBROMOGLUTARONITRILE AND EUXYL K 400

Methyldibromoglutaronitrile	Euxyl K 400
Hair Shampoos	Cosmetic Creams
Hair Conditioners	Topical Medications
Hair Preparations	Fabric Softeners
Bubble Bath Solutions	Paper and Moistened Toilet Paper
Indoor Tanning Preparations	Liquid Soaps
Face and Neck Preparations	Latex Paints
Permanent Wave Solutions	Adhesives and Glues
Blushers	Metalworking Fluids

Source: http://www2.mst.dk/common/Udgivramme/Frame.asp?pg=http://www2.mst.dk/udgiv/publications/2001/87-7944-596-9/html/helepubl_eng.htm and Source: www.dormer.com

TABLE 2

SYNONYMS OF METHYLDIBROMOGLUTARONITRILE AND EUXYL K 400

Methyldibromoglutaronitrile Synonyms	Euxyl K 400 Synonyms
Dibromo-2,4-dicyanobutane	2-bromo-2-(bromomethyl) glutaronitrile
2-Bromo-2-(bromomethyl) glutaronitrile	2-bromo-2-(bromomethyl) pentanedinitrile
2-Bromo-2-(bromomethyl) pentanedinitrile	1,2-dibromo-2,4-dicyanobutane
Glutaronitrile	Dibromodicyanobutane
2-bromo-2-(bromomethyl)	Merquat 2200
Pentanedinitrile	2-phenoxyethanol
2-bromo-2-(bromomethyl)	Tektamer 38

Source: <http://householdproducts.nlm.nih.gov>
Source: www.dormer.com

(haptens) with a molecular weight less than 500 Daltons.

On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated that includes cytokines, i.e., interleukin 2 and interferon gamma, T cells and Langerhan cells. This complex interaction leads to the clinical picture of ACD.

CLINICAL ILLUSTRATION

A patient presented with a concomitant hand and perianal pruritic dermatitis. Of note was his regular use of moistened brown paper towels as a substitute for toilet paper.

HISTORY OF TOILETRY PRACTICE

Long before the invention of toilet paper, man rose to the challenge of personal hygiene. Early cleansing aids included stones, clay, grass, fur, leaves, and corncobs, just to name a few.

The Ancient Romans were regarded as highly civilized as they provided their citizens with communal sponges on the ends of sticks soaked in brine (saltwater) in the public toilets.⁵

Demographics and availability of supplies played a direct role as to which toiletry materials would be chosen. Aristocrats in Europe during the 17th century, for example, were privy to wool, lace, and rose water, while the less-fortunate classes living on coastal fronts were known to use mussel shells.⁶ Likewise, coconut shells were known to have been popular with the locals for this purpose on tropical islands, such as Hawaii.⁶

But it wasn't until the 14th Century during the Ming Dynasty that the Chinese Emperor Hongwu became the first to enjoy the luxury of toilet paper.⁷ The Emperor's toilet paper was handmade by the Bureau of Imperial Supplies and supplied in 60-cm x 90-cm sheets

and likewise disposed of with imperial discretion.⁸ Because of this exclusivity, it would be centuries before this innovation would become known to the masses.

Not all disposals of waste were quite as sanitary or as discreet. For example, in Medieval times, chamber pots were emptied onto streets from windows, often accompanied by an announced verbal warning, such as "gardez l'eau" (French for "watch out for the water"). This custom was practiced all over Europe and it is thought that the English word for "toilet," "loo," is derived from a mispronunciation of the "gardylloo" phrase.⁹

ALL THE NEWS FIT TO BE WIPED WITH

Centuries later, on Apr. 24, 1704, a huge advance in public access to information created a boom in personal hygiene — the first printing of the *Boston News-Letter* published by John Campbell, considered to be America's first newspaper.¹⁰ This newly popular information highway — the newspaper — afforded an after-reading dual purpose as a cleansing material.

Soon thereafter came the first printing of the *Old Farmers Almanac* by Robert B. Thomas (published circa 1792).¹¹ The *Almanac*, which is still in circulation today, provided vital weather forecasts, agricultural advice and important farming information such as the hour of the sunrise. Publishers capitalized on the multi-purpose use of these almanacs by stylizing these early editions with a hole punched in it for hanging on the outhouse door!¹²

The *Old Farmers Almanac*, however, wasn't alone in the outhouse. Factory-made toilet paper had made a debut in 1857 when Joseph Gayetty manufactured Gayetty's Medicated Paper in the United States. The Gayetty toilet paper consisted of loose flat sheets of paper imprinted with the Gayetty name that were pre-moistened and medicated with aloe and sold in boxes of 500 for 50 cents.⁵

In addition, two large companies were also manufacturing toilet paper in the United States by the late 1870s. One was the Albany Perforated Wrapping Paper Company; it sold both a non-medicated and a medicated toilet paper. The other was the company developed by the two brothers E. Irvin and Clarence Scott from Pennsylvania (founders of the Scott Paper Company c. 1879), who introduced the novelty of toilet paper on a roll.¹²

With the backdrop of the conservative Victorian era and the “unmentionability” of the products, these wares were originally sold under private-label businesses, such as with the hotel’s name that distributed them. Consumers could purchase toilet tissue, for example, with the Waldorf Astoria hotel’s name.¹³

Not all Americans could afford to travel to a high-class hotel to purchase these wares, and as a result, Sears and Roebuck’s catalogues became especially popular for their absorbent non-coated paper.

In fact, when Sears made the transition to the in-vogue glossy paper, a wave of consumer complaints appeared against the catalogue.⁶ The public outcry was so great that Sears was inspired to publish a humorous spin-off catalogue “Rears and Sorebutt” in the 1930s.¹⁴ Fortunately, for many American consumers, at the time Sears had made the paper transition, larger quantities of toilet tissue were already commercially available.

New toiletry companies debuted with innovations to capture the growing consumer market, such as the Northern Tissue Company (now Quilted Northern) which marketed the first splinter-free paper in 1935!¹²

A NOT-SO-HUMOROUS TOILET PAPER SHORTAGE

For the next 40 years, Americans continued to enjoy the privilege of a steady increase in the ready availability of toilet tissue, until in the early 1970s, when America suffered a toilet paper shortage. The late comedian Johnny Carson (on NBC’s “Tonight Show”) joked that “You know what’s disappearing from the supermarket shelves? Toilet paper. There’s an acute shortage of toilet paper in the United States.”

Little did he know that a comment suggesting that there was a toilet paper shortage would prompt viewers to empty out stores’ stocks of toilet paper in less than 24 hours! The shortage lasted for 3 weeks, and Johnny Carson publicly apologized for causing this frenzy.⁶

Furthermore, the increasingly abundant supply of toilet tissues was paralleled by a number of useful advances — from folded sheets with a shiny side (recently phased out of grade schools), to perforation, to quilted. And, despite the failure of Gayetty’s pre-moistened and medicated

TABLE 3

PRESERVATIVES MOST FREQUENTLY CAUSING SENSITIZATION

Preservative	Positive Reaction
Quaternium-15 (2%)	9.3%
Formaldehyde (1% aqs)	8.4%
MDGBN/PE (2.5%)	5.8%
Imidazolidinylurea (2%)	3.0%
DMDM Hydrantoin (1%)	2.8%
MCI/MI (100 ppm aqs)	2.3%
Paraben Mix (1%)	0.6%

Source: Pratt HD, Belsito DV, DeLeo VA, Fowler JF. *Dermatitis*. 2004;15(4):176-183.

paper in the 1800s, moist toilet paper has made a comeback.

In the early 1990s, moistened tissues were re-introduced in the United Kingdom and by 2001 in the United States. It is postulated that these two cultural markets were the first to break through because of their indifference to the use of bidets, as compared to Europe-at-large. Regardless, with the re-introduction of the moistened paper novelty brought with it the need for preservation of the wares.

PRESERVATIVES IN PERSONAL HYGIENE PRODUCTS

The American Academy of Dermatology estimates that the average adult uses at least seven different skincare products daily ranging from fragrances, moisturizers, cleansers, cosmetics, deodorants, and haircare products.¹⁵ Preservative chemicals are used broadly in cosmetics, medications, foods and paper products to inhibit the growth of fungi and bacteria that can cause spoilage and may cause skin infections. An additional goal of preservatives is to protect products from oxygen and light damage.

Preservatives are second only to fragrances as the most frequently sensitizing ingredients in cosmetic and personal hygiene products.

Toilet paper can contain both of the most frequent sensitizing allergens, namely preservatives (such as formaldehyde and MDGN), and if scented, fragrances such as cinnamic aldehyde and cinnamic alcohol.¹⁶

Consumers should be made aware of the meaning of terms on labels such as hypoallergenic and preservative-free. “hypoallergenic” and “preservative-free.” Products that are preservative-free may have a

reduced ability to prevent contamination during a product’s expected lifetime.¹⁷

Both of these are terms used by manufacturers to imply a low likelihood of developing an allergic skin reaction. Unfortunately, no legal standards exist to assess that manufacturers’ claims are true.¹⁸

HISTORY OF METHYLDIBROMOGLUTARONITRILE

The preservative methyldibromoglutaronitrile was first introduced in 1983 in detergents, glues and paints. It was found to be a useful wood preservative, in color photographic processing solutions, in seed disinfectants, and *paper*.

Furthermore it is used as a preservative for latex emulsions, water-based paints, glues, joint cements, and liquid detergents. By 1985 it was introduced in Europe for use in cosmetic products.¹⁹ Since then, it has achieved a wide utility. (See Table 1.)

Initially, MDGN was introduced as an alternative to other sensitizing preservatives such as methylchloroisothiazolinone:methylisothiazolinone (MCI/MI).

The approved initial maximum concentration of 0.1% was allowed for both leave-on and rinse-off cosmetic products, with the exception of sunscreens for which the MDGN was not allowed to exceed a concentration of 0.025%.²⁰

Early animal studies had shown that MDGN was a weak sensitizer. Wahlkvist had reported that a contact allergenic potential could be detected for MDGN and Euxyl K400 in two animal studies, but the preservative failed to demonstrate sensitization to MDGN in a guinea pig maximization test.²¹

Over the next decade, however, as MDGN became more widespread, an

alarming increase was noted in the incidence of sensitivity.²² And, by 2002, the use of MDGN was restricted to rinse-off products.

As an aside, Euxyl 400 (Schulke & Mayr, Hamburg, Germany) is a trade name for the combination preservative MDGN and phenoxyethanol in a ratio of 1:4.¹⁶

While Euxyl 400 is effective against bacteria, yeasts and molds, it may not be used in medicines or as a disinfectant.¹⁹

Table 2 illustrates common synonyms for MDGN and Euxyl K 400.

ALLERGY TO MDGN

The first reported case of occupational contact dermatitis to MDGN was in 1983 and occurred in a 28-year-old maintenance mechanic who worked in a baby food processing plant and developed eczema of the hands and forearms.^{22,23} The patient's job involved repairing automated labeling equipment that fastened commercial labels to jars of baby food with a paste glue. The baby food company had

recently obtained a new glue formulation containing MDGN, under the trade name Tektamer 38. Patch testing to Tektamer was positive, and the patient's symptoms resolved when the paste glue formulation was changed.

Other reports of occupational contact allergy to MDGN include four hair-dressers who were using a shampoo containing it.

In addition, patients may have contact allergic contact dermatitis (dermatitis caused by contact with a substance via a spouse) to MDGN.

A 29-year-old woman developed recurrent episodes of vesicular and papular lesions on her extremities. A detailed history and patch testing proved the culprit to be the methylidibromoglutaronitrile component of the Euxyl K 400 in the moisturizing hand cream used by her husband.²⁴

The North American Contact Dermatitis Group recorded sensitization rates for 2001/2002 to preservatives and demonstrated that MDGN/PE (2%) had

5.8% positive reactions among 4,913 patients who were patch-tested.²⁵ (**See Table 3.**) The prevalence of MDGN allergy in the United States from 1992 to 1994 was 1.3%.²⁶ Zachariae patch-tested 766 patients in 2003 for a range of allergens, including MDGN, and concluded that MDGN was not suitable for any cosmetic product.²⁷

By 2005, the European Scientific Committee for Cosmetic Products had recommended that MDGN be banned from rinse-off products; however, it will probably take several years before it is vanished completely from the European market.²⁸

In Europe, the United States, and the United Kingdom, awareness of contact allergy to MDGN has been increasing.²⁶ In 2004 Opiel et al in Germany found that in a retrospective analysis of 9,948 patients, MDGN was among the top-10 allergens.²⁹

Of note, in the Netherlands, 40% to 50% of patients allergic to MDGN and Euxyl 400 presented with perianal dermatitis. The culprit exposure in these patients was found to be moistened toilet tissue containing Euxyl 400.¹⁹

TESTING FOR METHYLDIBROMOGLUTARONITRILE AND EUXYL K400 SENSITIVITY

The recommended concentration for testing MDGN has not been established. Tosti et al recommend MDGN 0.5% in petrolatum vehicle with an emulsifier such as soy lecithin. Euxyl 400 is often tested in 2.5% petrolatum vehicle.^{19,30,31}

False test results can be obtained because of low concentrations of the preservative in the product.³²

When suspecting an allergy to cosmetics and in patients with perianal dermatitis, testing for MDGN should be routine.³³

VALUE OF THIS PATIENT CASE

This case illustrates the importance of a thorough history when suspecting contact dermatitis in a patient with perianal dermatitis. Questions should be asked about personal hygiene products used, such as the type of toilet paper (i.e., moistened, scented paper towels) and sanitary napkins, as well as topical ointments and preparations.

The patient was educated on the importance of **avoidance** of the brown paper



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Form 3

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Medicis (Vanos)

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towels (and other sources of MDGN), and both his hand and perianal dermatitis cleared. Of note, his hand dermatitis returned when he again used the brown paper towels (positive-use test). This persuaded the patient to believe the association between the paper towels and his dermatitis, and he began strict avoidance of his known allergen.

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