Formaldehyde-releasers: relationship to formaldehyde contact allergy. Contact allergy to formaldehyde and inventory of formaldehyde-releasers

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This is one of series of review articles on formaldehyde and formaldehyde-releasers (others: formaldehyde in cosmetics, in clothes and in metalworking fluids and miscellaneous). Thirty-five chemicals were identified as being formaldehyde-releasers. Although a further seven are listed in the literature as formaldehyde-releasers, data are inadequate to consider them as such beyond doubt. Several (nomenclature) mistakes and outdated information are discussed. Formaldehyde and formaldehyde allergy are reviewed: applications, exposure scenarios, legislation, patch testing problems, frequency of sensitization, relevance of positive patch test reactions, clinical pattern of allergic contact dermatitis from formaldehyde, prognosis, threshold for elicitation of allergic contact dermatitis, analytical tests to determine formaldehyde in products and frequency of exposure to formaldehyde and releasers. The frequency of contact allergy to formaldehyde is consistently higher in the USA (8–9%) than in Europe (2–3%). Patch testing with formaldehyde is problematic; the currently used 1% solution may result in both false-positive and false-negative (up to 40%) reactions. Determining the relevance of patch test reactions is often challenging. What concentration of formaldehyde is safe for sensitive patients remains unknown. Levels of 200–300 p.p.m. free formaldehyde in cosmetic products have been shown to induce dermatitis from short-term use on normal skin.

Key words: contact allergy; formaldehyde; formaldehyde releaser; patch testing; review article; threshold. © John Wiley & Sons A/S, 2009.

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Formaldehyde is a common cause of contact allergy. In Europe, 2–3% of patients suspected of contact dermatitis have positive patch test reactions, and in the USA prevalence rates of sensitization of 8–9% are reported in this selected group of patients. Allergic contact dermatitis caused by formaldehyde is often chronic, presumably because it is difficult to avoid exposure to the allergen completely. Indeed, formaldehyde may be found in many cosmetics, toiletries, household products such as washing and cleaning agents and in a great number of industrial applications including adhesives, paints, lacquers and metalworking fluids. Often, the products are not preserved with formaldehyde itself, but with agents that release formaldehyde under usage conditions, the so-called formaldehyde-releasers (or formaldehyde donors). Well-known examples are quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin and 2-bromo-2-nitropropane-1,3-diol, preservatives frequently used in cosmetic products. Industrial products such as metalworking fluids frequently contain formaldehyde donors, such as the Bioban® product range of biocides and tris(N-hydroxyethyl) hexahydrotriazine (better known by its trade name Grotan® BK). Other products containing and releasing formaldehyde are the formaldehyde resins including urea formaldehyde and melamine formaldehyde resins. These were formerly used extensively as textile...
finishes and caused dermatitis from clothing in formaldehyde-sensitive individuals due to their high content of free formaldehyde. The finishes used currently by the clothing manufacturers release far less free formaldehyde, but are even today reported as causes of clothing allergic contact dermatitis.

Lists of formaldehyde-releasers have been published in articles and recent textbooks (1–8). Such lists are commonly handed out to patients allergic to formaldehyde with the instruction to avoid contact with these chemicals and products containing them. However, for most formaldehyde-releasers, the current understanding of their relationship to formaldehyde allergy appears to be limited and mainly based on patch test studies. Thus, it is often assumed that concomitant positive patch test reactions to formaldehyde and a releaser or to two or more releasers are caused by allergy to formaldehyde, though definite proof of this is often lacking (9–11). Whether it is really necessary to avoid all formaldehyde-releasing preservatives in patients allergic to formaldehyde is largely unknown. Indeed, only with a few compounds such as diazolidinyl urea (12) and imidazolidinyl urea (13), have experimental use test exposure studies have been performed in patients allergic to formaldehyde. Some authors have suggested that for formaldehyde-sensitive patients, it is sufficient to avoid only those formaldehyde-releasers that, in addition to formaldehyde, also elicited a positive patch test reaction (14). Others, however, think that it is prudent for formaldehyde-sensitive subjects to avoid only those formaldehyde-releasing preservatives in addition to formaldehyde (15–17).

The purpose of this study is to review the literature on the formaldehyde-releasers and their relationship to formaldehyde sensitivity with emphasis on (i) frequency of sensitization, (ii) patch test reactions to formaldehyde and a releaser or to two or more releasers, and (iii) the content of free formaldehyde. The finishes used currently by the clothing manufacturers release far less free formaldehyde, but are even today reported as causes of clothing allergic contact dermatitis.
<table>
<thead>
<tr>
<th>Commonly used name</th>
<th>IUPAC name</th>
<th>Other synonyms</th>
<th>Current trade names&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CAS number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylhemiformal (INCI)</td>
<td>Phenylmethoxymethanol</td>
<td>(Benzoxyl)methanol</td>
<td>Akyosept®B [Preventol® D2; See there]</td>
<td>14548-60-8</td>
</tr>
<tr>
<td>Bioban CS 1135&lt;sup&gt;®&lt;/sup&gt;</td>
<td>4,4-Dimethyloxazolidine; 3,4,4-trimethyloxazolidine</td>
<td>Bioban CS 1135&lt;sup&gt;®&lt;/sup&gt;</td>
<td>81099-36-7 (ingred. 75673-43-7 and 51200-87-4)</td>
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<tr>
<td>Bioban CS 1246&lt;sup&gt;®&lt;/sup&gt;</td>
<td>5-Ethyl-3,7-dioxo-1-azabicyclo[3.3.0] octane</td>
<td>7-Ethylbicyclo-oxazolidine</td>
<td>Bioban CS-1246&lt;sup&gt;®&lt;/sup&gt;; Chemtan A60&lt;sup&gt;®&lt;/sup&gt;; Oxazolidine-E&lt;sup&gt;®&lt;/sup&gt;; Zoldine ZE&lt;sup&gt;®&lt;/sup&gt;;</td>
<td>7747-35-5</td>
</tr>
<tr>
<td>Bioban P-1487&lt;sup&gt;®&lt;/sup&gt;</td>
<td>4-[2-([Morpholin-4-ylmethyl]-2-nitrobutyl]morpholine; 4-(2-nitrobutyl) morpholine</td>
<td>Mixtue of nitrobutylmorpoline and ethylnitrtrimethyleneedimorpholine</td>
<td>Bioban P-1487&lt;sup&gt;®&lt;/sup&gt;</td>
<td>37304-88-4 (ingred. 1854-23-5 and 2224-44-4)</td>
</tr>
<tr>
<td>2-Bromo-2-nitropropane -1,3-diol (INCI)</td>
<td>As in column 1</td>
<td>Bromonitropropanediol; Bronopol</td>
<td>Bronopol&lt;sup&gt;®&lt;/sup&gt;; Chemynol BP&lt;sup&gt;®&lt;/sup&gt;; Myacide Pharma BP&lt;sup&gt;®&lt;/sup&gt;; Onyoxide 500&lt;sup&gt;®&lt;/sup&gt;</td>
<td>52-51-7</td>
</tr>
<tr>
<td>Diazolidinyl urea (INCI)</td>
<td>1-[1,3-bis(hydroxymethyl)-2, 5-dioxo-imidazolidin-4-y1]-1,3-bis(hydroxymethyl) urea</td>
<td>N,N'-bis(hydroxymethyl) urea</td>
<td>Abiol Forte&lt;sup&gt;®&lt;/sup&gt;; Germall II&lt;sup&gt;®&lt;/sup&gt;; Liposerve DU&lt;sup&gt;®&lt;/sup&gt;; Nipa Biopure&lt;sup&gt;®&lt;/sup&gt;</td>
<td>78491-02-8</td>
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<tr>
<td>Dihydroxydimethylolethyleneurea, methylated</td>
<td>4,5-Dihydroxy-1,3-bis(hydroxymethyl)-imidazolidin-2-one, methylated</td>
<td>Dimethylolglyoxalurea, methylated</td>
<td>Fixapret&lt;sup&gt;®&lt;/sup&gt; (various); Freerex PKF&lt;sup&gt;®&lt;/sup&gt;; Knittex LE&lt;sup&gt;®&lt;/sup&gt;; Pemafresh&lt;sup&gt;®&lt;/sup&gt; (various); Sumitex&lt;sup&gt;®&lt;/sup&gt; (various)</td>
<td>68411-81-4</td>
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<tr>
<td>1,3-Dimethyl-4,5-dihydroxyethyleneurea</td>
<td>4,5-Dihydroxy-1,3-dimethylimidazolidin-2-one</td>
<td>Fixapret NF&lt;sup&gt;®&lt;/sup&gt;</td>
<td>3923-79-3</td>
<td></td>
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<td>Dimethylhydantoin formaldehyde resin</td>
<td>5,5-Dimethylimidazolidine-2, 4-dione, formaldehyde</td>
<td>Formaldehyde, polymer with 5,5-dimethyl-2,4-imidazolidinedione; DMHF</td>
<td>26811-08-5</td>
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<td>Dimethylolhydroxyethyleneurea</td>
<td>4,5-Dihydroxy-1,3-bis(hydroxymethyl)-imidazolidin-2-one</td>
<td>1,3-Bis(hydroxymethyl)-4,5-dihydroxy-2-imidazolidinone</td>
<td>Fixapret&lt;sup&gt;®&lt;/sup&gt; (various); Pemafresh&lt;sup&gt;®&lt;/sup&gt; (various)</td>
<td>1854-26-8</td>
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<tr>
<td>Dimethylolethyleneurea</td>
<td>1,3-Bis(hydroxymethyl) imidazolidin-2-one</td>
<td>Fixapret AH&lt;sup&gt;®&lt;/sup&gt;</td>
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<td>Other synonyms</td>
<td>Current trade names (^b)</td>
<td>CAS number</td>
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<tr>
<td>Dimethylolpropyleneurea</td>
<td>1,3-Bis(hydroxymethyl) -1,3-diazinan-2-one</td>
<td>DMPU; Tetrahydro-1,3-bis(hydroxymethyl)-1H-pyrimidin-2-one</td>
<td>Fixapret PH(^\circ); Knitex PRS(^\circ)</td>
<td>3270-74-4</td>
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<tr>
<td>Dimethylol urea (INCI)</td>
<td>1,3-Bis(hydroxymethyl) urea</td>
<td>N,N'-Bis(hydroxymethyl)urea; Carbamol; Dihydroxymethylurea; N,N'-dimethylurea; Dimethylurea; Oxyurea (MI); Urea formaldehyde</td>
<td>Kairol S(^\circ); Methylural(^\circ); Permafresh 477(^\circ); Urofix(^\circ)</td>
<td>140-95-4</td>
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<tr>
<td>DMDM hydantoin (INCI)</td>
<td>1,3-Bis(hydroxymethyl)-5, 5-dimethyl-imidazolidine-2,4-dione</td>
<td>Dimethyloldimethyl- hydantoin; 1,3-dimethylol-5,5-dimethyl- hydantoin; DMDMH</td>
<td>Cosept DM(^\circ); Dekafald(^\circ); Glydan(^\circ) (2000, XL-1000); Lanodant DM(^\circ); Mackstat DM(^\circ); Microcare DH(^\circ)</td>
<td>6440-58-0</td>
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<tr>
<td>Ethylene urea</td>
<td>Imidazolidin-2-one</td>
<td>2-Imidazolidinone (MI); 2-Oximidazolidine</td>
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<td>120-93-4</td>
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<td>Forcide 78(^\circ) F</td>
<td>((Z)-3-(Bis(2-hydroxyethyl)amino)-2-(2-hydroxyethyl- (hydroxyethyl)amino) prop-2-en-1-ol)</td>
<td>2-Hydroxymethylamino- ethanol-tri-N-ethylhydroxy-2-amino-methylene</td>
<td>Forcide 78(^d)</td>
<td>77044-78-1</td>
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<td>Forcide 78(^\circ) II(^d)</td>
<td>1,3,5-Triethyl-1,3,5-triazinane (b)</td>
<td>(b) Hexahydro-1,3,5-triethyl-s-triazine; (b) Triethyl-trimethylenetriamine mixture of (a) triazinetriethanol (see there) and (b) hexahydro-1,3,5-triethyl-1,3,5-triazine</td>
<td>(b) Vancide-TH(^\circ); Forcide 78(^d)</td>
<td>7779-27-3 (b)</td>
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<td>Formaldehyde (INCI, MI)</td>
<td>Formaldehyde</td>
<td>Formalin; Methanal; Methyl aldehyde; Oxyurea</td>
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<td>50-00-0</td>
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<tr>
<td>Glyoxalurea</td>
<td>4,5-Dihydroxyimidazolidin-2-one</td>
<td>Dihydroxyethyleneurea; Glyoxalmonoureine</td>
<td></td>
<td>3720-97-6</td>
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<tr>
<td>Imidazolidinyl urea (INCI, MI)</td>
<td>3-[[3-(Hydroxymethyl)-2,5-dioxoimidazolidin-4-yl]-1-[[3-(hydroxymethyl)-2,5-dioxoimidazolidin-4-yl] carbamoylethynol]methyl]urea</td>
<td>Bis(methylolhydrantoin urea) methane; Imidurea (MI)</td>
<td>Germall 115(^\circ); Liposerve IT(^\circ); Nipa Biopure 100(^\circ); Protacide U-13(^\circ); Unicide U-13(^\circ)</td>
<td>39236-46-9</td>
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<td>Commonly used name</td>
<td>IUPAC name</td>
<td>Other synonyms</td>
<td>Current trade names&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CAS number</td>
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<td>MDM hydantoin (INCI)</td>
<td>1-(Hydroxymethyl)-5,5-dimethyl-imidazolidine-2,4-dione</td>
<td>1-Hydroxymethyl-5,5-dimethyl hydantoin (MI); MDMH; Methylol dimethyl hydantoin; Monomethylol dimethyl hydantoin</td>
<td>Glycoserve&lt;sup&gt;®&lt;/sup&gt;</td>
<td>116-25-6</td>
</tr>
<tr>
<td>Methenamine (INCI, MI)</td>
<td>Not available</td>
<td>Aminof orm; Formamine; Hexamethylene tetramine; Hexamine; Methenamide</td>
<td>Cystamine&lt;sup&gt;®&lt;/sup&gt;; Urotropine&lt;sup&gt;®&lt;/sup&gt;; Vulkacit H30&lt;sup&gt;®&lt;/sup&gt;</td>
<td>100-97-0</td>
</tr>
<tr>
<td>N,N′-Methylenebis(5-methyloxazolidine)</td>
<td>5-Methyl-3-[(5-methyloxazolidin-3-yl) methyl]oxazolidine</td>
<td></td>
<td>Grotan OX&lt;sup&gt;®&lt;/sup&gt;</td>
<td>66204-44-2</td>
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<td>4,4′-Methyleneimorpholine</td>
<td>4-(Morpholin-4-yl)morpholine</td>
<td>Bismorpholinomethane; Dimorpholinomethane; 4,4′-methylenebis-morpholine</td>
<td></td>
<td>5625-90-1</td>
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<td>N-Methylol-chloracetamide</td>
<td>2-Chloro-N-(hydroxymethyl) acetamide</td>
<td>Chloracetamide-N-methylol</td>
<td>Grotan DF-35&lt;sup&gt;®&lt;/sup&gt;</td>
<td>2832-19-1</td>
</tr>
<tr>
<td>Methylol urea</td>
<td>Hydroxymethylurea</td>
<td>N-(hydroxymethyl)urea; Methyl hydroxyurea; Mono(hydroxymethyl)urea; Monomethylolurea</td>
<td></td>
<td>1000-82-4</td>
</tr>
<tr>
<td>Parafomaldehyde</td>
<td>Formaldehyde</td>
<td>Paraform; Poly(oxymethylene)</td>
<td>Aldacide&lt;sup&gt;®&lt;/sup&gt;; Formogene&lt;sup&gt;®&lt;/sup&gt;</td>
<td>30525-89-4</td>
</tr>
<tr>
<td>Polyoxymethylene melamine (INCI)</td>
<td>Not available</td>
<td>Melamine, polymer with formaldehyde; Melamine/formaldehyde resin; Nanoplast</td>
<td></td>
<td>9003-08-1</td>
</tr>
<tr>
<td>Polyoxymethylene urea (INCI)</td>
<td>Formaldehyde; urea</td>
<td>Polynoxylin; Urea—formaldehyde resin; Urea, polymer with formaldehyde</td>
<td>Karbamol&lt;sup&gt;®&lt;/sup&gt; (B/M); Kaurit&lt;sup&gt;®&lt;/sup&gt; (285FL, 240); Uformite&lt;sup&gt;®&lt;/sup&gt;</td>
<td>9011-05-6</td>
</tr>
<tr>
<td>Preventol D2&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Phenylmethoxymethoxy-methylbenzene</td>
<td>Bis(benzyloxy)methane; Mixture of hydroxymethylene and polyhydroxymethylene monobenzylether; 1,1′-(Methylenebis(oxymethylene)) bis-benzene</td>
<td>Preventol D2&lt;sup&gt;®&lt;/sup&gt;, This trade name is also often used for benzylhemiformal</td>
<td>2749-70-4</td>
</tr>
<tr>
<td>Propyleneglycol hemiformal</td>
<td>Not available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quaternium-15 (INCI, MI)</td>
<td>N-(3-Chloroallyl)hexaniminium chloride; Chloroallylhexaniminium chloride; 1-(3-Chloroallyl)-3,5,7-triaza-1-azonia-adamantane chloride; Hexamethylene tetramine chloroallyl chloride</td>
<td>Cosept 200&lt;sup&gt;®&lt;/sup&gt;; Dowicide Q&lt;sup&gt;®&lt;/sup&gt;; Dowicil&lt;sup&gt;®&lt;/sup&gt; (75, 200)</td>
<td></td>
<td>4080-31-3</td>
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<tr>
<td><strong>Table 2. (Continued)</strong></td>
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</tr>
<tr>
<td>Sodium hydroxymethylglycinate (INCI)</td>
<td>Not available</td>
<td>Glycine, $N$-(hydroxymethyl)-, sodium salt (1:1); $N$-hydroxymethylglycine (monosodium salt; Sodium $N$-(hydroxymethyl)glycinate</td>
<td>Suttocide A®</td>
<td>70161-44-3</td>
</tr>
<tr>
<td>Tetramethylo acetylenediurea</td>
<td>2,4,6,8-Tetrakis(hydroxymethyl)-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione</td>
<td>Tetrakis(hydroxymethyl) glycoluril; Tetramethylo glycoluril</td>
<td>Fixapret 140®</td>
<td>5395-50-6</td>
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<tr>
<td>Tris($N$-hydroxyethyl) hexahydrotriazine</td>
<td>2-[4,6-Bis(2-hydroxyethyl)1,3,5-triazinan-2-yl]ethanol</td>
<td>Hexahydro-1,3,5-tris(hydroxyethyl)triazine; Triazinetriethanol; Trihydroxyethylhexahydro s-triazine; 1,3,5-Trihydroxyethylhexahydrotriazine</td>
<td>Forcide 78® (see there); Grotan® (B, BK, HD); Onyxide 200®; Roksol T 1–7®</td>
<td>4719-04-4</td>
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<tr>
<td>Tris(hydroxymethyl)-nitromethane (INCI, MI)</td>
<td>2-(Hydroxymethyl)-2-nitropropane-1,3-diol</td>
<td>Nitromethylidynamethanol; Trimethylolnitromethane; Tris nitro</td>
<td>Tris Nitro®</td>
<td>126-11-4</td>
</tr>
</tbody>
</table>

(B) **Chemicals for which adequate clinical data are lacking to identify them as formaldehyde-releasers beyond doubt**

<p>| | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>5-Bromo-5-nitro-1,3-dioxane (INCI)</td>
<td>5-Bromo-5-nitro-1,3-dioxane</td>
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<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>2-(Hydroxymethoxy) ethoxymethanol</td>
</tr>
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<td>Commonly used name</td>
<td>IUPAC name</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------------</td>
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<tr>
<td>Hydantoin</td>
<td>Imidazolidine-2,4-dione</td>
</tr>
<tr>
<td>(Hydroxymethyl)-5,5-dimethyl-2,4-imidazolidinedione</td>
<td>Not available</td>
</tr>
<tr>
<td>3-(Hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione</td>
<td>As in column 1</td>
</tr>
<tr>
<td>Methylal (INCI, MI)</td>
<td>Dimethoxymethane</td>
</tr>
<tr>
<td>N-Methylethanolamine</td>
<td>2-(Hydroxymethylamino)ethanol</td>
</tr>
</tbody>
</table>


\(^a\)The data in this table are – in addition to the references mentioned in the table’s heading – retrieved from and/or verified in the following sources:

3. The following databases:
   a. Chemical Name Synonym Finder (www.chemindustry.com);
   b. Comparative Toxicogenomics Database (http://ctd.mdibl.org/voc.go?type=chem);
   d. Chemfinder.com (http://chemfinder.cambridgesoft.com/);
   e. The pubchem project (http://pubchem.ncbi.nlm.nih.gov/).
4. Other relevant internet sources, notably the websites of the manufacturers of the various chemicals.

\(^b\)Trade names mentioned by various sources are included in this table only when their existence could be verified by internet searching for manufacturers selling the products under these trade names.

\(^\circ\)Description of Forcide 78\(^\circ\) as in Hamann (19) and the above-mentioned chemical databases.

\(^\circ\)Forcide 78\(^\circ\) is also used as a trade name by Redox Pty Ltd (www.redox.com/mds/data/TRIAZI80.html) for a preservative containing 75–80% triazinetriethanol.

\(^\circ\)Description of Forcide 78\(^\circ\) as in Andersen et al. (20).

\(^\circ\)Preventol D2\(^\circ\) is also used as a trade name for benzylhemiformal by Lanxess Energizing Chemistry (www.protectedbypreventol.com).
relationship to formaldehyde and other formalde-
hyde-releasers, (iii) the relevance of positive patch
test reactions, (iv) the amount of formaldehyde
released by the various chemicals and, consequently,
(v) the risk they pose for individuals allergic to
formaldehyde. Do we have adequate knowledge to
give formaldehyde allergic patients proper advice on
avoidance of formaldehyde-releasers?

This review is presented as a series. In this
article, formaldehyde sensitivity is reviewed, an
inventory of the formaldehyde-releasers is presented
and the frequency of their presence in various
product categories is summarized. In other parts,
formaldehyde-releasers commonly used in cosmetic
products are discussed, formaldehyde in textile
finishes is considered, and finally releasers in industrial
products, notably metalworking fluids, and miscel-
laneous releasers are reviewed.

Identification and Selection of
Formaldehyde-releasers

Formaldehyde-releasers were defined as: (i) sub-
stances that release formaldehyde as a result of
decomposition and/or (ii) chemicals synthesized
from formaldehyde that may still contain residues
of free formaldehyde (e.g. melamine/formaldehyde
and urea-formaldehyde resins).

Reports on chemicals ascertained or claimed
to be formaldehyde-releasers were found in text-
books (1–3), reviews (4–8), case reports and origi-
nal articles. Exact identification of some substances
described as formaldehyde-releasers has been prob-
lematic or even impossible, as a considerable num-
ber of synonyms and trade names are used in the
literature, without identifying active ingredients.
Several frequently used trade names (also in
recent textbooks and patient information leaflets
found on the internet) currently appear to be out
of use or are applied to the wrong ingredients,
some chemical names could not be identified in
any database and some substances have incor-
rectly been identified as formaldehyde-releasers
(Table 1).

Included in this article are only those formalde-
hyde-releasers that could unequivocally or with a
high degree of certainty be identified, for instance,
by their Chemical Abstract Service Registry Num-
bers (CAS numbers) or their chemical structure.
Thus, a total of 42 formaldehyde-releasers were
found in the literature. These are presented alpha-
betically in Table 2 with their (suggested) com-
mon name (INCI name if existing), IUPAC name,
other synonyms, (some) verified trade names and
CAS numbers. Due to difficulties in identifying
some presumed formaldehyde-releasers in the lit-
erature data (4, 6, 18) as described above, this
list cannot be expected to be complete. Moreover,
7 of the 42 chemicals have been mentioned as
formaldehyde-releasers in one or more publications,
but data are inadequate to label them as such beyond
doubt (Table 2B). Over half of the formaldehyde-
releasers are commercially available for patch test-
ing (Table 3).

Not included in this review are:

1. Compounds that may (possibly) cross-react to
formaldehyde, such as glutaraldehyde (21) and
glyoxal (22, 23).
2. Chemicals in which formaldehyde may be
formed by air oxidation (e.g. polyoxyethylene
dodecyl alcohols) or degradation, but for which
no relevant clinical data are available (24, 25).
3. Formaldehyde resins in which formaldehyde
allergy does not play an important role, such as
phenol-3 formaldehyde resins (26) and p-tert-
butyl phenolformaldehyde resin (27).
4. Tosylamide/formaldehyde resin, a resin based
on toluenesulfonamide and formaldehyde, is
the major ingredient in most nail lacquers.
Free formaldehyde is present in the majority
of nail lacquers, with concentrations varying
from 0.02% to 0.5% (28). Despite this, the
allergen in nail lacquers appears to be the resin
itself and people do not become sensitized
to formaldehyde from the use of these nail
cosmetics: the amount of free formaldehyde
in finished, dried nail lacquer is believed to
be nil (29) and nail lacquers do not seem to
cause dermatitis in patients already allergic
to formaldehyde. This may be explained by
application of the resin to the nail (avoiding
contact with the skin), only very infrequent
application of the product and swift evaporation
of any free formaldehyde.

Formaldehyde

Formaldehyde (methanal) is a colourless gas with
a characteristic pungent odour. Formalin is a
37–40% aqueous solution of formaldehyde, to
which 10–15% methyl alcohol has been added to
inhibit polymerization (16). This simple aldehyde
is ubiquitous in the environment, and is generated
in and released from the smoke of burning wood,
coal, charcoal, tobacco, natural gas and kerosene.
Formaldehyde also occurs naturally in certain foods
such as coffee (especially instant coffee), dried
bean curd, cod fish, caviar, maple syrup, shiitake
mushrooms and smoked ham. It is an irritant as
well as an allergen and a potential respiratory
carcinogen (15). It can be formed by breaking, con-
version and oxidation of ingested aspartame (an
Table 3. Formaldehyde-releasers commercially available for patch testing

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Chemotechnique&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Trolab&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Brial&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylhemiformal</td>
<td>1% pet.</td>
<td>1% pet.</td>
<td>1% pet.</td>
</tr>
<tr>
<td>Bioban&lt;sup&gt;®&lt;/sup&gt; CS 1135</td>
<td>1% pet.</td>
<td>1% pet.</td>
<td>1% pet.</td>
</tr>
<tr>
<td>Bioban&lt;sup&gt;®&lt;/sup&gt; CS 1246</td>
<td>1% pet.</td>
<td>1% pet.</td>
<td>1% pet.</td>
</tr>
<tr>
<td>Bioban&lt;sup&gt;®&lt;/sup&gt; P 1487</td>
<td>0.5% pet.</td>
<td>1% pet.</td>
<td>1% pet.</td>
</tr>
<tr>
<td>2-Bromo-2-nitropropane-1,3-diol</td>
<td>0.25% pet.</td>
<td>0.5% pet.</td>
<td>0.5% pet.</td>
</tr>
<tr>
<td>Diazolidinyl urea</td>
<td>2% pet.</td>
<td>2% pet.</td>
<td>2% pet.</td>
</tr>
<tr>
<td>1,3-Dimethyl-4,5-dihydroxyethyleneurea</td>
<td>4.5% aqua</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethyol dihydroxyethyleneurea</td>
<td>4.5% aqua</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethylol dihydroxyethylene urea, modified</td>
<td>5% aqua</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMDM hydantoin</td>
<td>2% aqua</td>
<td>2% aqua</td>
<td>2% aqua</td>
</tr>
<tr>
<td>Ethylene urea</td>
<td>1% pet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylene urea, melamine formaldehyde mix</td>
<td>5% pet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>1% aqua</td>
<td>1% aqua</td>
<td>1% aqua</td>
</tr>
<tr>
<td>Imidazolidinyl urea</td>
<td>2% pet.</td>
<td>2% pet.</td>
<td>2% pet.</td>
</tr>
<tr>
<td>Melamine/formaldehyde resin</td>
<td>7% pet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methenamine (hexamethylenetetramine)</td>
<td>2% pet.</td>
<td>1% pet.</td>
<td>1% pet.</td>
</tr>
<tr>
<td>N,N&lt;sup&gt;-&lt;/sup&gt; Methylenebis(5-methyloxazolidine)</td>
<td>1% pet.</td>
<td>1% pet.</td>
<td>1% pet.</td>
</tr>
<tr>
<td>N&lt;sup&gt;-&lt;/sup&gt;Methylol-chloracetamide</td>
<td>0.1% pet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyoxyethylene urea (urea-formaldehyde resin)</td>
<td>10% pet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quaternium—15</td>
<td>1% and 2% pet.</td>
<td>1% pet.</td>
<td>1% pet.</td>
</tr>
<tr>
<td>Tris(N-hydroxyethyl)hexahydrotriazine (triazinetriethanol, Grotan&lt;sup&gt;®&lt;/sup&gt; BK)</td>
<td>1% aqua</td>
<td>1% pet.</td>
<td>1% pet.</td>
</tr>
<tr>
<td>Tris(hydroxymethyl)nitromethane (Tris Nitro)</td>
<td>1% pet.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Available at: www.chemotechnique.se.<br><sup>b</sup>Available at: www.hermal.com.<br><sup>c</sup>Available at: www.brial.com.

artificial sweetener) and possibly causes migraines in formaldehyde allergic individuals (30).

Applications and exposure

Formaldehyde can be used as a disinfectant because it kills most bacteria and fungi. It was first commercially used in embalming fluid and as a preservative for laboratory specimens. Later, it was used to make plywood and asphalt shingles. It has also been added in bonded leather, waterproof glues, fertilizers and photographic developers. Exposure to formaldehyde is difficult to estimate because the chemical, besides being used as such, is incorporated into a large variety of products and reactants in many chemical processes, including formaldehyde-releasers, polymerized plastics, metalworking fluids (31, 32), medicaments, fabrics, cosmetics and detergents (Table 4).

In finished products, there may be several sources of formaldehyde, some of which are ‘hidden’ or ‘occult’ (16):

1. formaldehyde added as an active ingredient for preservation;
2. formaldehyde released from formaldehyde donors (usually preservatives);
3. excess formaldehyde used to synthesize the releaser;
4. formaldehyde which is used for the preservation of raw materials used to prepare the product;
5. formaldehyde in formaldehyde-based raw materials used to prepare the product;
6. formaldehyde used to sterilize vessels for the storage of raw materials or products;
7. formaldehyde released by package materials such as formaldehyde resins coating cosmetic and pharmaceutical tubes (39, 40);
8. formaldehyde formed in situ by degradation of non-formaldehyde-containing components of the product (41). Auto-oxidation of ethoxylated alcohols, which are widely used in cleaners, toiletries and laundry products, may lead to the formation of formaldehyde (24). Polysorbate 80, a non-ionic surfactant present in many cosmetic and pharmaceutical products, after air oxidation was shown to cause formaldehyde formation in concentrations of 70–500 p.p.m. (42). Lower concentrations of 2.5–6 p.p.m. have been found with polysorbate 20, 40 and 60 (43).

Legislation in the EU

Exposure to formaldehyde in the EU is subject to restrictions because of its toxicological properties. The maximum allowed concentration in finished products is 0.2%. Annex VI of Cosmetics Directive 76/768/EC further stipulates that all finished products containing formaldehyde or substances in this Annex which release formaldehyde must be labelled with the warning ‘contains formaldehyde’ where the concentration of free formaldehyde in the finished
Table 4. Examples of products that may contain formaldehyde and applications (adapted from Andersen et al. (1), Flyvholm (16, 33), Feinman (34) and Rietschel and Fowler (35))a

<table>
<thead>
<tr>
<th>Product/Category</th>
<th>Example Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesives</td>
<td>(glues, pastes and cements)</td>
</tr>
<tr>
<td>Agricultural chemicals</td>
<td>(seed disinfectants)</td>
</tr>
<tr>
<td>Antifreeze agents</td>
<td></td>
</tr>
<tr>
<td>Antiperspirants</td>
<td></td>
</tr>
<tr>
<td>Asphalt shingles</td>
<td></td>
</tr>
<tr>
<td>Binders (polymers)</td>
<td></td>
</tr>
<tr>
<td>Castings</td>
<td></td>
</tr>
<tr>
<td>Cellulose esters</td>
<td></td>
</tr>
<tr>
<td>Chipboard production</td>
<td></td>
</tr>
<tr>
<td>Cleaning products</td>
<td>(36)</td>
</tr>
<tr>
<td>Clothing (wash and wear, crease-resistant)</td>
<td></td>
</tr>
<tr>
<td>Colouring agents</td>
<td></td>
</tr>
<tr>
<td>Construction materials</td>
<td></td>
</tr>
<tr>
<td>Corrosion inhibitors</td>
<td></td>
</tr>
<tr>
<td>Cosmetics</td>
<td>(37)</td>
</tr>
<tr>
<td>Cutting fluids</td>
<td>(31, 32)</td>
</tr>
<tr>
<td>Dental preparations and dentifrices</td>
<td></td>
</tr>
<tr>
<td>Deodorizers</td>
<td></td>
</tr>
<tr>
<td>Disinfectants</td>
<td></td>
</tr>
<tr>
<td>Dry cleaning materials</td>
<td></td>
</tr>
<tr>
<td>Embalming fluids</td>
<td></td>
</tr>
<tr>
<td>Explosives manufacture</td>
<td></td>
</tr>
<tr>
<td>Filling agents (stopping, putty, etc.)</td>
<td></td>
</tr>
<tr>
<td>Fish meal industry</td>
<td></td>
</tr>
<tr>
<td>Flame retardant</td>
<td></td>
</tr>
<tr>
<td>Flooring materials</td>
<td></td>
</tr>
<tr>
<td>Footwear (resins and plastics)</td>
<td></td>
</tr>
<tr>
<td>Fumigants</td>
<td></td>
</tr>
<tr>
<td>Hardeners</td>
<td></td>
</tr>
<tr>
<td>Hydrocarbons (e.g. oil)</td>
<td></td>
</tr>
<tr>
<td>Impregnating agents</td>
<td></td>
</tr>
<tr>
<td>Laboratory chemicals</td>
<td></td>
</tr>
<tr>
<td>Latex rubber</td>
<td></td>
</tr>
<tr>
<td>Medications: wart remedies, anhydrotics</td>
<td></td>
</tr>
<tr>
<td>Metal coatings (not paints)</td>
<td></td>
</tr>
<tr>
<td>Metal and tyre cleaners</td>
<td></td>
</tr>
<tr>
<td>Metalworking fluids (31, 32)</td>
<td></td>
</tr>
<tr>
<td>Mildew preventatives (fruits and vegetables)</td>
<td></td>
</tr>
<tr>
<td>Mineral wool production</td>
<td></td>
</tr>
<tr>
<td>Orthopaedic casts</td>
<td></td>
</tr>
<tr>
<td>Paints, lacquers and coatings</td>
<td></td>
</tr>
<tr>
<td>Paint removers</td>
<td></td>
</tr>
<tr>
<td>Paper industry (38)</td>
<td></td>
</tr>
<tr>
<td>Phenolic resins in adhesives and footwear</td>
<td></td>
</tr>
<tr>
<td>Photographic paper and solutions</td>
<td></td>
</tr>
<tr>
<td>Plywood</td>
<td></td>
</tr>
<tr>
<td>Polishes and finishes</td>
<td></td>
</tr>
<tr>
<td>Printing inks</td>
<td></td>
</tr>
<tr>
<td>Starch (spray and powdered)</td>
<td></td>
</tr>
<tr>
<td>Surface active agents</td>
<td></td>
</tr>
<tr>
<td>Tanning agents</td>
<td></td>
</tr>
<tr>
<td>Textiles</td>
<td></td>
</tr>
<tr>
<td>Tissue fixatives</td>
<td></td>
</tr>
<tr>
<td>Toiletries (33)</td>
<td></td>
</tr>
<tr>
<td>Urea plastics in adhesives and footwear</td>
<td></td>
</tr>
</tbody>
</table>

aThese applications have been reported in the literature, but we have not checked whether formaldehyde may at this time indeed be present in such products; some of the information may therefore be outdated. The list is not intended to suggest that exposure may cause clinically relevant reactions.

Patch testing with formaldehyde

Patch testing with formaldehyde is not very reliable. Formerly, test concentrations of 3–5% were used, resulting in many false-positive reactions. Currently, 1% aqua is the standard for patch testing. However, even this concentration may result in false-positive reactions as less than 50% of positive reactions are reproducible on retesting (45). Irritant, doubtful and follicular reactions to formaldehyde also occur (46). Conversely, false-negative reactions may not be infrequent either (8, 46, 47). Trattner et al. tested 3734 patients with both 1% aqua and 2% aqua between 1992 and 1996. A total of 121 of them had a positive reaction to one or both test preparations. Of 98 patients who reacted to formaldehyde 2% aqua (judged to be truly allergic reactions), only 59 (60%) reacted to the currently used formaldehyde 1% aqua. This may indicate that up to 40% of allergic patients are missed when tested with formaldehyde 1% aqua only (46).

Frequency of sensitization

Into the 1980s, prevalence rates of sensitization to formaldehyde were high in the USA (48), Canada (49), many European countries (50, 51) and Japan (52). In Japan, from a high frequency of 18% in 1977, the frequency dropped to 2.8% a couple of years later. This fall reflected its Government regulations which restricted the levels of formaldehyde allowed in underclothes to 75 p.p.m. or less for adults and 15 p.p.m. or less for babies. Previously, garments had contained as much as 10 000 p.p.m. (52).

Formaldehyde per se was previously used as a preservative in cosmetics, as a disinfectant, as an antiperspirant and in textile finish resins releasing large amounts of formaldehyde, resulting in high sensitization rates (53). However, its use in cosmetics has largely been abandoned and replaced with formaldehyde donors due to allegations of carcinogenicity. As a disinfectant, it was partly replaced by other compounds such as glutaraldehyde and glyoxal. Also, low formaldehyde textile resins were introduced. Thus, since the 1980s, there has been a decline in the frequency of sensitization in most countries. The decrease in patch test reactions may also partly be explained by test procedures. In the past, higher concentrations of formaldehyde than the currently recommended 1% aqueous formaldehyde solution were used for patch testing, which has probably resulted in more irritant reactions, erroneously considered to represent truly positive allergic patch test reactions.

Currently, the frequency of sensitization to formaldehyde remains at a stable and relatively low level of around 2–3% in most (European) countries in...
the general patch test population (Table 5). In the USA, however, rates of 8–9% are rule rather than exception.

From large-scale studies, it appears that women are affected 1.2–1.5 times more frequently than men. Table 5 summarizes the experience in routine patch testing with formaldehyde back to 1990. The older literature has been reviewed in Fransway and Schmitz (11) and Fransway (29).

Relevance of positive patch test reactions to formaldehyde

From the 29 studies summarized in Table 5, data on relevance have been provided in eight (28%) only. Remarkably, six of these studies (75%) were performed in the USA. The percentages of patients in whom the positive reaction to formaldehyde was considered to be relevant have varied widely. The highest percentage was 90% in a UK study, but this was based on 14 patients only (69). In a Danish study, relevance was assumed in 78% of patients who were allergic to either 1% or 2% aqua (46). In the USA studies, the positive patch test reactions were considered to be relevant in 65–75% of the cases. However, in five investigations performed by the North American Contact Dermatitis Group (NACDG), the percentages also included patients with ‘possible relevance’. Possible relevance was considered if the patient was exposed to circumstances in which the skin contact with materials known to contain formaldehyde would likely occur and the rash distribution and clinical situation fit. This could, also according to the authors themselves, result in an overestimation of the true possible relevance of the test allergen (68). Indeed, in only 12–33% of the cases were the reactions scored as ‘definite/probable’ relevance.

Currently, most reactions to formaldehyde are believed to result from contact with cosmetics and household products (46, 79) in which formaldehyde-releasers are frequently used, especially in women. Over half of 67 skin creams in Denmark investigated in 2000 for the presence of preservatives, for example, contained formaldehyde-releasers (80). A 1992 study of washing and cleaning agents showed that formaldehyde-releasing compounds were among the most commonly used preservatives in such products (36). Sensitization to formaldehyde may also be caused by occupational exposure, especially in metalworkers and the medical professions (81–83). Occupational sensitization occurs more frequently in men (81). The most detailed pertinent information has been published by Fransway and Schmitz (11). These authors investigated 300 patients allergic to formaldehyde for the relevance of their positive patch tests. In two-thirds of the cases, formaldehyde sensitivity was assessed as a significant contributory or the single most causative factor in the patient’s dermatosis. In these patients, a definable source of exposure to formaldehyde and temporal consistency with dermatitis flare were present. 29% had chronic dermatitis (including atopic dermatitis) and were exposed to topical products containing formaldehyde (releasers), 21% were primarily sensitized to topical cosmetics, medicaments or emollients. Occupational sensitization was seen in 43 patients (14%) in whom 12 were nurses, 6 medical technicians, 7 beauticians and 7 machinists. Clothing exposure accounted for only nine cases (3%) (11).

Clinical pattern of allergic contact dermatitis from formaldehyde

Patients allergic to formaldehyde are often women with hand eczema with/without facial dermatitis (81, 84). This is explained by the hands being exposed to household cleansing agents (e.g. washing-up liquids) where formaldehyde is often found in combination with detergents that impair barrier function and increase penetration (84). Facial dermatitis may be caused by the application of cosmetics containing formaldehyde (releasers). Hand eczema from formaldehyde sensitivity is also found more often in nurses and other medical professions (paramedicals) and in metal workers (29, 32, 82, 83).

Allergic contact dermatitis due to formaldehyde released from textile permanent-press finished is characterized by a distribution of lesions on skin areas having direct contact with fabric, particularly areas in which the garment moves over the skin surface (the inner thigh, the neck [collars in men]), and in the relatively moister locations of the body, such as the periaxillary areas, groin, waist and the antecubital and popliteal fossae. Widespread eruptions may also be seen with sparing of the hands and face, although in patients allergic to formaldehyde these body parts may also be involved from the use of cosmetics containing formaldehyde-releasers (85).

Prognosis of formaldehyde allergic contact dermatitis

As formaldehyde is so widely distributed in the environment, it is difficult to avoid. It may not appear on labels, as formaldehyde can be present in products as contaminants from ‘hidden’ or ‘occult’ sources, that manufacturers are unaware of. Many patients find it difficult to read and correctly interpret the labels of cosmetic products; they do not only
Table 5. Frequency of sensitization to formaldehyde in patients suspected of contact dermatitis

<table>
<thead>
<tr>
<th>Country</th>
<th>Years of study</th>
<th>Number of patients</th>
<th>Test concentrations and vehicle</th>
<th>Positive All (%)</th>
<th>Women (%)</th>
<th>Men (%)</th>
<th>Current relevance (%)</th>
<th>Comments/setting</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>2004–2005</td>
<td>6958</td>
<td>1% aqua</td>
<td>2.0</td>
<td>2.3</td>
<td>1.4</td>
<td>NS</td>
<td>Multicentre study</td>
<td>Jong et al. (54)</td>
</tr>
<tr>
<td>Denmark</td>
<td>1985–2005</td>
<td>14 980</td>
<td>1% aqua</td>
<td>2.9</td>
<td>3.2</td>
<td>2.2</td>
<td>NS</td>
<td>One centre, Copenhagen</td>
<td>Carlsen et al. (45)</td>
</tr>
<tr>
<td>USA</td>
<td>2001–2005</td>
<td>3836</td>
<td>1% aqua</td>
<td>9.0</td>
<td>76</td>
<td>NS</td>
<td></td>
<td>Mayo Clinic, three locations</td>
<td>Davis et al. (55)</td>
</tr>
<tr>
<td>Israel</td>
<td>1998–2004</td>
<td>2156</td>
<td>1% aqua</td>
<td>1.8</td>
<td></td>
<td></td>
<td>NS</td>
<td>One centre, Tel Aviv</td>
<td>Lazarov (56)</td>
</tr>
<tr>
<td>Turkey</td>
<td>1992–2004</td>
<td>1038</td>
<td>1% aqua</td>
<td>1.3</td>
<td>1.1</td>
<td>1.5</td>
<td>NS</td>
<td>One centre, Ankara</td>
<td>Akyol et al. (57)</td>
</tr>
<tr>
<td>Germany + Austria+ Switzerland</td>
<td>2001–2004</td>
<td>31 045</td>
<td>1% aqua</td>
<td>1.7</td>
<td></td>
<td></td>
<td>NS</td>
<td>Multicentre study, IVDK</td>
<td>Worm et al. (58)</td>
</tr>
<tr>
<td>Europe</td>
<td>2004</td>
<td>9956</td>
<td>1% aqua</td>
<td>2.0</td>
<td></td>
<td></td>
<td>NS</td>
<td>Thirty-one centres in 11 countries, ESSCA</td>
<td>Uter (59)</td>
</tr>
<tr>
<td>Europe</td>
<td>2002–2003</td>
<td>9213</td>
<td>1% aqua</td>
<td>2.0</td>
<td></td>
<td></td>
<td>NS</td>
<td>Seventeen centres in nine countries, ESSCA</td>
<td>Uter et al. (60)</td>
</tr>
<tr>
<td>Finland</td>
<td>2000–2002</td>
<td>11 798</td>
<td>1% aqua</td>
<td>2.5</td>
<td></td>
<td></td>
<td>NS</td>
<td>Multicentre study</td>
<td>Hasan et al. (61)</td>
</tr>
<tr>
<td>USA</td>
<td>2001–2002</td>
<td>4909</td>
<td>1% aqua</td>
<td>8.4</td>
<td></td>
<td></td>
<td>15/55b</td>
<td>Multicentre study, NACDG</td>
<td>Pratt et al. (62)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1997–2001</td>
<td>12 058</td>
<td>1% aqua</td>
<td>4.1</td>
<td>4.7</td>
<td>3.1</td>
<td>NS</td>
<td>Multicentre study</td>
<td>Machovcova et al. (63)</td>
</tr>
<tr>
<td>Israel</td>
<td>1999–2000</td>
<td>943</td>
<td>1% aqua</td>
<td>1.9</td>
<td>1.4</td>
<td>2.6</td>
<td>NS</td>
<td>One centre, Petah Tgwa</td>
<td>Freireich-Astman et al. (64)</td>
</tr>
<tr>
<td>Europe</td>
<td>1996–2000</td>
<td>26 210</td>
<td>1% aqua</td>
<td>2.3</td>
<td>2.4</td>
<td>2.0</td>
<td>NS</td>
<td>Ten centres in seven countries, EECDRG</td>
<td>Bruynzeel et al. (65)</td>
</tr>
<tr>
<td>Sweden</td>
<td>2000</td>
<td>3790</td>
<td>1% aqua</td>
<td>2.6</td>
<td></td>
<td></td>
<td>NS</td>
<td>Multicentre study, NACDG</td>
<td>Lindberg et al. (66)</td>
</tr>
<tr>
<td>USA</td>
<td>1998–2000</td>
<td>1321</td>
<td>1% aqua</td>
<td>7.9</td>
<td></td>
<td></td>
<td>NS</td>
<td>Mayo Clinic, three locations</td>
<td>Wetter et al. (67)</td>
</tr>
<tr>
<td>USA</td>
<td>1998–2000</td>
<td>5830</td>
<td>1% aqua</td>
<td>9.2</td>
<td></td>
<td></td>
<td>12/49b</td>
<td>Multicentre study, NACDG</td>
<td>Marks et al. (68)</td>
</tr>
<tr>
<td>UK</td>
<td>2000</td>
<td>2063</td>
<td>1% aqua</td>
<td>2.1</td>
<td></td>
<td></td>
<td>90</td>
<td>Relevance (90%) = current + past relevance in one centre (674 patients)</td>
<td>Britton et al. (69)</td>
</tr>
</tbody>
</table>
Table 5. (Continued)

<table>
<thead>
<tr>
<th>Country</th>
<th>Years of study</th>
<th>Number of patients</th>
<th>Test concentrations and vehicle</th>
<th>Positive All (%)</th>
<th>Women (%)</th>
<th>Men (%)</th>
<th>Current relevance (%)</th>
<th>Comments/setting</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>1993–1999</td>
<td>32 779</td>
<td>1% aqua</td>
<td>1.9</td>
<td>NS</td>
<td></td>
<td></td>
<td>Multicentre study, IVDK</td>
<td>Brasch et al. (70)</td>
</tr>
<tr>
<td>USA</td>
<td>1996–1998</td>
<td>3440</td>
<td>1% aqua</td>
<td>9.3</td>
<td>63c</td>
<td></td>
<td></td>
<td>Multicentre study, NACDG</td>
<td>Marks et al. (71)</td>
</tr>
<tr>
<td>USA</td>
<td>1988–1997</td>
<td>927</td>
<td>1% aqua</td>
<td>6.8</td>
<td>NS</td>
<td></td>
<td></td>
<td>One centre, Boston</td>
<td>Albert et al. (9)</td>
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<tr>
<td>Belgium</td>
<td>1995–1997</td>
<td>8521</td>
<td>1% aqua</td>
<td>0.9</td>
<td>NS</td>
<td></td>
<td></td>
<td>One centre, Leuven</td>
<td>Goossens et al. (72)</td>
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<tr>
<td>Denmark</td>
<td>1992–1996</td>
<td>3734</td>
<td>1% aqua</td>
<td>2.2</td>
<td>78d</td>
<td></td>
<td></td>
<td>One centre, Copenhagen</td>
<td>Trattner et al. (46)</td>
</tr>
<tr>
<td>Denmark</td>
<td>1992–1996</td>
<td>3734</td>
<td>2% aqua</td>
<td>2.6</td>
<td>78d</td>
<td></td>
<td></td>
<td>One centre, Copenhagen</td>
<td>Trattner et al. (46)</td>
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<tr>
<td>USA</td>
<td>1994–1996</td>
<td>3111</td>
<td>1% aqua</td>
<td>9.2</td>
<td>33/42b</td>
<td></td>
<td></td>
<td>Multicentre study, NACDG</td>
<td>Marks et al. (73)</td>
</tr>
<tr>
<td>Finland</td>
<td>1995–1996</td>
<td>9378</td>
<td>1% aqua</td>
<td>3.0</td>
<td>NS</td>
<td></td>
<td></td>
<td>Multicentre study</td>
<td>Hasan et al. (61)</td>
</tr>
<tr>
<td>People's Republic of China</td>
<td>1988–1996</td>
<td>1135</td>
<td>1% aqua</td>
<td>4.1</td>
<td>NS</td>
<td></td>
<td></td>
<td>One centre, Xuzhou</td>
<td>Liu et al. (74)</td>
</tr>
<tr>
<td>Germany, Austria</td>
<td>1990–1995</td>
<td>36 786</td>
<td>1% aqua/pet.</td>
<td>2.1/2.2/1.9</td>
<td>NS</td>
<td></td>
<td></td>
<td>Multicentre study, IVDK</td>
<td>Schnuch et al. (75)</td>
</tr>
<tr>
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<td>1992–1994</td>
<td>3526</td>
<td>1% aqua</td>
<td>7.8</td>
<td>64c</td>
<td></td>
<td></td>
<td>Multicentre study, NACDG</td>
<td>Marks et al. (76)</td>
</tr>
<tr>
<td>Austria</td>
<td>1992–1993</td>
<td>11 516</td>
<td>1% aqua</td>
<td>0.9/0.9/0.9</td>
<td>NS</td>
<td></td>
<td></td>
<td>Multicentre study</td>
<td>Kränke et al. (77)</td>
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<tr>
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<td>2295</td>
<td>1% aqua/pet.</td>
<td>5.7</td>
<td>NS</td>
<td></td>
<td></td>
<td>Multicentre study</td>
<td>Perrenoud et al. (78)</td>
</tr>
</tbody>
</table>

EECDRG, European Environmental and Contact Dermatitis Research Group http://orgs.dermis.net/content/e05eecdrg/index_ger.html; ESSCA, European Surveillance System on Contact Allergies www.essca-dc.org; IVDK, Informationsverbund Dermatologischer Kliniken (Information Network of Departments of Dermatology) www.ivdk.org; NACDG: North American Contact Dermatitis Group; NS, not stated.

aData provided back to approximately 1990. For pre-1990 literatures, see Fransway and Schmitz (11) and Fransway (29).
bDefinite/probable relevance (first number)/possible relevance (second number).
c‘Percentage includes: ‘possible relevance’.
dPercentage relevance for the 1% and 2% positive reactions together.
have to look for the name formaldehyde but also for those of the formaldehyde donors (86). In addition, it appears that labelling is not always reliable: in 5/67 creams purchased in Denmark, formaldehyde-releasers were present but were not declared on the label (80).

Indeed, in a group of 57 patients allergic to formaldehyde and well-instructed how to avoid products containing the allergen, 77% were still exposed to formaldehyde at follow-up 1–5 years later as shown by the analysis of the products (cosmetics, washing powders, dishwashing liquids, gloves and paper) brought in by them (84). Thus, even in patients actively trying to avoid products containing formaldehyde, the dermatitis will infrequently heal completely. Most patients will still suffer from exacerbations of dermatitis (81, 84, 87), though fewer in number than in those not paying attention to their allergy (84).

**Threshold for elicitation of contact allergic reactions in patients allergic to formaldehyde**  
*Patch test studies with formaldehyde and formaldehyde-containing products*

In their now classic and often cited investigations, Jordan et al. (88) performed double-blind controlled studies on formaldehyde threshold responses in nine allergic patients by repeated (three times, day 0, day 3, day 5, final reading at day 7) applications of patch tests at the same site in the axilla for 1 week with formaldehyde 0, 30, 60 and 100 p.p.m. in a 12% methanol in water vehicle. Five of them were selected on the basis of their known strong allergy to formaldehyde. At day 3, three patients had positive reactions to 100 p.p.m. formaldehyde, two to 60 p.p.m. and one to 30 p.p.m. More positive responses were observed 2 days later (day 5) and at day 7 (2 days after the removal of the third patch test materials): Four of nine patients had positive reactions to 30 p.p.m., 5 out of 9 to 60 and 6 out of 9 to 100 p.p.m. Two subjects reacting to 30 p.p.m. at 5 days were retested later and again had positive reactions after 5 days. Four non-allergic control subjects were negative (88).

The same protocol was later used to patch test two commercial creams preserved with 0.1% quaternium-15 (analysis with a polarographic method identified 100 p.p.m. free formaldehyde in both) in the same nine patients. Cream A was positive already at day 3 in 3 out of 9 patients and in 6 out of 9 at the final reading at day 7. For Cream B, these figures were 2 out of 9 and 5 out of 9, respectively. These results closely corresponded to the patch tests with solutions of 60–100 p.p.m. formaldehyde in methanol/aqua. 

Flyvholm et al. (89) patch tested 20 patients allergic to formaldehyde with a serial dilution of 25, 50, 250, 500, 5000 and 10 000 (1%) p.p.m. formaldehyde aqua. All 20 reacted to 10 000 p.p.m., 9 out of 20 to 5000 p.p.m., 3 out of 20 to 1000 p.p.m. (0.1%), 2 had a positive reaction down to 500 p.p.m. and 1 patient was positive to 250 p.p.m. formaldehyde aqua (89). Retesting the patient reacting to 250 p.p.m. 1 year later with 50, 100 and 250 p.p.m. showed a negative reaction.

In a similar study, 8 out of 35 formaldehyde allergic subjects reacted with closed patch testing down to 1000 p.p.m.; lower concentrations were not tested (90). In a dose-finding study using TRUE-test® materials, 5 out of 22 formaldehyde-sensitive patients reacted to concentrations <630 p.p.m. with serial dilutions of formaldehyde and one reacted down to 150 p.p.m. (91).

**Use tests with formaldehyde-containing products**

More important than the threshold for positive patch test responses is to determine which concentrations of formaldehyde may cause eczematous reactions when formaldehyde-containing products are applied under normal use conditions. In the above-mentioned studies of Jordan et al. (88), 11 formaldehyde-sensitive patients pump-sprayed 29 p.p.m. formaldehyde in a double-blind fashion from a 12% methanol/water vehicle into one axilla twice a day for 2 weeks. The vehicle served as a control in the other axilla. Two of the patients developed very mild perifollicular dermatitis to the formaldehyde site but not the control site. It was concluded that formaldehyde levels below 30 p.p.m. can be tolerated by most sensitive subjects if continually applied to areas like the axilla (88). The threshold for no response to a formaldehyde-containing antiperspirant in another study was 80 p.p.m., patients were reacting down to 150 p.p.m. (cited by (62). In an old study involving one formaldehyde-sensitive individual, flare of vesicular hand eczema could be provoked by immersing the finger in a 0.2 p.p.m. formaldehyde solution for 40 min (92).

In various studies, repeated open application tests (ROATs) have been performed with products, usually cosmetic creams, containing varying concentrations of formaldehyde-releasers such as diazolidinyl urea, quaternium-15, imidazolidinyl urea, 2-bromo-2-nitropropane-1,3-diol or DMDM hydantoin. The results of these studies are discussed in another part of this systematic review. The lowest concentrations of formaldehyde to which patients reacted were 200–300 p.p.m. It should be realized that most of these tests were conducted for a maximum of 1 week and on normal skin, usually on the upper arm. Prolonging the period of application to
2 weeks (or longer), applying the product to more sensitive areas such as the axilla, the neck or the face (12) may well result in more positive reactions and/or lower thresholds for a positive response. This may also be true for the situation where a product is used on damaged skin, which is often done with lubricants on dry or dermatitic skin.

Analytical tests to determine formaldehyde in products

There are several tests to determine the formaldehyde content in products.

The chromotropic acid method. This semi-quantitative method is based on a chemical reaction of chromotropic acid and free formaldehyde giving a violet discoloration. By comparing the intensity of the sample colour with those of standards, a rough estimation of the concentration of formaldehyde can be obtained. Unfortunately, other aldehydes and ketones can also react with chromotropic acid, giving yellow-brown discolorations that can interfere with the test (93–95).

The acetylacetone method. In this semi-quantitative method, formaldehyde reacts with acetylacetone in the presence of ammonia to form the yellow compound 3,5-diacetyl-1,4-dihydrolutidine (this method is sometimes also referred to as the lutidine method) (96). The intensity of the yellow colour can be compared with that of the standards to estimate the content of formaldehyde in the sample. If the product to be analysed is coloured itself, an extraction procedure with 1-butanol can first be performed. Quantification of the formaldehyde concentration can be achieved by using an UV-spectrophotometer (93, 96). This method was found to be more efficient for formaldehyde detection in a clinical laboratory (94). In about 80% of the cases, the results obtained with this test are similar to those with the chromotropic acid method (95).

High performance liquid chromatography (HPLC). This is a reliable method, of which various modifications have been described (94, 97–100).

Official EU method. The EU has an official method for determining total and free formaldehyde content in cosmetic products (101). The total formaldehyde content determined by this method also represents the amount of formaldehyde that may be available by the permitted formaldehyde-releasers, except for 2-bromo-2-nitropropane-1,3-diol and 5-bromo-5-nitro-1,3-dioxane, present in a product. The analysis is performed in three steps in the following sequence: identification of formaldehyde, spectrophotometric determination of total formaldehyde content in the products containing formaldehyde (based on the acetylacetone method) and HPLC determination (employing post-column derivatization) of free formaldehyde in the products that contain >0.05% total formaldehyde (101). For a detailed description of this method see Rastogi (37).

Tests for formaldehyde in clothing. The test most frequently used for determining formaldehyde in clothing is the American Association of Textile Chemists and Colorists (AATCC) Test Method 112–1990, ‘Formaldehyde release from fabric, sealed jar method’ (102, 103).

Tests for determining formaldehyde in the presence of formaldehyde donors. Quantification of free formaldehyde in the presence of formaldehyde donors is problematic. With the commonly applied methods, including the official EU method, the equilibrium formaldehyde – formaldehyde donor – is disturbed by the presence of the reagent, which binds free formaldehyde. This leads to new release of formaldehyde to maintain the equilibrium and thus, such methods may give too high and non-reproducible results. Quantitative $^{13}$C NMR spectroscopy is a purely physical method that does not affect the equilibrium and offers and excellent solution to this problem (104).

Frequency of Exposure to Formaldehyde and Formaldehyde-releasers

Data from Denmark: PROBAS database

The Danish Product Register Database (PROBAS) was established in 1979. It is a governmental database common for the authorities in the working environment and the external environment. PROBAS in March 2009 contained information on approximately 30 000 chemical products sold or used in production in Denmark that have been notified by their Danish or foreign enterprises. The main part of the registered products is notified (declared) according to legal demands for providing information on hazardous chemical products for occupational use. Other product categories are included, but often do not cover all marketed products (e.g. cosmetics and toiletries). The registration includes information on chemical composition with components identified by CAS numbers, danger labelling, product category, industrial area of use and quantities imported or manufactured. The registered data are kept confidential and public access is not possible (105).

The legislation on notification was changed in July 2004. In short, the products to be notified were extended to include most products covered by laws demanding material safety data sheets. Furthermore, information on quantities has to be updated every
other year. For information on the chemical composition of products, a 1% limit was introduced. Thus, only substances making up more than 1% of any given product have to be declared. However, for certain groups of substances, the limits are lower. Preservatives, for example, must always be reported. For toxic substances, carcinogens, mutagens and reproductive toxicants, the limit is 0.1%. Substances with lower limits in the EU list of toxic substances or the EU directive on classification should also be declared (106). As these rules demand the name of sensitizers to be declared on the label if the content is above 0.1%, the lower limit for contact allergens will be 0.1% (107). Further details on PROBAS are provided in Flyvholm et al. (105) and Flyvholm (108).

The data presented here include products registered by March 2009 which are active on the Danish market and computerized with information on chemical composition. All products containing the studied substances either directly or from raw materials are included. Data on substances notified by less than three companies were excluded.

**Formaldehyde (releasers) in PROBAS.** Table 6 provides the PROBAS data on formaldehyde and formaldehyde-releasers. For each chemical, the following data are tabulated: total number of registered products containing it, number of products per product category containing the chemical plus percentage, use volume of each chemical and each category in tonnes/year, and product category specification.

Formaldehyde was registered in 2363 products with a total volume of 26 153 tonnes per year. The main product categories by volume were raw materials and intermediate products (25 967 tonnes) followed by biocides/pesticides for non-agricultural uses (659 tonnes). By number of products, paints/lacquers/ varnishes were the most frequently registered product categories for formaldehyde (n = 1306), followed by cleaning agents (n = 222).

The highest volumes of registered use of formaldehyde-releasers were scored by polyoxymethylene urea (7596 tonnes) and tris(N-hydroxyethyl)hexahydrotriazine (1709 tonnes). By number of registered products, the most frequent were 2-bromo-2-nitropropane-1,3-diol (n = 549), 1,6-dihydroxy-2,5-dioxahexane (n = 289) and polyoxymethylene urea (n = 182).

The most important product categories containing formaldehyde or formaldehyde-releasers are biocides/pesticides, paints/lacquers/ varnishes, cleaning/washing agents and metalworking fluids (cooling agents for metal processing) (Table 6).

Nineteen of the 42 formaldehyde-releasers could not be found in PROBAS. In most cases, e.g. the formaldehyde-releasers used as durable press chemical finishes, they are used in products (in this example clothes and textiles) not covered by the database because Danish law does not require their notification in PROBAS. This also explains why the numbers of registered products containing typical cosmetics preservatives such as quaternium-15, imidazolidinyl urea and diazolidinyl urea are so low: only a very limited number of cosmetics are registered in PROBAS. The same holds true for some other releasers such as Bioban® CS 1135 and Bioban® P-1487, which are reportedly used in metalworking fluids. These need not to be notified and their absence in PROBAS, therefore, does not indicate that they are actually not used in such cooling agents for metal processing.

The data on the occurrence of formaldehyde and formaldehyde-releasers in registered chemical product should be interpreted with caution. Thus, when formaldehyde and formaldehyde-releasers are registered in a particular product category, this can form an important part of an exposure assessment. However, when no registration is found for a certain product type, it cannot be concluded that this particular category will not contain the allergen. Products for 'private consumer use only', for example, are not registered in PROBAS at all.

**Other data on exposure to formaldehyde and formaldehyde-releasers**

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. 30% proved to contain (free and bound) formaldehyde (37). 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 (43). A 1993 study of washing and cleaning agents showed that formaldehyde-releasing compounds were among the most commonly registered preservatives in such products (36). In 1998, 100 moisturizers sold in Sweden were analysed for the presence and amount of preservatives. Thirty-five products contained a formaldehyde-releaser. Ten products contained more than 200 p.p.m. formaldehyde; in nine of these a formaldehyde-releaser was present. The concentrations of the releasers did not exceed the EU-permitted maximum in any case (109).

In the USA, imidazolidinyl urea was present in 13.0%, DMDM hydantoin in 5.0%, quaternium-15 in 3.7%, diazolidinyl urea in 3.6% and formaldehyde per se as a preservative in <1% of approximately 20 000 formulae registered with the FDA in 1996. Imidazolidinyl urea ranked third in the top 10 of
Table 6. Presence of formaldehyde and formaldehyde releasers in chemical products registered in the Danish Product Register Database, March 2009 as active on the market. Data on substances notified by less than three companies are not shown.*

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Number of registered products</th>
<th>Percentage of products in category</th>
<th>Volume Tonnes/year</th>
<th>Product category</th>
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<tbody>
<tr>
<td>Formaldehyde</td>
<td>2363</td>
<td>26 152.95</td>
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</tr>
<tr>
<td>56</td>
<td>5.38</td>
<td>103.11</td>
<td>Adhesives</td>
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</tr>
<tr>
<td>63</td>
<td>10.59</td>
<td>8.31</td>
<td>Binding agents - for binding together the individual constituents in the product</td>
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</tr>
<tr>
<td>51</td>
<td>4.59</td>
<td>658.52</td>
<td>Biocides - pesticides for non agricultural uses</td>
<td></td>
</tr>
<tr>
<td>222</td>
<td>5.37</td>
<td>0.53</td>
<td>Cleaning/washing agents</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>7.67</td>
<td>0.01</td>
<td>Colouring agents</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>8.42</td>
<td>21.04</td>
<td>Construction materials (building materials)</td>
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</tr>
<tr>
<td>7</td>
<td>2.27</td>
<td>0.00</td>
<td>Cooling agents for metal processing</td>
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</tr>
<tr>
<td>12</td>
<td>3.72</td>
<td>0.01</td>
<td>Cosmetics</td>
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<td>79</td>
<td>6.86</td>
<td>6.49</td>
<td>Filling agents</td>
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<td>11</td>
<td>31.43</td>
<td>1.22</td>
<td>Fixing agents - for fixing chemicals/particles to surfaces and fibres (not photo chemicals)</td>
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</tr>
<tr>
<td>18</td>
<td>10.34</td>
<td>0.08</td>
<td>Flooring materials (joint-less floors)</td>
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<tr>
<td>10</td>
<td>7.04</td>
<td>0.00</td>
<td>Galvano-technical agents - for metal surface treatment</td>
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</tr>
<tr>
<td>59</td>
<td>76.62</td>
<td>0.01</td>
<td>Glazing materials, enamels etc.</td>
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</tr>
<tr>
<td>5</td>
<td>1.52</td>
<td>0.05</td>
<td>Hardeners</td>
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</tr>
<tr>
<td>18</td>
<td>9.18</td>
<td>3.04</td>
<td>Impregnation/proofing - for protection from damp, fungus etc.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.46</td>
<td>0.00</td>
<td>Insulating materials - to protect from noise, cold, electricity, dust etc.</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>10.00</td>
<td>2.49</td>
<td>Laboratory chemicals</td>
<td></td>
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<td>0.00</td>
<td>Lubricants</td>
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<td>2.44</td>
<td>4.99</td>
<td>Metal surface treatment remedies</td>
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</tr>
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<td>7</td>
<td>5.11</td>
<td>9.65</td>
<td>Moulding compounds</td>
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<td>1.57</td>
<td>0.00</td>
<td>Paint and varnish removers</td>
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</tr>
<tr>
<td>1306</td>
<td>22.53</td>
<td>2.97</td>
<td>Paint, lacquers and varnishes</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.17</td>
<td>0.02</td>
<td>pH-regulating agents</td>
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</tr>
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<td>6</td>
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<td>Plant protection - agricultural pesticides</td>
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</tr>
<tr>
<td>15</td>
<td>3.00</td>
<td>0.02</td>
<td>Polishing agents</td>
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<tr>
<td>58</td>
<td>11.26</td>
<td>0.02</td>
<td>Printing inks</td>
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<tr>
<td>6</td>
<td>1.01</td>
<td>0.04</td>
<td>Process regulators (synthesis regulators)</td>
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</tr>
<tr>
<td>14</td>
<td>2.36</td>
<td>25 967.47</td>
<td>Raw materials and intermediate products</td>
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</tr>
<tr>
<td>3</td>
<td>2.14</td>
<td>0.00</td>
<td>Rinsing agents</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>4.31</td>
<td>0.08</td>
<td>Rust inhibitors</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.22</td>
<td>0.12</td>
<td>Sanitation agents - for cleaning up liquids and other materials</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>15.38</td>
<td>0.03</td>
<td>Sequestering agents</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.56</td>
<td>0.06</td>
<td>Softeners (plastic-, rubber-, paint-, adhesive softeners)</td>
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</tr>
<tr>
<td>14</td>
<td>7.57</td>
<td>0.02</td>
<td>Surface treatment for paper, cardboard and other non-metals</td>
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<tr>
<td>16</td>
<td>2.40</td>
<td>0.33</td>
<td>Surface-active agents - (surfactants, detergents)</td>
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<td>35</td>
<td>39.33</td>
<td>1.50</td>
<td>Toners</td>
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<td>8</td>
<td>10.67</td>
<td>0.01</td>
<td>Writing agents</td>
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<td>Benzylhemiformal</td>
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<td>0.85</td>
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<td>3</td>
<td>0.97</td>
<td>0.03</td>
<td>Cooling agents for metal processing</td>
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</tr>
<tr>
<td>65</td>
<td>1.12</td>
<td>0.01</td>
<td>Paint, lacquers and varnishes</td>
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</tr>
<tr>
<td>Bioban CS 1246®</td>
<td>16</td>
<td>0.19</td>
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<td>2.27</td>
<td>0.18</td>
<td>Cooling agents for metal processing</td>
<td></td>
</tr>
<tr>
<td>2-Bromo-2-nitropropane-1,3-diol</td>
<td>549</td>
<td>69.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>2.59</td>
<td>0.10</td>
<td>Adhesives</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.85</td>
<td>0.13</td>
<td>Binding agents - for binding together the individual constituents in the product</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>1.98</td>
<td>43.34</td>
<td>Biocides - pesticides for non agricultural uses</td>
<td></td>
</tr>
<tr>
<td>111</td>
<td>2.69</td>
<td>0.70</td>
<td>Cleaning/washing agents</td>
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</tr>
<tr>
<td>8</td>
<td>1.33</td>
<td>0.01</td>
<td>Colouring agents</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.28</td>
<td>0.00</td>
<td>Construction materials (building materials)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>5.88</td>
<td>0.14</td>
<td>Cosmetics</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1.13</td>
<td>0.00</td>
<td>Filling agents</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>7.65</td>
<td>0.10</td>
<td>Impregnation/proofing - for protection from damp, fungus etc.</td>
<td></td>
</tr>
<tr>
<td>Chemical</td>
<td>Number of registered products</td>
<td>Percentage of products in category</td>
<td>Volume Tonnes/year</td>
<td>Product category</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------</td>
<td>----------------------------------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------------------------</td>
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<tr>
<td>Dimethylol urea</td>
<td>78</td>
<td>7.50</td>
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<td></td>
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<tr>
<td>Dimethyloxy-2,5-dioxahexane</td>
<td>289</td>
<td>26.13</td>
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<td></td>
</tr>
<tr>
<td>5-Bromo-5-nitro-1,3-dioxane</td>
<td>62</td>
<td>0.47</td>
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<td></td>
</tr>
<tr>
<td>5-Deoxy-5-nitro-1,3-dioxane</td>
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<td>0.61</td>
<td></td>
<td>Cleaning/washing agents</td>
</tr>
<tr>
<td>5-Deoxy-5-nitro-1,3-dioxane</td>
<td>24</td>
<td>7.43</td>
<td></td>
<td>Cosmetics</td>
</tr>
<tr>
<td>5-Deoxy-5-nitro-1,3-dioxane</td>
<td>5</td>
<td>1.00</td>
<td></td>
<td>Polishing agents</td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>10</td>
<td>0.90</td>
<td>24.85</td>
<td>Biocides - pesticides for non agricultural uses</td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
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<td>0.31</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>11</td>
<td>1.83</td>
<td>0.00</td>
<td>Colouring agents</td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>5</td>
<td>1.62</td>
<td>0.39</td>
<td>Cooling agents for metal processing</td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>8</td>
<td>0.69</td>
<td>0.01</td>
<td>Filling agents</td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>174</td>
<td>3.00</td>
<td>0.22</td>
<td>Paint, lacquers and varnishes</td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>15</td>
<td>2.91</td>
<td>0.50</td>
<td>Printing inks</td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>3</td>
<td>1.62</td>
<td>0.00</td>
<td>Surface treatment for paper, cardboard and other non-metals</td>
</tr>
<tr>
<td>1,6-Dihydroxy-2,5-dioxahexane</td>
<td>4</td>
<td>0.60</td>
<td>0.01</td>
<td>Surface-active agents - (surfactants, detergents)</td>
</tr>
<tr>
<td>Methenamine</td>
<td>117</td>
<td>9.98</td>
<td>53.25</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>36</td>
<td>0.29</td>
<td>0.04</td>
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</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
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<td>1.53</td>
<td>0.28</td>
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</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>10</td>
<td>0.24</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>3</td>
<td>0.61</td>
<td>0.02</td>
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</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>49</td>
<td>0.85</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>3</td>
<td>0.59</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>91</td>
<td>0.31</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>11</td>
<td>0.76</td>
<td>2.77</td>
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</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>3</td>
<td>1.57</td>
<td>1.77</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>13</td>
<td>0.31</td>
<td>1.04</td>
<td>Cleaning/washing agents</td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>11</td>
<td>0.76</td>
<td>2.77</td>
<td>Lubricants</td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>3</td>
<td>1.57</td>
<td>1.77</td>
<td>Paint and varnish removers</td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>83</td>
<td>0.67</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>4</td>
<td>0.67</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>3</td>
<td>0.26</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>47</td>
<td>0.81</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Methylenebis(5-methyloxazolidine)</td>
<td>13</td>
<td>2.52</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>
most frequently used cosmetic preservatives after methyl- and propylparaben, DMDM hydantoin seventh, quaternium-15 ninth and diazolidinyl urea tenth (110). 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 cosmetic products registered at the FDA was in 2003 (111).

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 (80).

Discussion

The main subject of this literature study is the relationship between formaldehyde-releasers and sensitivity to formaldehyde. In this part of our four-part review, we have identified the currently known – and alleged – formaldehyde-releasers (Table 2). They are discussed in detail in the other parts of this review. Therefore, the discussion here is limited to some aspects of formaldehyde contact allergy.

It is remarkable that the frequency of sensitization to formaldehyde in the USA has consistently been (much) higher than in European countries for the past 20 years. The regularly reported ongoing prevalence study of the NACDG showed steady

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Number of registered products</th>
<th>Percentage of products in category</th>
<th>Volume Tonnes/year</th>
<th>Product category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N-Methylol ethanolamine</strong></td>
<td>33</td>
<td>2.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>2.60</td>
<td>2.08</td>
<td>Cooling agents for metal processing</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>0.33</td>
<td>0.08</td>
<td>Paint, lacquers and varnishes</td>
</tr>
<tr>
<td><strong>Paraformaldehyde</strong></td>
<td>8</td>
<td>1.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Polyoxymethylene urea</strong></td>
<td>182</td>
<td>7595.94</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>1.25</td>
<td>1122.75</td>
<td>Adhesives</td>
</tr>
<tr>
<td></td>
<td>148</td>
<td>2.55</td>
<td>56.49</td>
<td>Paint, lacquers and varnishes</td>
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<tr>
<td><strong>Quaternium-15</strong></td>
<td>30</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>3.41</td>
<td>0.00</td>
<td>Cosmetics</td>
</tr>
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<td><strong>Sodium hydroxymethylglycinate</strong></td>
<td>60</td>
<td>1.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>1.16</td>
<td>0.90</td>
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<td>4</td>
<td>2.86</td>
<td>0.03</td>
<td>Rinsing agents</td>
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<tr>
<td><strong>Tetramethylol acetylene diurea</strong></td>
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<td>1.70</td>
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<td>7</td>
<td>1.17</td>
<td>0.07</td>
<td>Colouring agents</td>
</tr>
<tr>
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<td>7</td>
<td>0.61</td>
<td>0.03</td>
<td>Filling agents</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>1.14</td>
<td>1.58</td>
<td>Paint, lacquers and varnishes</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.20</td>
<td>0.01</td>
<td>Polishing agents</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.62</td>
<td>0.01</td>
<td>Surface treatment for paper, cardboard and other non-metals</td>
</tr>
<tr>
<td><strong>Tris(hydroxymethyl)-nitromethane</strong></td>
<td>84</td>
<td>0.19</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>0.31</td>
<td>0.08</td>
<td>Cleaning/washing agents</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>0.69</td>
<td>0.08</td>
<td>Paint, lacquers and varnishes</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.48</td>
<td>0.01</td>
<td>Sanitation agents - for cleaning up liquids and other materials</td>
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<tr>
<td><strong>Tris(N-hydroxyethyl) hexahydrotriazine</strong></td>
<td>103</td>
<td>1708.54</td>
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<td></td>
</tr>
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<td>7</td>
<td>0.63</td>
<td>1.02</td>
<td>Biocides - pesticides for non agricultural uses</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.22</td>
<td>0.05</td>
<td>Cleaning/washing agents</td>
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<tr>
<td></td>
<td>11</td>
<td>3.57</td>
<td>0.97</td>
<td>Cooling agents for metal processing</td>
</tr>
<tr>
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<td>5</td>
<td>0.35</td>
<td>3.10</td>
<td>Lubricants</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>0.71</td>
<td>3.47</td>
<td>Paint, lacquers and varnishes</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.78</td>
<td>0.02</td>
<td>Printing inks</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.59</td>
<td>0.04</td>
<td>Rust inhibitors</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3560</td>
<td>12.10</td>
<td>40 125.11</td>
<td></td>
</tr>
</tbody>
</table>

*Cosmetics and metalworking fluids do not need to be notified by legal demand. Therefore, the data for these product categories are not representative for the Danish market.
prevalence rates of 7.8% in 1992–1994 (76), 9.2% in 1994–1996 (73), 9.3% in 1996–1998 (71), 9.2% in 1998–2000 (68) and 8.4% in 2001–2002 (62). These figures are paralleled by data from other USA clinics: 6.8% (1988–1997, Boston, Albert et al. (9)), 7.9% (1998–2000 Mayo Clinic, Wetter et al. (67)) and 9.0% (2001–2005, Mayo Clinic, Davis et al. (55)). In most European countries, prevalence rates vary between 2% and 3% (Table 5), and in the recent multicentre European investigations performed by the European Environmental and Contact Dermatitis Research Group (EECDRG) and the European Surveillance System on Contact Allergies (ESSCA), prevalence rates were between 2.0% and 2.3% (59, 60, 65). These figures, both from the USA and from Europe, thus seem to be reproducible and real. With the current knowledge, the causes of such major differences are not readily found. This topic will be dealt with separately.

Patch testing with formaldehyde is problematic. Former test concentrations of 3–5% resulted in many false-positive reactions. Currently, 1% aqua is the standard for patch testing. However, there are indications that this concentration is too low, resulting in (many) false-negative reactions: of 98 patients with an allergic reaction to formaldehyde 2% aqua, only 59 (60%) reacted to the currently used formaldehyde 1% aqua (46). This may indicate that up to 40% of allergic patients are missed when tested with formaldehyde 1% aqua only (46). We suggest that further research into this matter be done to clarify this important issue.

Determining the relevance of a positive reaction to formaldehyde is another challenging problem for the dermatologist. The use of formaldehyde and formaldehyde-releasers is widespread in cosmetics, toiletries, household products and industry. With current mandatory labelling in the USA and the EU, the presence of formaldehyde (releasers) in cosmetics is relatively easy to establish. However, this does not apply to household and industrial products*. The presence of free formaldehyde in concentrations over 0.05% (500 p.p.m.) must be declared on the label of such products, but it has been shown convincingly that exposure to lower levels may induce allergic contact dermatitis (12, 88, 112). Conversely, the fact that a product is labelled to contain formaldehyde or a formaldehyde-releaser does not implicitly mean that it is harmful to the formaldehyde-sensitive patient, as the concentration of free formaldehyde may well be below the elicitation threshold for the particular patient. From the formula it cannot be determined how much free formaldehyde is present.

To complicate things further, a patient is usually exposed to many products containing free formaldehyde that may separately not pose a threat, but when used in combination or sequentially this may break through the threshold for elicitation of allergic contact dermatitis. Therefore, only rarely – in the case of formaldehyde sensitivity – can a clear-cut relationship be established between the use of a particular product and induction or exacerbation of dermatitis, thereby ascertaining relevance. Indeed, in the NACDG studies, the percentages of patients with ‘possible relevance’ far exceeded that of the percentage for ‘definite/probable relevance’ (62, 68, 73). The difficulty of finding relevant products is also attested by the fact that even in patients actively trying to avoid products containing formaldehyde, the dermatitis will infrequently heal completely. Most patients will still suffer from exacerbations of dermatitis (81, 84, 87).

What concentration of formaldehyde is safe for sensitive patients remains, even though several investigations have addressed this issue, largely unknown. There is a lack of eliciting threshold data based on systematic investigations and an obvious need for experimental studies illustrating the relevance of formaldehyde exposure in a dose–response manner on healthy and diseased skin in formaldehyde-sensitive individuals (46).

Levels of 200–300 p.p.m. free formaldehyde in cosmetic products have been shown to induce dermatitis from short-term use on normal skin. It may be assumed that thresholds of elicitation are lower when these or other topical products are used on more sensitive skin (e.g. the axillae), for longer periods of time or on diseased skin. This demonstrates beyond doubt that EU legislation, stipulating that all finished products containing >500 p.p.m. free formaldehyde must be labelled with the warning ‘contains formaldehyde’, is not strict enough and the concentration required for the labelling should be lowered. We suggest that more extensive use test studies with formaldehyde-containing products in formaldehyde-sensitive studies be performed to determine a ‘no-effect level’ for elicitation of allergic contact dermatitis from single product usage.

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References


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