

University of Groningen

Formaldehyde-releasers in cosmetics

de Groot, Anton C.; White, Ian R.; Flyvholm, Mari-Ann; Lensen, Gerda; Coenraads, Pieter-Jan

Published in:
CONTACT DERMATITIS

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

de Groot, A. C., White, I. R., Flyvholm, M-A., Lensen, G., & Coenraads, P-J. (2010). Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy Part 1. Characterization, frequency and relevance of sensitization, and frequency of use in cosmetics. *CONTACT DERMATITIS*, 62(1), 18-31.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Review Article

Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy

Part 1. Characterization, frequency and relevance of sensitization, and frequency of use in cosmetics

ANTON C. DE GROOT¹, IAN R. WHITE², MARI-ANN FLYVHOLM³, GERDA LENSEN¹ AND PIETER-JAN COENRAADS¹

¹Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, ²St John's Institute of Dermatology, St Thomas' Hospital, London, UK, and ³National Research Centre for the Working Environment, Copenhagen, Denmark

In this part of a series of review articles on formaldehyde-releasers and their relationship to formaldehyde contact allergy, formaldehyde-releasers in cosmetics are discussed. In this *first part* of the article, key data are presented including frequency of sensitization and of their use in cosmetics. In Europe, low frequencies of sensitization have been observed to all releasers: 2-bromo-2-nitropropane-1,3-diol 0.4–1.2%, diazolidinyl urea 0.5–1.4%, imidazolidinyl urea 0.3–1.4%, quaternium-15 0.6–1.9% (for DMDM hydantoin no recent data are available). All releasers score (far) higher prevalences in the USA; the possible explanations for this are discussed. The relevance of positive patch test reactions has been insufficiently investigated. In the USA, approximately 20% of cosmetics and personal care products (stay-on products: 17%, rinse-off products 27%) contain a formaldehyde-releaser. The use of quaternium-15 is decreasing. For Europe, there are no comparable recent data available. In the *second part* of the article, the patch test relationship of the releasers in cosmetics to formaldehyde contact allergy will be reviewed and it will be assessed whether products preserved with formaldehyde-releasers may contain enough free formaldehyde to pose a threat to individuals who have contact allergy to formaldehyde.

Key words: 2-bromo-2-nitropropane-1,3-diol; 5-bromo-5-nitro-1,3-dioxane; benzylhemiformal; cosmetics; diazolidinyl urea; DMDM hydantoin; formaldehyde; formaldehyde-releaser; imidazolidinyl urea; quaternium-15; sodium hydroxymethylglycinate; toiletries. © John Wiley & Sons A/S, 2010.

Accepted for publication 7 June 2009

Introduction

In a previous article, contact allergy to formaldehyde was reviewed and an inventory was made of formaldehyde-releasers (1). An important source of human skin contact with formaldehyde is the use of cosmetics containing formaldehyde-releasers as preservatives. These preservatives are added to water-containing cosmetics (which includes personal care products/toiletries) to prevent the growth of micro-organisms that may enter during manufacture or during their usage. Microbial contamination may cause discoloration, malodours, and physical

and chemical degradation of products, in addition to the potential adverse events of pathogens on consumers. Formaldehyde-releasers used in cosmetics and permitted in the EU are shown in Table 1 (in the USA, there is no relevant legislation, either on the ingredients used in cosmetics or on their permitted concentration in the final product). The antimicrobial activity of these preservatives probably results from formaldehyde release, but it has also been postulated that at least some of these substances act as preservatives *independent* of formaldehyde release (2). In this article (*first*

part), key data on these formaldehyde-releasers are presented including synonyms, molecular formula, chemical structure, applications (cosmetics are their main application product group, but they are also used in non-cosmetic products), frequency of sensitization in unselected and selected patient populations and relevance of the observed positive patch test reactions. Data on their frequency of use in cosmetics are discussed. In the *second part*, their patch test relationship to formaldehyde will be reviewed, and it will be assessed whether products preserved with formaldehyde-releasers may contain enough free formaldehyde to pose a threat to individuals who are contact allergic to formaldehyde.

Key Data on Formaldehyde-releasers Used in Cosmetics

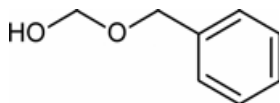
BENZYLHEMIFORMAL (INCI)

Chemical Abstracts Service registration number (CAS) 14548-60-8

Synonyms: (benzyloxy)methanol; phenylmethoxymethanol; (phenylmethoxy)methanol.

Molecular formula: C₈H₁₀O₂.

Chemical structure:



Applications

Permitted in cosmetics (only rinse-off products) in the EU in a maximum concentration of 0.15%. Benzylhemiformal is also used in non-cosmetic applications: biocide in metalworking fluids, slurries, filler suspensions, adhesives, various emulsions and dispersions, paints and lacquers, paper industry, spinning baths in the textile industry, polishes, waxes, and cleaning products.

Frequency of sensitization

There appear to be no published reports on the frequency of sensitization to benzylhemiformal in a population of patients patch tested for suspected contact dermatitis (not further selected). The experience with testing benzylhemiformal in *selected* patient groups is limited in number and geographic area; all studies having been performed by the IVDK (Germany, Austria, Switzerland) (Table 2). In three small series of patients with suspected metalworking fluid dermatitis, 1–2.9% reacted to benzylhemiformal 1% pet (3–5). In a larger series of 947 and 1759 patients, 2.3% and 2.4% had positive patch tests (6). It was not quite clear how these

patients had been selected and there may have been an overlap in the two populations. The relevance of the observed positive patch test reactions was not stated and it is unknown whether these patients also reacted to formaldehyde.

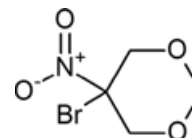
5-BROMO-5-NITRO-1,3-DIOXANE (INCI)

CAS 30007-47-7

Synonyms: bromonitrodioxane.

Molecular formula: C₄H₆BrNO₄.

Chemical structure:



Applications

For cosmetic application in the EU permitted only in rinse-off cosmetics, maximum concentration 0.1%.

5-Bromo-5-nitro-1,3-dioxane is also used in non-cosmetic applications: biocide in cleaning/washing agents, rinsing agents, water systems, glossing agents, laboratory chemicals, metalworking fluids, protein preparations, antibodies and antisera preparations, and column matrices. Also used in leather processing and as a stabilizer and surfactant.

Frequency of sensitization

Contact allergy to 5-bromo-5-nitro-1,3-dioxane appears to be rare or at least rarely reported. In the period 1985–1997 in Belgium, 8521 patients were patch tested, and only one positive reaction to 5-bromo-5-nitro-1,3-dioxane was observed. It was not stated, however, how many patients had been tested with 5-bromo-5-nitro-1,3-dioxane (8).

2-BROMO-2-NITROPROPANE-1,3-DIOL (INCI)

CAS 52-51-7

Synonyms: bronopol (INN); bromonitropropane-diol.

Molecular formula: C₃H₆BrNO₄.

Chemical structure:

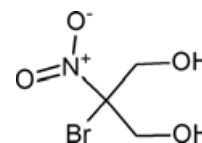


Table 1. Formaldehyde releasers permitted in cosmetics in the EU with their maximum concentration

| Preservative | Maximum allowed concentration (%) | Comments |
|--|-----------------------------------|---|
| Benzylhemiformal | 0.15 | Permitted in rinse-off products only |
| 5-Bromo-5-nitro-1,3-dioxane | 0.1 | Permitted in rinse-off products only; formation of nitrosamines must be avoided |
| 2-Bromo-2-nitropropane-1,3-diol | 0.1 | Formation of nitrosamines must be avoided |
| Diazolidinyl urea | 0.5 | |
| 4,4-Dimethyloxazolidine ^a | 0.1 | Present in Bioban CS 1135 [®] , a preservative in metalworking fluids |
| DMDM hydantoin | 0.6 | |
| 5-Ethyl-1-aza-3,7-dioxabicyclo-[3.3.0] octane ^a | 0.3 | Prohibited in oral hygiene products and products intended to come into contact with mucous membranes. Present in Bioban CS 1246 [®] , a preservative in metalworking fluids. |
| Formaldehyde | 0.2 | Maximum 0.1% for products for oral hygiene |
| Imidazolidinyl urea | 0.6 | |
| Methenamine (hexamethylenetetramine) ^a | 0.15 | |
| Paraformaldehyde ^a | 0.2 | Maximum 0.1% for products for oral hygiene |
| Quaternium-15 | 0.2 | |
| Sodium methylhydroxyglycinate | 0.5 | |

^aWill be discussed later in this series of articles.

Table 2. Frequency of sensitization to benzylhemiformal in selected patients

| Country | Years of study | Number of patients tested | Test concentration & vehicle | Positive (%) | | | Current relevance % | Mode of selection | Ref. |
|-------------------|----------------|---------------------------|------------------------------|--------------|-------|-----|---------------------|---|------|
| | | | | All | Women | Men | | | |
| IVDK | 2004–2005 | 102 | 1% pet. | 1 | | | NS | Patients with suspected metalworking fluid dermatitis | (3) |
| IVDK | 2002–2003 | 199 | 1% pet. | 1.5 | | | NS | Patients with suspected metalworking fluid dermatitis | (4) |
| IVDK | 1999–2001 | 105 | 1% pet. | 2.9 | | | NS | Metalworkers exposed to water-based metalworking fluids | (5) |
| IVDK ^a | 1992–1995 | 1759 | 1% pet. | 2.4 | | | NS | NS. Selected from 35 062 patients | (6) |
| IVDK ^a | 1990–1993 | 947 | 1% pet. | 2.3 | | | NS | NS. Approximately 30% were patients working with metals and metal objects | (7) |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland (Information Network of Departments of Dermatology) www.ivdk.org; NS, not stated.

^aIt may be assumed that there is an overlap in the patient populations in these IVDK studies.

Applications

Permitted in cosmetics in the EU up to a level of 0.1%. Typical use levels are 0.01–0.1%. 2-Bromo-2-nitropropane-1,3-diol is active against fungi, yeasts, and Gram-positive and Gram-negative bacteria, especially against *Pseudomonas aeruginosa*. 2-Bromo-2-nitropropane-1,3-diol is also used in non-cosmetic applications: adhesives/glues, cleaning agents, binding agents, colouring agents, construction materials, filling agents, flooring agents, humidifiers, impregnating agents, metalworking fluids, milk processing plants, paints/lacquers, paper mills water circulating systems, pharmaceutical products, polishes, printing inks, slurries, surface treatment for paper, cardboard and

other non-metals, viscosity adjustors, and washing detergents (9). 2-Bromo-2-nitropropane-1,3-diol can degrade to formaldehyde, 2-(hydroxymethyl)-2-nitropropane-1,3-diol (Tris nitro, a formaldehyde-releaser used in metalworking fluids) and bromonitroethanol. Heat and alkaline conditions hasten this process (10).

Frequency of sensitization

Recent experience with routine testing of 2-bromo-2-nitropropane-1,3-diol in patients suspected of contact dermatitis is summarized in Table 3. Both 0.25% pet and 0.5% petrolatum 2-bromo-2-nitropropane-1,3-diol preparations have been used for patch testing. In the American studies, frequencies of sensitization ranged from 2.1% to 3.3%

(mean, adjusted for sample size: 2.8%) (11–16). In the studies performed in European countries, prevalences were consistently lower, ranging from 0.4% to 1.2% (mean, adjusted for sample size: 0.9%) (17–22). Relevance was established or considered ‘probable’ in 7–80% of the positive patients.

2-Bromo-2-nitropropane-1,3-diol has also been tested in selected groups of patients, e.g. in patients with suspected metalworking fluid dermatitis and (presumably) in patients suspected of cosmetic allergy (Table 4). This selection did not result in higher rates of sensitization. In none of the studies was commented on the relevance of the observed positive patch test reactions.

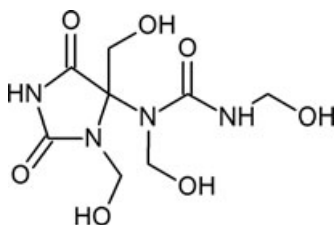
DIAZOLIDINYL UREA (INCI)

CAS 78491-02-8

Synonyms: 1-(1,3-bis(hydroxymethyl)-2,5-dioxoimidazolidin-4-yl)-1,3-bis(hydroxymethyl)urea; *N,N'*-bis(hydroxymethyl)urea.

Molecular formula: C₈H₁₄N₄O₇.

Chemical structure:



It has been shown that diazolidinyl urea cannot be explained by a single chemical structure (28). The product consists of several compounds with presumably ‘compound BHU’ as dominant (30–40%): 1-(3,4-bis-hydroxymethyl-2,5-dioxo-imidazolidin-4-yl)-1,3-bis-hydroxymethyl-urea. The remainder part is probably many polymers of allantoin-formaldehyde condensation products. Only about 50% of the theoretical amount of formaldehyde in diazolidinyl urea can be released upon complete hydrolysis. Under basic and neutral conditions diazolidinyl urea will degrade to only one compound, ‘compound HU’: (4-hydroxymethyl-2,5-dioxo-imidazolidin-4-yl)-urea, which is also present in imidazolidinyl urea.

Applications

In cosmetics (9) permitted in the EU in a maximum concentration of 0.5%. Typical use levels are 0.1–0.3%, often combined with methyl- and propylparaben for optimal antifungal activity.

Frequency of sensitization

Recent experience with routine testing of diazolidinyl urea in patients suspected of contact dermatitis is summarized in Table 5. Test concentrations have included 1% and 2%, both in pet. and aq. Most studies were US multicentre studies [North American Contact Dermatitis Group (NACDG), Mayo Clinic, three locations] and frequencies of sensitization ranged from 2.4% to 3.7% (mean, adjusted for sample size: 3.1%) (11–16, 26). In the few studies performed in European countries, prevalences were consistently lower, ranging from 0.5% to 1.4% (mean, adjusted for sample size: 1%, excluding pre-1990 data) (17, 18, 29, 30). Relevance was established or considered ‘probable’ in 24–75% of the positive patch test reactions. The 1% petrolatum test substance tended to detect more cases of sensitization than the patch tests with 1% aqua.

Diazolidinyl urea has also been tested in selected populations of patients (Table 6). This resulted in only one small study in a higher percentage of positive reactions (26). In none of the studies was relevance mentioned nor was it specified how the patients were selected.

As mentioned under ‘Chemical structure’, diazolidinyl urea consists of numerous components. This implies that although a number of contact allergic reactions to diazolidinyl urea may be caused by the release of formaldehyde, specific reactions to the various other components in the biocide are also likely to occur. A study in guinea pigs indicated that diazolidinyl urea may be rated as a mild sensitizer. Cross-reactions to imidazolidinyl urea (5/8 animals) and formaldehyde (6/8 animals) were demonstrated in animals sensitized to diazolidinyl urea (31). Jordan (32) induced sensitization to 2% diazolidinyl urea in 19 of 150 patients; approximately 50% of these sensitized patients also became sensitive to imidazolidinyl urea. In comparison, only two of another 150 were sensitized to the same level (2%) of imidazolidinyl urea (28, 32). The presence of formaldehyde, ‘compound HU’, and possibly other common components in both diazolidinyl urea and imidazolidinyl urea may explain why many patients in the patch test react to both preservatives.

DMDM HYDANTOIN (INCI)

CAS 6440-58-0

Synonyms: 1,3-bis(hydroxymethyl)-5,5-dimethyl-2,4-imidazolidine-2,4-dione; dimethyloldimethylhydantoin; 1,3-dimethylol-5,5-dimethylhydantoin; DMDMH.

Molecular formula: C₇H₁₂N₂O₄.

Table 3. Frequency of sensitization to 2-bromo-2-nitropropane-1,3-diol in patients suspected of contact dermatitis^a

| Country | Years of study | Number of patients | Test concentration & vehicle | Positive (%) | | | Current relevance % | Comments | Ref. |
|-------------|----------------|--------------------|------------------------------|--------------|-------|-----|---------------------|---|------|
| | | | | All | Women | Men | | | |
| UK | 2004–2005 | 6958 | 0.25% pet. | 1.2 | 1.3 | 1.0 | NS | Multicentre study | (17) |
| USA | 2001–2005 | 3841 | 0.25% pet. | 2.1 | | | 51 | Mayo Clinic, three locations | (11) |
| USA | 2001–2002 | 4897 | 0.5% pet. | 3.3 | | | 7/63 ^b | Multicentre study, NACDG | (12) |
| UK | 2000 | 3063 | 0.5% pet. | 0.8 | | | 80 | Relevance (80%) = current and past relevance in one of the centres (674 patients) | (18) |
| USA | 1998–2000 | 5800 | 0.5% pet. | 3.1 | | | 6/58 ^b | Multicentre study, NACDG | (13) |
| USA | 1996–1998 | 4094 | 0.5% pet. | 3.2 | | | 69 ^c | Multicentre study, NACDG | (14) |
| IVDK | 1992–1998 | 33 368 | 0.5% pet. | 1.1 | | | NS | Multicentre study, IVDK | (19) |
| USA | 1994–1996 | 3074 | 0.5% pet. | 2.3 | | | 37/32 ^b | Multicentre study, NACDG | (15) |
| USA | 1992–1994 | 3477 | 0.5% pet. | 2.2 | | | 42 ^c | Multicentre study, NACDG | (16) |
| Austria | 1992–1993 | 11 516 | 0.5% pet. | 0.4 | 0.4 | 0.2 | NS | Multicentre study | (20) |
| Switzerland | 1989–1990 | 2295 | 0.5% pet. | 1.2 | | | NS | Multicentre study | (21) |
| Europe | <1990* | 8149 | 0.5% pet. | 0.5 | | | 45 | EECDRG. 80% of the patients came from the London area | (22) |

EECDRG, European Environmental and Contact Dermatitis Research Group; IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland (Information Network of Departments of Dermatology) www.ivdk.org; NACDG, North American Contact Dermatitis Group; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bDefinite or probable relevance (first number)/possible relevance (second number).

^cPercentage includes 'possible relevance'.

*Exact year is unknown but it must have been before 1990.

Table 4. Frequency of sensitization to 2-bromo-2-nitropropane-1,3-diol in selected patients^a

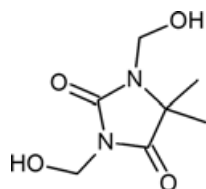
| Country | Years of study | Number of patients tested | Test concentration & vehicle | Positive (%) | | | Current relevance % | Mode of selection | Ref. |
|-------------------|----------------|---------------------------|------------------------------|--------------|-------|-----|---------------------|---|------|
| | | | | All | Women | Men | | | |
| IVDK | 2004–2005 | 90 | 0.5% pet. | 0 | | | NS | Patients with suspected metalworking fluid dermatitis | (3) |
| IVDK | 2002–2003 | 199 | 0.5% pet. | 1.1 | | | NS | Patients with suspected metalworking fluid dermatitis | (4) |
| Finland | 2000–2002 | 6562 | 0.5% pet. | 0.2 | | | NS | NS. Selected from approximately 11 800 patients | (25) |
| IVDK | 1999–2001 | 148 | 0.5% pet. | 1.4 | | | NS | Metalworkers exposed to water-based metalworking fluids | (5) |
| USA | 1998–2000 | 991 | 0.25% pet. | 2.0 | | | NS | NS | (26) |
| Finland | 1995–1996 | 5150 | 0.5% pet. | 0.5 | | | NS | NS. Selected from approximately 9400 patients | (25) |
| IVDK ^b | 1992–1995 | 16 934 | 0.5% pet. | 1.1 | | | NS | NS. Selected from 35 062 patients | (6) |
| IVDK ^b | 1990–1994 | 1781 | 0.5% pet. | 1.8 | | | NS | NS. Selected from 28 349 patients | (27) |
| IVDK ^b | 1990–1994 | 11 443 | 0.5% pet. | 1.2 | | | NS | NS. Selected from 28 349 patients | (27) |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland (Information Network of Departments of Dermatology) www.ivdk.org; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bIt may be assumed that there is an overlap in the patient populations in these IVDK studies.

Chemical structure:



Applications

Preservative mainly used in cosmetics. Permitted in cosmetics in the EU at a maximum concentration of 0.6%. At recommended use levels,

DMDM hydantoin is active against fungi, yeast, and Gram-positive and Gram-negative bacteria (33).

Frequency of sensitization

Recent experience with routine testing of DMDM hydantoin in patients suspected of contact dermatitis is summarized in Table 7. Test concentrations have included 1% in pet. and aq. and earlier 3% aq. Most studies were US multicentre studies (NACDG, Mayo Clinic, three locations) (11–16, 26). Frequencies of sensitization have ranged from 0.5% to 3.4% but were usually in the 1.3–2.5% range (mean, adjusted for sample size: 2%). The petrolatum-based test substances usually scored slightly higher than

the aqueous preparations. Relevance was established or considered 'probable' in 15–86% of the positive patch test reactions. In Europe, only old data are available.

In several studies, selected patients (not stated how they were selected) have been tested with DMDM hydantoin 2% aq. and/or 2% pet. (Table 8). Neither the selection process nor the use of higher test concentrations resulted in an increase in frequencies of detection of sensitization. In an IVDK study, relevance was found in 31% of the positive patch test reactions. Causative products were mainly cosmetics (30%) and topical drugs (22%); the other products were not mentioned (36).

IMIDAZOLIDINYL UREA (INCI)

CAS 39236-46-9

Synonyms: Imidurea (INN); bis(methylolhydantoin urea)methane; *N,N'*-methylenebis(*N'*-(1[or 3]-hydroxymethyl)-2,5-dioxo-4-imidazolidinyl)urea.

Molecular formula: C₁₁H₁₆N₈O₈.

Chemical structure:

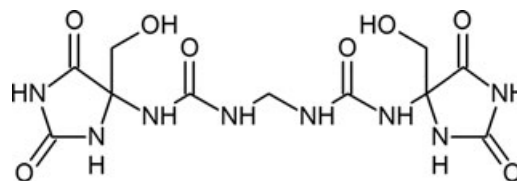


Table 5. Frequency of sensitization to diazolidinyl urea in patients suspected of contact dermatitis^a

| Country | Years of study | Number of patients | Test concentration & vehicle | Positive (%) | | | Current relevance % | Comments/setting | Ref. |
|-----------------|----------------|--------------------|------------------------------|--------------|-------|-----|---------------------|---|------|
| | | | | All | Women | Men | | | |
| UK | 2005 | 6958 | 2% pet. | 1.1 | 1.2 | 0.9 | NS | Multicentre study | (17) |
| USA | 2001–2005 | 3842 | 1% pet. | 3.5 | | | 75 | Mayo Clinic, three locations | (11) |
| USA | 2001–2005 | 3840 | 1% aq. | 2.4 | | | 75 | Mayo Clinic, three locations | (11) |
| USA | 2001–2002 | 4897 | 1% pet. | 3.1 | | | 31/63 ^b | Multicentre study, NACDG | (12) |
| USA | 2001–2002 | 4897 | 1% aq. | 3.2 | | | 33/58 ^b | Multicentre study, NACDG | (12) |
| Sweden | 2000 | 3790 | 1% pet. | 1.4 | | | NS | Multicentre study | (29) |
| USA | 1998–2000 | 1033 | 1% pet. | 2.9 | | | NS | Mayo Clinic, three locations | (26) |
| USA | 1998–2000 | 1319 | 1% aq. | 2.5 | | | NS | Mayo Clinic, three locations | (26) |
| UK | 2000 | 3062 | 2% pet. | 0.7 | | | 90 | Relevance (90%) = present and past relevance in one centre (674 patients) | (18) |
| USA | 1998–2000 | 5802 | 1% pet. | 3.0 | | | 24/64 ^b | Multicentre study, NACDG | (13) |
| USA | 1998–2000 | 5778 | 1% aq. | 2.6 | | | 28/55 ^b | Multicentre study, NACDG | (13) |
| USA | 1996–1998 | 4096 | 1% pet. | 3.7 | | | 92 ^c | Multicentre study, NACDG | (14) |
| USA | 1996–1998 | 4094 | 1% aq. | 2.9 | | | 85 ^c | Multicentre study, NACDG | (14) |
| USA | 1994–1996 | 3085 | 1% pet. | 3.7 | | | 48/39 ^b | Multicentre study, NACDG | (15) |
| USA | 1994–1996 | 3060 | 1% aq. | 3.7 | | | 44/41 ^b | Multicentre study, NACDG | (15) |
| USA | 1992–1994 | 3481 | 1% pet. | 3.0 | | | 65 ^c | Multicentre study, NACDG | (16) |
| USA | 1992–1994 | 3471 | 1% aq. | 3.1 | | | 65 ^c | Multicentre study, NACDG | (16) |
| The Netherlands | 1984–1988 | 2400 | 2% aq. | 0.5 | | | NS | One centre, Nijmegen | (30) |

NACDG, North American Contact Dermatitis Group; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bDefinite or probable relevance (first number)/possible relevance (second number).

^cPercentage includes 'possible relevance'.

Table 6. Frequency of sensitization to diazolidinyl urea in selected patients^a

| Country | Years of study | Number of patients tested | Test concentration & vehicle | Positive (%) | | | Current relevance % | Mode of selection | Ref. |
|-------------------|----------------|---------------------------|------------------------------|--------------|-------|-----|---------------------|---|------|
| | | | | All | Women | Men | | | |
| Finland | 2000–2002 | 6539 | 1% pet. | 0.9 | | | NS | NS. Selected from approximately 11 800 patients | (25) |
| USA | 1998–2000 | 285 | 2% pet. | 4.9 | | | NS | NS | (26) |
| Finland | 1995–1996 | 2911 | 1% pet. | 1.2 | | | NS | NS. Selected from approx. 9400 patients | (25) |
| IVDK ^b | 1992–1995 | 14 881 | NS | 1.0 | | | NS | NS. Selected from 35 062 patients | (6) |
| IVDK ^b | 1990–1994 | 7812 | 2% pet. | 1.3 | | | NS | NS. Selected from 28 349 patients | (27) |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland (Information Network of Departments of Dermatology) www.ivdk.org; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bIt may be assumed that there is an overlap in the patient populations in these IVDK studies.

Table 7. Frequency of sensitization to DMDM hydantoin in patients suspected of contact dermatitis^a

| Country | Years of study | Number of patients | Test concentration & vehicle | Positive (%) | | | Current relevance % | Comments | Ref. |
|-----------------|----------------|--------------------|------------------------------|--------------|-------|-----|---------------------|-------------------------------|------|
| | | | | All | Women | Men | | | |
| USA | 2001–2005 | 3757 | 1% pet. | 2.2 | | | 75 | Mayo Clinic, three locations | (11) |
| USA | 2001–2005 | 3428 | 1% aq. | 1.3 | | | 86 | Mayo Clinic, three locations | (11) |
| USA | 2001–2002 | 4897 | 1% pet. | 2.8 | | | 29/64 ^b | Multicentre study, NACDG | (12) |
| USA | 2001–2002 | 4897 | 1% aq. | 2.2 | | | 34/57 ^b | Multicentre study, NACDG | (12) |
| USA | 1998–2000 | 1321 | 1% pet. | 0.8 | | | NS | Mayo Clinic, three locations | (26) |
| USA | 1998–2000 | 1042 | 1% aq. | 0.5 | | | NS | Mayo Clinic, three locations | (26) |
| USA | 1998–2000 | 5801 | 1% pet. | 2.0 | | | 15/75 ^b | Multicentre study, NACDG | (13) |
| USA | 1998–2000 | 5767 | 1% aq. | 1.6 | | | 20/60 ^b | Multicentre study, NACDG | (13) |
| USA | 1994–1999 | 474 | NS | 3.4 | | | NS | One centre study, Kansas City | (34) |
| USA | 1996–1998 | 4093 | 1% pet. | 2.6 | | | 93 ^c | Multicentre study, NACDG | (14) |
| USA | 1996–1998 | 4093 | 1% aq. | 1.9 | | | 82 ^c | Multicentre study, NACDG | (14) |
| USA | 1994–1996 | 3082 | 1% pet. | 2.3 | | | 49/39 ^b | Multicentre study, NACDG | (15) |
| USA | 1994–1996 | 3064 | 1% aq. | 2.1 | | | 44/39 ^b | Multicentre study, NACDG | (15) |
| USA | 1992–1994 | 3485 | 1% pet. | 1.6 | | | 56 ^c | Multicentre study, NACDG | (16) |
| USA | 1992–1994 | 3479 | 1% aq. | 1.8 | | | 56 ^c | Multicentre study, NACDG | (16) |
| Switzerland | 1989–1990 | 2295 | 3% aq. | 1.7 | | | NS | Multicentre study | (21) |
| The Netherlands | 1985 | 501 | 3% aq. | 1.2 | | | NS | Multicentre study | (35) |

NACDG, North American Contact Dermatitis Group; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bDefinite or probable relevance (first number)/possible relevance (second number).

^cPercentage includes 'possible relevance'.

Table 8. Frequency of sensitization to DMDM hydantoin in selected patients^a

| Country | Years of study | Number of patients tested | Test concentration & vehicle | Positive (%) | | | Current relevance % | Mode of selection | Ref. |
|---------|----------------|---------------------------|------------------------------|--------------|-------|-----|---------------------|-----------------------------------|------|
| | | | | All | Women | Men | | | |
| USA | 2001–2005 | 411 | 2% aq. | 1.2 | | | 60 | NS | (11) |
| IVDK | 1994–2000 | 34 321 | 2% aq. | 0.5 | | | 31 ^b | NS. Selected from 67 915 patients | (36) |
| IVDK | 1994 | 1808 | 2% pet. | 0.3 | | | 31 ^b | NS. Selected from 67 915 patients | (36) |
| IVDK | 1990–1994 | 1374 | 2% pet. | 1.1 | | | NS | NS. Selected from 28 349 patients | (27) |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland (Information Network of Departments of Dermatology) www.ivdk.org; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bRelevance of the two study protocols together.

It has been shown that imidazolidinyl urea cannot be explained by a single chemical structure (28). The product consists of 'compound HU': (4-hydroxymethyl-2,5-dioxo-imidazolidin-4-yl)-urea (10%), allantoin (20%), two unidentified presumably formaldehyde releasing compounds (10%) and 60% (most likely) numerous polymers of allantoin-formaldehyde condensation products. Only about 75% of the theoretical amount of formaldehyde in imidazolidinyl urea (2 moles of formaldehyde per mole imidazolidinyl urea) can be released upon complete hydrolysis (37). 'Compound HU' is also present in diazolidinyl urea degraded under basic and neutral conditions.

Applications

In cosmetics (9) permitted in the EU in a maximum concentration of 0.6%. The typical use level is

0.3%, often in combination with methyl- and propylparaben for optimal antifungal activity.

Frequency of sensitization

Recent experience with routine testing of imidazolidinyl urea in patients suspected of contact dermatitis is summarized in Table 9. Test concentrations have included 2% in pet. and aq. Most studies were US multicentre studies (NACDG, Mayo Clinic, three locations) (11–16, 26, 38) and frequencies of sensitization ranged from 1.3% to 3.3%. The petrolatum-based test substances nearly always scored higher than the aqueous ones (mean for the petrolatum-based preparation, adjusted for sample size: 2.7%). Frequencies of sensitization in Europe were consistently lower and ranged from 0.3 to 1.4% (mean, adjusted for sample size: 0.7%) (17, 18, 20,

21, 25, 29). Relevance was established or considered 'probable' in 21–90% of the positive patch test reactions.

In several studies, selected patients have been tested with imidazolidinyl urea 2% pet. (Table 10). This did not result in higher prevalences of sensitization, not even in a group suspected of cosmetic dermatitis (25).

As mentioned under 'Chemical structure', imidazolidinyl urea consists of numerous components. This implies that although a number of contact allergic reactions to imidazolidinyl urea may be caused by the release of formaldehyde, specific reactions to the various other components in the biocide are also likely to occur (28). The presence of formaldehyde, 'compound HU' and possibly other common components in both imidazolidinyl urea and diazolidinyl urea may explain why many patients in the patch test react to both preservatives.

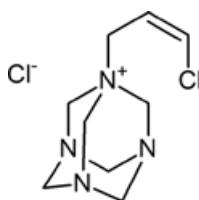
QUATERNIUM-15 (INCI)

CAS 4080-31-3

Synonyms: chloroallylhexaminium chloride; *N*-(3-chloroallyl)hexaminium chloride; 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride; hexamethylenetetramine chloroallyl chloride.

Molecular formula: C₉H₁₆ClN₄.Cl.

Chemical structure:



Applications

Permitted in cosmetics in the EU in a maximum concentration of 0.2% with typical use levels of 0.05–0.2%, quaternium-15 is a highly active, broad-spectrum preservative providing effective antimicrobial activity against bacteria (particularly effective against *Pseudomonas* species), yeast, and molds. It has been frequently used in cosmetics (9). Quaternium-15 may also be present in non-cosmetic applications including metalworking fluids, detergents and soaps, floor waxes and polishes, inks, latex-based paints, laundry starch, paper and pulp products, textile finishing solutions, spinning emulsions, printing pastes, joint cements (40), and photocopier toner.

Frequency of sensitization

Quaternium-15 pet is included in most baseline patch testing series including that in Europe. Recent experience with routine testing is summarized in

Table 11. Test concentrations have included 1% and 2% in pet. As with formaldehyde (1), there are major differences in the frequencies of sensitization between USA and European studies. In the multicentre studies from the USA frequencies of sensitization have ranged from 7.1% to 9.6% (mean, adjusted for sample size: 8.8%) (11–16, 39). In the European studies, prevalences were consistently lower, ranging from 0.6% to 1.9% (mean, adjusted for sample size: 1.1%) (17, 18, 20, 21, 25, 29, 41–45). In other non-European countries such as Israel and Turkey, equally low rates were observed (46–48). Relevance was established or considered 'probable' in 29–90% of the positive patch test reactions. In the USA, the 2% pet. test substance detected more cases of sensitization than the 1% patch test material, but direct comparisons in the same populations are lacking and the 1% preparation was used in one study only (39). Of the positive patch test reactions to quaternium-15 in 89 patients, 60 (67%) were considered relevant. The most frequently incriminated products were moisturizers ($n = 46$), hair preparations (non-colouring, $n = 19$), and makeup ($n = 4$). There were three cases of occupational contact dermatitis, caused by hair products and a barrier cream (49).

The IVDK has tested selected patients with quaternium-15, but it was not stated how they were selected; this did not result in higher frequencies of detection of sensitization (Table 12).

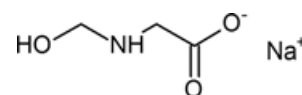
SODIUM HYDROXYMETHYLGLYCINATE (INCI)

CAS 70161-44-3

Synonyms: glycine, *N*-(hydroxymethyl)-, sodium salt (1:1); hydroxymethylaminoacetic acid, sodium salt; *N*-(hydroxymethyl)glycine, monosodium salt; sodium *N*-(hydroxymethyl)glycinate.

Molecular formula: C₃H₆NO₃.Na.

Chemical structure:



Applications

Preservative in cosmetics (maximum permitted in the EU: 0.5%). Non-cosmetic applications include as neutralizing agent for acids/acrylics polymers, in cleaning/washing agents, and in rinsing agents.

Frequency of sensitization

There appear to be no documented cases of sensitization to sodium hydroxymethylglycinate.

Table 9. Frequency of sensitization to imidazolidinyl urea in patients suspected of contact dermatitis^a

| Country | Years of study | Number of patients | Test concentration & vehicle | Positive (%) | | | Current relevance % | Comments | Ref. |
|-------------|----------------|--------------------|------------------------------|--------------|-------|-----|---------------------|--|------|
| | | | | All | Women | Men | | | |
| UK | 2004–2005 | 6958 | 2% pet. | 0.9 | 1.0 | 0.7 | NS | Multicentre study | (17) |
| USA | 2001–2005 | 3819 | 2% pet. | 2.8 | | | 74 | Mayo Clinic, three locations | (11) |
| USA | 2001–2005 | 3843 | 2% aq. | 2.1 | | | 76 | Mayo Clinic, three locations | (11) |
| USA | 2001–2002 | 4897 | 2% pet. | 3.0 | | | 26/66 ^b | Multicentre study, NACDG | (12) |
| USA | 2001–2002 | 4909 | 2% aq. | 1.8 | | | 30/61 ^b | Multicentre study, NACDG | (12) |
| USA | 2002–2004 | 5784 | 2% aq. | 1.3 | | | NS | Multicentre study, NACDG | (38) |
| USA | 2002–2004 | 5784 | 2% pet. | 2.5 | | | NS | Multicentre study, NACDG. | (38) |
| | | | | | | | | The test preparation was found to contain 3.1% imidazolidinyl urea | |
| Finland | 2000–2002 | 11 794 | 2% pet. | 0.8 | | | NS | Multicentre study | (25) |
| USA | 1998–2000 | 1321 | 2% pet. | 3.3 | | | NS | Mayo Clinic, three locations | (26) |
| USA | 1998–2000 | 1322 | 2% aq. | 1.7 | | | NS | Mayo Clinic, three locations | (26) |
| USA | 1998–2000 | 5821 | 2% pet. | 2.0 | | | 27/52 ^b | Multicentre study, NACDG | (13) |
| USA | 1998–2000 | 5784 | 2% aq. | 2.5 | | | 21/69 ^b | Multicentre study, NACDG | (13) |
| UK | 2000 | 3063 | 2% pet. | 0.5 | | | 90 | Relevance (90%) = current and past relevance in one centre (674 patients) only | (18) |
| Sweden | 2000 | 3790 | 2% pet. | 1.4 | | | NS | Multicentre study | (29) |
| USA | 1996–1998 | 4094 | 2% pet. | 3.2 | | | 92 ^c | Multicentre study, NACDG | (14) |
| USA | 1996–1998 | 4101 | 2% aq. | 2.5 | | | 86 ^c | Multicentre study, NACDG | (14) |
| USA | 1988–1997 | 927 | 2% pet. | 1.9 | | | NS | One centre, Boston | (39) |
| USA | 1994–1996 | 3080 | 2% pet. | 3.1 | | | 45/43 ^b | Multicentre study, NACDG | (15) |
| USA | 1994–1996 | 3101 | 2% aq. | 2.6 | | | 47/34 ^b | Multicentre study, NACDG | (15) |
| USA | 1992–1994 | 3482 | 2% pet. | 2.6 | | | 58 ^c | Multicentre study, NACDG | (16) |
| USA | 1992–1994 | 3523 | 2% aq. | 1.9 | | | 54 ^c | Multicentre study, NACDG | (16) |
| Austria | 1992–1993 | 11 516 | 2% pet. | 0.3 | 0.3 | 0.3 | NS | Multicentre study | (20) |
| Switzerland | 1989–1990 | 2295 | 2% pet. | 1.0 | | | NS | Multicentre study | (21) |

NACDG, North American Contact Dermatitis Group; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bDefinite or probable relevance (first number)/possible relevance (second number).

^cPercentage includes 'possible relevance'.

Table 10. Frequency of sensitization to imidazolidinyl urea in selected patients^a

| Country | Years of study | Number of patients tested | Test concentration & vehicle | Positive (%) | | | Current relevance % | Mode of selection | Ref. |
|-------------------|----------------|---------------------------|------------------------------|--------------|-------|-----|---------------------|---|------|
| | | | | All | Women | Men | | | |
| Finland | 1995–1996 | 1954 | 2% pet. | 1.1 | | | NS | Patients suspected of cosmetic dermatitis | (25) |
| IVDK ^b | 1992–1995 | 17 327 | 2% pet. | 0.6 | | | NS | NS. Selected from 35 062 patients | (6) |
| IVDK ^b | 1990–1994 | 11 452 | 2% pet. | 0.6 | | | NS | NS. Selected from 28 349 patients | (27) |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland (Information Network of Departments of Dermatology) www.ivdk.org; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bIt may be assumed that there is an overlap in the patient populations in these IVDK studies.

Frequency of Use of Formaldehyde-releasers in Cosmetics and Toiletries

USA

In the USA, imidazolidinyl urea was present in 13%, DMDM hydantoin in 5%, quaternium-15 in 3.7%, diazolidinyl urea in 3.6% and formaldehyde *per se* as a preservative in <1% of approximately 20 000 cosmetic formulae voluntarily registered by cosmetic companies in the FDA Voluntary Cosmetic Registration Database in 1996. Imidazolidinyl urea ranked 3rd in the top-10 of most

frequently used cosmetic preservatives after methyl- and propylparaben, DMDM 7th, quaternium-15 9th, and diazolidinyl urea 10th (50). In 2003, the most frequently used formaldehyde donor was –again –imidazolidinyl urea (present in 2038 products), followed by DMDM hydantoin (993 products), diazolidinyl urea (725 products), quaternium-15 (516 products), and 2-bromo-2-nitropropane-1,3-diol (168 products). Formaldehyde *per se* as a preservative was present in only 118 products. It was not stated what the total number of at the FDA registered cosmetic products was in 2003 (51).

The most recent data from the FDA Voluntary Cosmetic Registration Program Database are shown in Table 13 (1) (Anton de Groot 2009, data obtained from FDA). Approximately one in every five cosmetics will contain a formaldehyde-releaser; for the stay-on cosmetics, this is one in six, and in rinse-off products (where they are less likely to cause harm) one in four. The most frequent releaser is still imidazolidinyl urea (7%), followed by DMDM hydantoin (5.4%), diazolidinyl urea (4.5%), and quaternium-15 (1.4%). 5-Bromo-5-nitro-1,3-dioxane, 2-bromo-2-nitropropane-1,3-diol, formaldehyde *per se*, and (the more recently introduced) sodium methylhydroxyglycinate are present

in <1% of all products; benzylhemiformal is not used at all.

Another US database, the SKIN DEEP cosmetic safety database collected and published by the Environmental Working Group (www.cosmeticsdatabase.com), has the ingredients of 41 113 cosmetics and personal care products on file (2091 brands, 1338 companies, 8295 ingredients). As in the FDA data, benzylhemiformal is not used at all, and 5-bromo-5-nitro-1,3-dioxane (0.03%), 2-bromo-2-nitropropane-1,3-diol (0.3%), formaldehyde (0.1%), and sodium methylhydroxyglycinate (0.5%) are present in <1% of the products. In this database, which was filled from 2004 on, diazolidinyl urea was the most frequently present

Table 11. Frequency of sensitization to quaternium-15 in patients suspected of contact dermatitis^a

| Country | Years of study | Number of patients | Test concentration & vehicle | Positive (%) | | | Current relevance % | Comments/setting | Ref. |
|----------------|----------------|--------------------|------------------------------|--------------|-------|-----|---------------------|---|------|
| | | | | All | Women | Men | | | |
| Denmark | 1985–2005 | 14 993 | 1% pet. | 0.9 | 1.1 | 0.5 | NS | One centre, Copenhagen | (41) |
| United Kingdom | 2004–2005 | 6958 | 1% pet. | 1.9 | 2.2 | 1.1 | NS | Multicentre study | (17) |
| USA | 2001–2005 | 3841 | 1% pet. | 8.1 | | | 76 | Mayo Clinic, three locations | (11) |
| Israel | 1998–2004 | 2156 | 1% pet. | 0.8 | | | NS | One centre, Tel Aviv | (46) |
| Turkey | 1992–2004 | 1038 | 1% pet. | 0.8 | 1.2 | 0 | NS | One centre, Ankara | (47) |
| Europe | 2004 | 7454 | 1% pet. | 1.4 | | | NS | 31 departments, 11 countries, ESSCA | (42) |
| Europe | 2002–2003 | 5845 | 1% pet. | 1.2 | | | NS | 17 centres in nine countries, ESSCA | (43) |
| USA | 2001–2002 | 4910 | 2% pet. | 8.4 | | | 29/56 ^b | Multicentre study, NACDGM | (12) |
| Finland | 2000–2002 | 11 802 | 1% pet. | 0.8 | | | NS | Multicentre study | (25) |
| Czech Republic | 1997–2001 | 7642 | 1% pet. | 0.7 | 0.8 | 0.5 | NS | Multicentre study | (44) |
| United Kingdom | 2000 | 3063 | 1% pet. | 1.3 | | | 90 | Relevance (90%) = current and past relevance in one centre (674 patients) only- | (18) |
| Sweden | 2000 | 3790 | 1% pet. | 1.2 | | | NS | Multicentre study | (29) |
| Europe | 1996–2000 | 26 210 | 1% pet. | 1.3 | 1.5 | 1.0 | NS | 10 centres, seven countries, EECDRG | (45) |
| Israel | 1999–2000 | 943 | 1% pet. | 0.6 | 0.7 | 0.5 | NS | One centre, Petah Tiqwa | (48) |
| USA | 1998–2000 | 5832 | 2% pet. | 9.2 | | | 35/52 ^b | Multicentre study, NACDGM | (13) |
| USA | 1996–1998 | 3436 | 2% pet. | 9.0 | | | 89 ^c | Multicentre study, NACDGM | (14) |
| USA | 1988–1997 | 927 | 1% pet. | 7.1 | | | NS | One centre, Boston | (39) |
| USA | 1994–1996 | 3110 | 2% pet. | 9.2 | | | 58/27 ^b | Multicentre study, NACDGM | (15) |
| Finland | 1995–1996 | 9364 | 1% pet. | 1.1 | | | NS | Multicentre study | (25) |
| USA | 1992–1994 | 3500 | 2% pet. | 9.6 | | | 78 ^c | Multicentre study, NACDGM | (16) |
| Austria | 1992–1993 | 11 516 | 1% pet. | 0.6 | 0.7 | 0.5 | NS | Multicentre study | (20) |
| Switzerland | 1989–1990 | 2295 | 1% pet. | 1.0 | | | NS | Multicentre study | (21) |

EECDRG, European Environmental and Contact Dermatitis Research Group; ESSCA, European Surveillance System on Contact Allergies www.essca-dc.org; NACDGM, North American Contact Dermatitis Group; NS, not stated.

^aData provided back to 1990. For pre-1990 literature, see references (23, 24).

^bDefinite or probable relevance (first number)/possible relevance (second number).

^cPercentage includes 'possible relevance'.

Table 12. Frequency of sensitization to quaternium-15 in selected patients

| Country | Years of study | Number of patients tested | Test concentrations & vehicle. | Positive (%) | | | Current relevance % | Mode of selection | Ref. |
|-------------------|----------------|---------------------------|--------------------------------|--------------|-------|-----|---------------------|-----------------------------------|------|
| | | | | All | Women | Men | | | |
| IVDK ^a | 1992–1995 | 18 977 | 1% pet. | 0.5 | | | NS | NS. Selected from 35 062 patients | (6) |
| IVDK ^a | 1990–1994 | 11 017 | 1% pet. | 0.6 | | | NS | NS. Selected from 28 349 patients | (27) |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland (Information Network of Departments of Dermatology) www.ivdk.org; NS, not stated.

^aIt may be assumed that there is an overlap in the patient populations in these IVDK studies.

Table 13. Frequency of use of formaldehyde and releasers in 33 212 cosmetics and toiletries in the USA: FDA Voluntary Cosmetic Registration Database, 15 September 2008

| Preservative | Total number of products containing the preservative (% of total: $n = 33\ 212$) | Stay-on cosmetic (% of 25 077 stay-on cosmetics) | Rinse-off product (% of 835 rinse-off products) |
|---------------------------------|---|--|---|
| Benzylhemiformal | 0 | | |
| 5-Bromo-5-nitro-1,3-dioxane | 26 (0.1%) | 6 (0.02%) | 20 (0.2%) |
| 2-Bromo-2-nitropropane-1,3-diol | 174 (0.5%) | 144 (0.6%) | 30 (0.4%) |
| Diazolidinyl urea | 1496 (4.5%) | 1064 (4.2%) | 432 (5.3%) |
| DMDM hydantoin | 1780 (5.4%) | 754 (3.0%) | 1026 (12.6%) |
| Formaldehyde (solution) | 99 (0.3%) | 42 (0.2%) | 57 (0.7%) |
| Imidazolidinyl urea | 2333 (7.0%) | 1951 (7.8%) | 382 (4.7%) |
| Quaternium-15 | 473 (1.4%) | 249 (1.0%) | 224 (2.8%) |
| Sodium hydroxymethylglycinate | 82 (0.2%) | 31 (0.1%) | 51 (0.6%) |
| Total | 6463 (19.5%) | 4241 (16.9%) | 2222 (27.3%) |

formaldehyde-releaser (7.8%), followed by DMDM hydantoin (6.6%) and imidazolidinyl urea (3.9%). They are both used in stay-on and in rinse-off products. Quaternium-15 is present in 1.4% of the products, but in none of the 6614 moisturizers.

Europe

There is no European counterpart of the FDA programme and all our efforts to obtain information from the European Cosmetics Industry Association (COLIPA) have remained fruitless or even unanswered. Data on usage of formaldehyde and releasers in cosmetics sold in Europe, therefore, are scant and some possibly outdated. In 1992, 161 rinse-off products and 124 leave-on products produced in various European countries and the USA were investigated in Denmark for the presence of formaldehyde. Of them, 30% proved to contain (free and bound) formaldehyde. In eight products, free formaldehyde exceeded 500 p.p.m., but 7/8 were rinse-off products (52). In the same year, in Switzerland 34 cosmetic products were investigated for the presence of formaldehyde using three analytical methods including HPLC. Nineteen products (56%) were found to contain free formaldehyde (53). In 1998, 100 moisturizers sold in Sweden were analysed for the presence and amount of preservatives. Thirty-five products contained a formaldehyde-releaser: 23 imidazolidinyl urea, three diazolidinyl urea, three DMDM hydantoin, two 2-bromo-2-nitropropane-1,3-diol, and one quaternium-15. Ten products contained more than 200 p.p.m. formaldehyde (one product >500 p.p.m.), in nine of these a formaldehyde-releaser was present (four imidazolidinyl urea, four diazolidinyl urea, one quaternium-15). The concentrations of the releasers did not exceed the EEC permitted maximum in any case (54).

In 2000, Rastogi in Denmark analysed preservatives in 67 skin creams to verify the data on the product labels. Five (7%) contained 2-bromo-

2-nitropropane-1,3-diol, none 5-bromo-5-nitro-1,3-dioxane, and 34 (51%) contained formaldehyde, either from formaldehyde-releasers or from its presence *per se* (55). In 2005, data on the use of preservatives in various product categories were obtained for products registered in the Danish Product Register Database (PROBAS). The database has information on the ingredients of 1170 cosmetics and toiletries. 2-Bromo-2-nitropropane-1,3-diol was present in 36 products (3.1%), quaternium-15 in 13 (1.1%), diazolidinyl urea in 6 (0.5%), formaldehyde in 17 (1.5%), and imidazolidinyl urea in 184 (15.7%). DMDM hydantoin or other releasers were not registered in PROBAS (9).

Discussion

Frequency of sensitization

Benzylhemiformal and 5-bromo-5-nitro-1,3-dioxane do not appear to be important sensitizers. It should be appreciated, however, that these chemicals are not routinely tested and sensitization, therefore, may go undetected. For 5-bromo-5-nitro-1,3-dioxane, at this point it is unclear whether the chemical is actually—as suggested in literature—a formaldehyde-releaser. Quaternium-15 is the only formaldehyde-releaser that is included in the baseline series in the USA and in Europe and thus routinely tested in patients suspected of contact dermatitis. The major differences in the frequencies of sensitization to this preservative in the USA (7.1–9.6%; mean, adjusted for sample size: 8.8) and European studies (0.6–1.9%; mean, adjusted for sample size: 1.1) (Table 11) are remarkable. As Table 14 shows, this is also the case for the other releasers for which adequate data are available. On the lower end of the frequency range, the scores are five times higher in the USA, the means (adjusted for sample size) approximately three to four times and at the higher end, the scores are some 2.5 times higher in the USA than in Europe. What could be the cause of these differences?

Table 14. Frequency of sensitization of formaldehyde-releasers in the USA and Europe

| Chemical | Frequency of sensitization | | References |
|---------------------------------|--------------------------------------|---|------------|
| | USA (mean, adjusted for sample size) | Europe (mean, adjusted for sample size) | |
| 2-Bromo-2-nitropropane-1,3-diol | 2.1–3.3% (2.8) | 0.4–1.2% (0.9%) | Table 3 |
| Diazolidinyl urea | 2.4–3.7% (3.1) | 0.5–1.4% (1.0%) | Table 5 |
| DMDM hydantoin | 0.5–3.4% (2.0) | No adequate data | Table 7 |
| Imidazolidinyl urea | 1.3–3.3% (2.7) | 0.3–1.4% (0.7%) | Table 8 |
| Quaternium-15 | 7.1–9.6% (8.8) | 0.6–1.9% (1.1%) | Table 10 |

Table 15. Parameters that may influence frequencies of sensitization

| |
|---|
| Technical |
| Patch test systems (materials, e.g. Finn Chambers®) |
| Suppliers, test concentrations, test vehicles for allergens |
| Exposure time to the test allergen (1D or 2D) |
| Reading and interpretation of the reaction. Interpretation of weak positive reactions, recognition of irritant reactions |
| Mode of ascertaining relevance |
| Sometimes read after 2D only |
| Sometimes angry back syndrome not taken into account |
| In older publications probably more often irritant reactions |
| Technical problems with patch test materials: wrong concentrations (38, 56, 57) |
| Epidemiological |
| Referral pattern (secondary or tertiary centre, special interests) |
| Population characteristics: sex, age, occupation, etc. (MOHLFA) |
| Mode of selection for testing with the standard series |
| Mode of selection for testing with other series |
| Exposure of the population to allergens (regional, national, international), including local prescribing habits (e.g. Eucerin with bronopol) (10) |
| Miscellaneous |
| Different periods of investigation (in which trends may have changed) |
| Natural variations in reactions (test not absolutely reliable, discordant results with double or successive testing) |
| Multicentre or monocentre study |

Many parameters influence the frequencies of sensitization in patch test studies (Table 15). As a consequence, there are many possible explanations for the differences between the USA and Europe, including a different test protocol in the USA or larger exposure of the US population to the releasers in cosmetics and other sources. The technical part of the US test protocol does not differ substantially from that in Europe with one exception: quaternium-15 was usually tested at 2% in pet in the USA versus 1% in Europe (comparative studies are not available). However, the NACDG and the Mayo Clinic, from which most USA data originate, are tertiary referral centres, and thus it may be assumed that their population has undergone stricter selection, resulting in an increased likelihood of finding contact allergies therein. To study this possibility, we have compared the reported frequencies of sensitization to the 20 allergens that are routinely tested in both the USA and in Europe (de Groot AC, Coenraads PJ, Maibach HI, unpublished data). In 17 of the 20 allergens, frequencies of sensitization were higher in the USA. The highest scores were for

quaternium-15 (mean 7.1 times more frequent in the USA), neomycin (4.1), and formaldehyde (4.0). The high frequency of neomycin can readily be explained: this topical antibiotic is –contrary to the situation in Europe –widely used there (also by doctors) and can be obtained over-the-counter. In the USA, the mean frequency of sensitization of all 20 allergens together is about two times higher than in Europe. If we leave formaldehyde and quaternium-15 out (as we investigate these) and also neomycin (because we have a plausible explanation for its higher frequency), the mean frequency of sensitization to the other 17 allergens as a group is 1.4 times higher in the USA. Thus, we tentatively assume that frequencies of sensitization in the USA are on average 1.4 times higher than in Europe attributable to protocol differences including interpretation and selection of patients to be patch tested. This only partly explains the differences in sensitization frequency to 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea, imidazolidinyl urea, and quaternium-15 between the USA and Europe. The second possible explanation would be a higher exposure of the US population to formaldehyde-releasers. None of them are known important occupational sensitizers, and therefore the most important exposure should come from cosmetics, notably the stay-on products. The FDA data (Table 13) show that 2-bromo-2-nitropropane-1,3-diol and quaternium-15 are present in not more than 1% of the stay-on products on file. Although no such data are available for Europe, it seems very unlikely that the presence of quaternium-15 in 1% of all stay-on products (and in the SKIN DEEP cosmetic safety database collected and published by the Environmental Working Group in none of 6614 moisturizers) could result in a 7–9% frequency of sensitization in the USA in patients suspected of contact dermatitis. More leave-on products contain diazolidinyl urea (4.2%), DMDM hydantoin (3%), or imidazolidinyl urea (7.8%), but –again –comparison with Europe cannot be made because of lack of European data. In addition, we know nothing about the concentrations of the formaldehyde-releasers used in the USA. Although there are strict limitations in Europe (Table 1), there are no such limits to the concentrations in the USA. In addition, people in the USA might be heavier users of

cosmetics than individuals in the European population. A third possible explanation for the higher frequencies in the USA may be found in the relation between formaldehyde-releasers and formaldehyde contact allergy. In Table 16 (which will be discussed in detail in *part 2*), it is shown what percentage of patients allergic to formaldehyde did also react to the various formaldehyde-releasers in relevant studies. Adjusted for sample size, the percentage is 6% for 2-bromo-2-nitropropane-1,3-diol, 21% for diazolidinyl urea, 19% for DMDM hydantoin, 14% for imidazolidinyl urea, and 40% for quaternium-15. The mean frequencies of sensitization to formaldehyde, adjusted for sample size, are 8.7% in the USA and 2.2% in Europe [calculated from Table 5 in part I of this study (1)]. After correction for stricter selection ($1:1.4 = 0.71$), the mean frequency of formaldehyde sensitization in the USA is $0.71 \times 8.7\% = 6.2\%$. The difference with Europe then is $6.2 - 2.2\% = 4\%$. As 6% of patients allergic react to 2-bromo-2-nitropropane-1,3-diol, 6% of this $4\% = 0.24\%$ of the frequency of sensitization to 2-bromo-2-nitropropane-1,3-diol can be attributed to the higher frequency of sensitization to formaldehyde in the USA (Table 17). For diazolidinyl urea, this is $21\% \times 4\%$ (0.84%), for DMDM hydantoin $19\% \times 4\%$ (0.76%), for imidazolidinyl urea $14\% \times 4\%$ (0.56%), and for quaternium-15, which reacts in 40% of patients allergic to formaldehyde, $40\% \times 4\% = 1.6\%$. After these adjustments, the differences between the USA and Europe are far smaller for all releasers except

one (Table 17). Quaternium-15 in the USA would still yield 4.65% positive reactions under European conditions (i.e. after correction for selection and the higher frequency of formaldehyde allergy) versus 1.1% in Europe. Whether this is due to more frequent use in cosmetics or in other products is caused by higher concentrations in such products or can be explained by the generally higher patch test concentration in the USA (2% versus 1% in Europe) is unknown. We suggest that prospective studies be initiated where the routine series is supplemented with quaternium-15 2% in pet. In addition, the US cosmetics industry should be approached for information on use concentrations of quaternium-15 and the presence of quaternium-15 in non-cosmetic products should be investigated.

An interesting finding has been that for diazolidinyl urea, DMDM hydantoin, and imidazolidinyl urea, test substances in petrolatum yielded more positive reactions than the test allergens in aqueous solutions. This is unexpected, at least for cases caused by formaldehyde sensitivity. It may be assumed –as formaldehyde is released by hydrolysis, for which water is needed –that the amount of free formaldehyde in patch test substances with petrolatum as vehicle is very low or it is even absent. However, perspiration water under the test materials will probably release formaldehyde from the petrolatum test substance and also in the skin itself the substance may be metabolized leading to formaldehyde release (6).

Table 16. Percentages positive to formaldehyde-releasers in patients allergic to formaldehyde^a

| Country and period of study | Number of patients allergic to formaldehyde | Percentage of patients allergic to formaldehyde with positive reactions to: | | | | | Ref. |
|-----------------------------|---|---|-------------------|----------------|---------------------|---------------|------|
| | | 2-Bromo-2-nitropropane-1,3-diol | Diazolidinyl urea | DMDM hydantoin | Imidazolidinyl urea | Quaternium-15 | |
| UK 2004–2005 | 142 | 10 | 30 | | 23 | 52 | (58) |
| USA 1992–2004 | 2225 | | 24.5 | 19 | 17 | | (56) |
| UK 1982–1993 | 629 | 4 | 4 | | 6 | 47 | (59) |
| Austria 1992–1993 | 105 | 1 | | | 4 | 18 | (20) |
| USA 1982–1989 | 454 | 10 | | | 10 | 31 | (24) |
| USA <1980 | 30 | | | | | 30 | (60) |

Data on <20 patients are presented in references (10, 61).

^aOnly studies with at least 20 positive reactions to formaldehyde are included.

Table 17. Comparison between frequency of sensitization to formaldehyde-releasers in USA and Europe after adjusting for selection and higher frequency of sensitization to formaldehyde in the USA

| | Mean frequency of sensitization in the USA (%) | After correction for selection | Correction for higher prevalence of formaldehyde allergy | After correction | Mean frequency of sensitization in Europe (%) |
|---------------------------------|--|--------------------------------|--|------------------------|---|
| 2-Bromo-2-nitropropane-1,3-diol | 2.8 | $0.71 \times 2.8 = 1.99$ | $6\% \times 4\% = 0.24\%$ | $1.99 - 0.24 = 1.75\%$ | 0.9 |
| Diazolidinyl urea | 3.1 | $0.71 \times 3.1 = 2.20$ | $21\% \times 4\% = 0.84\%$ | $2.20 - 0.84 = 1.36\%$ | 1.0 |
| DMDM hydantoin | 2.0 | $0.71 \times 2.0 = 1.42$ | $19\% \times 4\% = 0.76\%$ | $1.42 - 0.76 = 0.66\%$ | No data available |
| Imidazolidinyl urea | 2.7 | $0.71 \times 2.7 = 1.92$ | $14\% \times 4\% = 0.56\%$ | $1.92 - 0.56 = 1.36\%$ | 0.7 |
| Quaternium-15 | 8.8 | $0.71 \times 8.8 = 6.25$ | $40\% \times 4\% = 1.6\%$ | $6.25 - 1.6 = 4.65\%$ | 1.1 |

Relevance

Determining the relevance of positive patch test reactions is considered one of the most difficult, if not *the* most difficult, aspect of patch testing (62). This is illustrated by the fact that of the 33 studies cited, only eight (24%) have provided data on relevance. Five of these eight were the continuing 2-year period studies of the NACDG (12–16). These investigators divide present relevance into ‘definite’, ‘probable’, and ‘possible’. Possible relevance is considered if the patient was exposed to circumstances in which skin contact with materials known to contain the putative allergen would likely occur and the rash distribution and clinical situation fit. This may result, as indicated by the NACDG itself, in an overestimation of present relevance (13). It should also be noted that the highly selected patient population that the NACDG patch tests is often sent back to the referring dermatologists for follow-up. This could –again according to the NACDG –result in an overestimation of the true possible relevance of a particular test allergen. In the eight studies with relevance figures, very different data on relevance considered ‘established’ or ‘probable’ have been reported: 2-bromo-2-nitropropane-1,3-diol 7–80%, diazolidinyl urea 24–75%, DMDM hydantoin 15–86%, imidazolidinyl urea 21–90%, and quaternium-15 29–90%. Unfortunately, in not one of these papers was it stated what the causative products containing the allergens were (with the exception of reference (22), they were not designed for providing this information). There is an urgent need for more detailed description of relevance assessments for these allergens including denomination of the causative products; this would greatly enhance both the reliability and the practical value of published reports (this statement is valid for all other allergens). Most cases of allergy to quaternium-15 seem to be related to cosmetic products (49) and this will probably be the case for the other releasers as well.

Frequency of use

From the FDA data in Table 13, it appears that approximately 20% of cosmetics and personal care products in the USA contain a formaldehyde-releaser (1/6 for stay-on cosmetics, 1/4 for rinse-off products). No such data are available for Europe; several older, sometimes selective studies from Scandinavia (9, 52–55) suggest that the picture in Europe may be similar. In the USA, the use of quaternium-15 is decreasing (1996: 3.7%; 2008: 1.4%) and this also holds true for imidazolidinyl urea (1996: 13%; 2008: 7%), though it is still the most widely used of the formaldehyde-releasers. DMDM hydantoin usage is stable and

is incorporated far more often in rinse-off products (12.6%) than in stay-on cosmetics (3.0%). There is a –slight –increase in the usage of diazolidinyl urea: 3.6% in 1996, 4.5% in 2008. The other releasers (benzylhemiformal, 5-bromo-5-nitro-1,3-dioxane, 2-bromo-2-nitropropane-1,3-diol, formaldehyde, sodium hydroxymethylglycinate) are used rarely or not at all (benzylhemiformal).

References

1. de Groot A C, Flyvholm M-A, Lensen G J, Menné T, Coenraads P J. Formaldehyde-releasers: relationship to formaldehyde contact allergy. Contact allergy to formaldehyde and inventory of formaldehyde-releasers. *Contact Dermatitis* 2009; 61: 63–85.
2. Flyvholm M-A, Andersen P. Identification of formaldehyde releasers and occurrence of formaldehyde and formaldehyde releasers in registered chemical products. *Am J Ind Med* 1993; 24: 533–552.
3. Geier J, Lessmann H, Becker D et al. Patch testing with components of water-based metalworking fluids: results of a multicentre study with a second series. *Contact Dermatitis* 2006; 55: 322–329.
4. 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: 118–130.
5. Geier J, Lessmann H, Schnuch A, Uter W. Contact sensitizations in metalworkers with occupational dermatitis exposed to water-based metalworking fluids: results of the research project “FaSt”. *Int Arch Occup Environ Health* 2004; 77: 543–551.
6. Geier J, Lessmann H, Schuch A, Fuchs Th. Kontaktallergien durch formaldehydabspaltende Biozide. *Allergologie* 1997; 20: 215–224.
7. Geier J, Kleinhans D, Peters K-P. Kontaktallergien durch industriell verwendete Biozide. Ergebnisse des Informationsverbunds Dermatologischer Kliniken (IVDK) und der Deutschen Kontaktallergiegruppe. *Dermatosen* 1996; 44: 154–159.
8. Goossens A, Claes L, Drieghe J, Put E. Antimicrobials, preservatives, antiseptics and disinfectants. *Contact Dermatitis* 1998; 39: 133–134.
9. Flyvholm M-A. Preservatives in registered chemical products. *Contact Dermatitis* 2005; 53: 27–32.
10. Storrs F J, Bell D E. Allergic contact dermatitis to 2-bromo-2-nitropropane-1,3-diol in a hydrophilic ointment. *J Am Acad Dermatol* 1983; 8: 157–170.
11. Davis M D, Scalf L A, Yiannias J A et al. Changing trends and allergens in the patch test standard series. A Mayo Clinic 5-year retrospective review, January 1, 2001, through December 31, 2005. *Arch Dermatol* 2008; 144: 67–72.
12. Pratt M D, Belsito D V, DeLeo V A et al. North American Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 2004; 15: 176–183.
13. Marks J G Jr, Belsito D V, DeLeo V A et al. North American Contact Dermatitis Group patch-test results, 1998–2000. *Am J Contact Dermat* 2003; 14: 59–68.
14. Marks J G Jr, Belsito D V, DeLeo V A et al. North American Contact Dermatitis Group patch test results, 1996–1998. *Arch Dermatol* 2000; 136: 272–273.
15. Marks J G Jr, Belsito D V, DeLeo V A 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: 911–918.
16. Marks J G, Belsito D V, DeLeo V A et al. North American Contact Dermatitis Group standard tray patch test results 1992 through 1994. *Am J Contact Dermat* 1995; 6: 160–165.

17. Jong C T, Statham B N, Green C M et al. Contact sensitivity to preservatives in the UK 2004–2005: results of a multicentre study. *Contact Dermatitis* 2007; 57: 165–168.
18. Britton J E, Wilkinson S M, English J S C et al. The British standard series of contact dermatitis allergens: validation in clinical practice and value for clinical governance. *Br J Dermatol* 2003; 148: 259–264.
19. Brinkmeier T, Geier J, Lepoittevin J-P, Frosch P J. Patch test reactions to Biobans in metalworkers are often weak and not reproducible. *Contact Dermatitis* 2002; 47: 27–31.
20. Kränke B, Szolar-Platzer C, Aberer W. Reactions to formaldehyde and formaldehyde releasers in a standard series. *Contact Dermatitis* 1996; 35: 192–193.
21. Perrenoud D, Bircher A, Hunziker T et al. Frequency of sensitization to 13 common preservatives in Switzerland. *Contact Dermatitis* 1994; 30: 276–279.
22. Frosch P J, White I R, Rycroft R J G et al. Contact allergy to bronopol. *Contact Dermatitis* 1990; 22: 24–26.
23. Fransway A F. The problem of preservation in the 1990s: I. Statement of the problem. Solution(s) of the industry, and the current use of formaldehyde and formaldehyde-releasing biocides. *Am J Contact Dermat* 1991; 2: 6–23.
24. Fransway A F, Schmitz N A. The problem of preservation in the 1990s: II. Formaldehyde and formaldehyde-releasing biocides: incidences of cross-reactivity and the significance of the positive response to formaldehyde. *Am J Contact Dermat* 1991; 2: 78–88.
25. 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: 40–45.
26. Wetter D A, Davis M D P, Yiannias J A et al. Patch test results from the Mayo Contact Dermatitis Group, 1998–2000. *J Am Acad Dermatol* 2005; 53: 416–421.
27. Schnuch A, Geier J, Uter W, Frosch P J. Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. *Br J Dermatol* 1998; 138: 467–476.
28. Lehmann S V, Hoeck U, Breinholdt J, Olsen C E, Kreilgaard B. Characterization and chemistry of imidazolidinyl urea and diazolidinyl urea. *Contact Dermatitis* 2006; 54: 50–58.
29. Lindberg M, Edman B, Fischer T, Stenberg B. Time trends in Swedish patch test data from 1992 to 2000. A multi-centre study based on age- and sex-adjusted results of the Swedish standard series. *Contact Dermatitis* 2007; 56: 205–210.
30. Perrett C M, Happle R. Contact sensitivity to diazolidinyl urea (Germall II). *Arch Dermatol Res* 1989; 281: 57–59.
31. Stephens T J, Drake K D, Drotman R B. Experimental delayed contact sensitization to diazolidinyl urea (Germall II) in guinea pigs. *Contact Dermatitis* 1987; 16: 164–168.
32. Jordan W P. Human studies that determine the sensitizing potential of haptens. Experimental allergic contact dermatitis. *Dermatol Clin* 1984; 2: 533–538.
33. de Groot A C, van Joost T, Bos J D, Van der Meeren H L M, Weyland J W. Patch test reactivity to DMDM hydantoin. Relationship to formaldehyde. *Contact Dermatitis* 1988; 18: 197–201.
34. Shaffer M P, Belsito D V. Allergic contact dermatitis from glutaraldehyde in health care workers. *Contact Dermatitis* 2000; 43: 150–156.
35. de Groot A C, Bos J D, Jagtman B A, Bruynzeel D P, van Joost Th, Weyland J W. Contact allergy to preservatives –II. *Contact Dermatitis* 1986; 15: 218–222.
36. Uter W, Frosch P J. Contact allergy from DMDM hydantoin, 1994–2000. *Contact Dermatitis* 2002; 47: 57–58.
37. Johansen M, Bundgaard H. Kinetics of formaldehyde release from the cosmetic preservative Germall 115. *Arch Pharm Chemi Sci Ed* 1981; 9: 117–122.
38. Rietschel R L, Bruze M, Gruvberger B et al. The relationship of vehicle and concentration of imidazolidinylurea, with attention to formaldehyde status. *Dermatitis* 2006; 17: 48–49.
39. Albert M R, Chang Y, Gonz ález E. Concomitant positive patch test reactions to allergens in a patch testing standard series from 1988–1997. *Am J Contact Dermat* 1999; 10: 219–223.
40. Fransway A F. Quaternium-15. In: *Practical Contact Dermatitis*, Guin JD (ed.): New York, McGraw-Hill, 1995: pp. 223–232.
41. Carlsen B C, Menné T, Johansen J D. 20 years of standard patch testing in an eczema population with focus on patients with multiple contact allergies. *Contact Dermatitis* 2007; 57: 76–83.
42. Uter W, on behalf of the 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: 174–181.
43. Uter W, Hegewald J, Aberer W et al. The European standard series in 9 European countries, 2002/2003 –First results of the European Surveillance System on Contact Allergies. *Contact Dermatitis* 2005; 53: 136–145.
44. Machovcova A, Dastychova E, Kostalova D et al. Common contact sensitizers in the Czech Republic. Patch test results in 12,058 patients with suspected contact dermatitis. *Contact Dermatitis* 2005; 53: 162–166.
45. Bruynzeel D P, Diepgen T L, Andersen K E et al (EECDRG). Monitoring the European Standard Series in 10 centres 1996–2000. *Contact Dermatitis* 2005; 53: 146–152.
46. Lazarov A. European Standard Series patch test results from a contact dermatitis clinic in Israel during the 7-year period from 1998 to 2004. *Contact Dermatitis* 2006; 55: 73–76.
47. Akyol A, Boyvat A, Peksari Y, Gürgey E. Contact sensitivity to standard series allergens in 1038 patients with contact dermatitis in Turkey. *Contact Dermatitis* 2005; 52: 333–337.
48. Freireich-Astman M, David M, Trattner A. Standard patch test results in patients with contact dermatitis in Israel: age and sex differences. *Contact Dermatitis* 2007; 56: 103–107.
49. Parker L U, Taylor J S. A 5-year study of contact allergy to quaternium-15. *Am J Contact Dermat* 1991; 2: 231–234.
50. Steinberg D. Frequency of use of preservatives in the United States. Paper given at Preservatech, Paris, 1996: Available at: www.creative-developments.co.uk/papers/Preservatives%201999.htm (last accessed 29 January 2009).
51. Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther* 2004; 17: 251–263.
52. Rastogi S C. A survey of formaldehyde in shampoos and skin creams on the Danish market. *Contact Dermatitis* 1992; 27: 235–240.
53. Gryllaki-Berger M, Mugny Ch, Perrenoud D, Pannatier A, Frenk E. A comparative study of formaldehyde detection using chromotropic acid, acetylacetone and HPLC in cosmetics and household products. *Contact Dermatitis* 1992; 26: 149–154.
54. Gruvberger B, Bruze M, Tammela M. Preservatives in moisturizers on the Swedish market. *Acta Derm Venereol* 1998; 78: 52–56.
55. Rastogi S C. Analytical control of preservative labelling on skin creams. *Contact Dermatitis* 2000; 43: 339–343.
56. Rietschel R L, Warshaw E M, Sasseville D et al. Sensitivity of petrolatum and aqueous vehicles for detecting allergy to imidazolidinylurea, diazolidinylurea, and DMDM hydantoin: A retrospective analysis from the North American Contact Dermatitis Group. *Dermatitis* 2007; 18: 155–162.
57. Aberer W, Reiter E, Gailhofer G. Pitfalls in patch testing: problems with rather than from Kathon CG. *Contact Dermatitis* 1993; 23: 380–381.
58. Statham B N, Bodger O. Cross reactivity of isothiazolinone and formaldehyde releasing preservatives. Presented at the Annual Scientific Meeting of the British Contact Dermatitis Society, July 2006, Birmingham.

59. Jacobs M-C, White I R, Rycroft R J G, Taub N. Patch testing with preservatives at St John's from 1982 to 1993. *Contact Dermatitis* 1995; 33: 247–254.
60. Fisher A A. Cosmetic dermatitis. Part II. Reactions to some commonly used preservatives. *Cutis* 1980; 26: 136.
61. Herbert C, Rietschel R L. Formaldehyde and formaldehyde releasers: how much avoidance of cross-reacting agents is required? *Contact Dermatitis* 2004; 50: 371–373.
62. Devos S A, van der Valk P G. Epicutaneous patch testing. *Eur J Dermatol* 2002; 12: 506–513.

Address:
Anton de Groot
Department of Dermatology
University Medical Center Groningen
University of Groningen
PO Box 30.001
9700 RB Groningen
The Netherlands
Tel: +31(0)521320332
e-mail: antondegroot@planet.nl