Formaldehyde-releasers

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Review Article

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 Several (nomenclature) mistakes and outdated information are discussed.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.

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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

Table 1. Data in the literature about formaldehyde-releasers that appear to be wrong or outdated (1–8)

Presented as formaldehyde releaser (chemical name and/or trade name)	Comments
Bakzid® P (mixture of cyclic amino-acetals and organic amine salts)	The trade name Bakzid® P is probably not used currently. However, some Bakzid® products contain the formaldehyde releaser tris(*N*-hydroxyethyl) hexahydrotriazine (triazinetriethanol)
Biocide® DS 5249 (1,2-benzisothiazolin-3-one + a formaldehyde releaser)	Trade name currently not used
Dantoin MDMH (methylaldimethoxy-methan formal)	Neither name can be identified
Forcide® 78 (mixture of triethylhexahydro *s*-triazine and trihydroxyethylhexahydro *s*-triazine)	Forcide® 78 is the current trade name for 2-hydroxymethylaminoethanol-tri-*N*-ethylhydroxy-2-aminomethylene
Glutaraldehyde	Glutaraldehyde occasionally cross-reacts with formaldehyde, but in the literature it is not found to be a formaldehyde releaser
Grotan® HD (*N*-methylol-chloracetamide)	Grotan® HD is a current trade name for tris(*N*-hydroxyethyl) hexahydrotriazine (triazinetriethanol)
Hexamidine	Hexamidine in the literature is not a found to be a formaldehyde releaser
Imidazolidinyl urea (Euxyl® K 200)	Trade name Euxyl® K 200 is probably currently not used
KM 103	This name is probably currently not in use. There are, however, various chemicals named KM followed by a number, of which KM 200 (alcohol) contains the formaldehyde releaser tris(*N*-hydroxyethyl) hexahydrotriazine (triazinetriethanol)
MDM hydantoin (Dantoin®, Dantoin® 685)	Dantoin® is used as synonym for 1,3-dichloro-5,5-dimethylhydantoin and for phenytoin sodium. The trade name Dantoin® 685 is probably currently not used
Parmetol®l K50 (*N*-methylol-chloracetamid, *O*-formal of benzyl alcohol)	The name Parmetol® K 50 was only found as being a registered trade name in Canada for a mixture of 13% chloroacetamide and 7.3% paraformaldehyde (under the company Gray Products)
Preventol® D1 (1-(3-chloroallyl)-3,5, 7-triaza-1-azoniaadamantanechloride benzyl formal)	Chemical name is incorrect, benzyl formal must be deleted. The trade name Preventol® D1 is probably currently not in use
Preventol® D2 (benzylhemiformal)	Preventol® D2 is in chemical databases used as a trade name for 1,1'-(methylenebis(oxymethylene)) bis-benzene, but also used for benzylhemiformal
Preventol® D3 (chlormethylacylamino methanol)	The trade name Preventol® D3 is probably currently not in use. Chemical name chlormethylacylamino methanol cannot be identified in chemical databases
Preventol® D3/D5 (*N*-methylol-chloracetamide)	The trade names Preventol® D3 and D5 are probably currently not in use

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 recommend avoidance of products containing *any* releaser (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

Table 2. Formaldehyde and reported formaldehyde-releasers[a] (adapted from Andersen et al. (1), Timmer (2), Flyvholm (3), Fiedler (4), Flyvholm and Andersen (5), Dahlquist and Fregert (6), Geier (7) and Geier et al. (8))

Commonly used name	IUPAC name	Other synonyms	Current trade names[b]	CAS number
(A) Chemicals for which adequate clinical data are available to identify them as formaldehyde-releasers beyond doubt				
Benzylhemiformal (INCI)	Phenylmethoxymethanol	(Benzyloxy)methanol	Akyposept®B [Preventol® D2; See there]	14548-60-8
Bioban CS 1135®	4,4-Dimethyloxazolidine; 3,4,4-trimethyloxazolidine		Bioban CS 1135®	81099-36-7 (ingred. 75673-43-7 and 51200-87-4)
Bioban CS 1246®	5-Ethyl-3,7-dioxa-1-azabicyclo[3.3.0] octane	7-Ethylbicyclo-oxazolidine	Bioban CS-1246®; Chemtan A60®; Oxazolidine-E®; Zoldine ZE®;	7747-35-5
Bioban P-1487®	4-[2-(Morpholin-4-ylmethyl)-2-nitro-butyl]morpholine; 4-(2-nitrobutyl) morpholine	Mixture of nitrobutylmorpholine and ethylnitrotrimethylenedi morpholine	Bioban P-1487®	37304-88-4 (ingred. 1854-23-5 and 2224-44-4)
2-Bromo-2-nitropropane -1,3-diol (INCI)	As in column 1	Bromonitropropanediol; Bronopol	Bronopol®; Chemynol BP®; Myacide Pharma BP®; Onyxide 500®	52-51-7
Diazolidinyl urea (INCI)	1-[1,3-bis(hydroxymethyl)-2, 5-dioxo-imidazolidin-4-yl]-1,3-bis(hydroxymethyl) urea	*N,N'*-bis(hydroxymethyl)urea	Abiol Forte®; Germall II®; Liposerve DU®; Nipa Biopure 200®	78491-02-8
Dihydroxydimethylolethyleneurea, methylated	4,5-Dihydroxy-1,3-bis(hydroxymethyl)-imidazolidin-2-one, methylated	Dimethylolglyoxalurea, methylated	Fixapret® (various); Freerez PKF®; Knittex LE®; Permafresh® (various); Sumitex® (various)	68411-81-4
1,3-Dimethyl-4,5-dihydroxyethyleneurea	4,5-Dihydroxy-1,3-dimethylimidazolidin-2-one		Fixapret NF®	3923-79-3
Dimethylhydantoin formaldehyde resin	5,5-Dimethylimidazolidine-2, 4-dione, formaldehyde	Formaldehyde, polymer with 5,5-dimethyl-2,4-imidazolidinedione; DMHF		26811-08-5
Dimethyloldihydroxyethyleneurea	4,5-Dihydroxy-1,3-bis (hydroxymethyl)-imidazolidin-2-one	1,3-Bis(hydroxymethyl)-4,5-dihydroxy-2-imidazolidinone	Fixapret® (various); Permafresh® (various)	1854-26-8
Dimethylolethyleneurea	1,3-Bis(hydroxymethyl) imidazolidin-2-one		Fixapret AH®	136-84-5

Table 2. (*Continued*)

Commonly used name	IUPAC name	Other synonyms	Current trade names[b]	CAS number
Dimethylolpropyleneurea	1,3-Bis(hydroxymethyl) -1,3-diazinan-2-one	DMPU; Tetrahydro-1,3-bis(hydroxymethyl)-1H-pyrimidin-2-one	Fixapret PH®; Knittex PRS®	3270-74-4
Dimethylol urea (INCI)	1,3-Bis(hydroxymethyl) urea	*N,N'*-Bis(hydroxymethyl)urea; Carbamol; Dihydroxymethylurea; *N,N'*-dimethylolurea; Dimethylurea; Oxymethurea (MI); Urea formaldehyde	Kaurit S®; Methural®; Permafresh 477®; Urofix®	140-95-4
DMDM hydantoin (INCI)	1,3-Bis(hydroxymethyl)-5, 5-dimethyl-imidazolidine-2,4-dione	Dimethyloldimethyl- hydantoin; 1,3-dimethylol-5,5-dimethyl- hydantoin; DMDMH	Cosept DM®; Dekafald®; Glydant® (2000, XL-1000); Lanodant DM®; Mackstat DM®; Microcare DH®	6440-58-0
Ethylene urea	Imidazolidin-2-one	2-Imidazolidinone (MI); 2-Oxoimidazolidine		120-93-4
Forcide 78® I[c]	(Z)-3-(Bis(2-hydroxyethyl)amino)-2-(2-hydroxyethyl-(hydroxymethyl)amino) prop-2-en-1-ol	2-Hydroxymethylamino- ethanol-tri-*N*-ethylhydroxy-2-amino-methylene	Forcide® 78[d]	77044-78-1
Forcide 78® II[e]	1,3,5-Triethyl-1,3,5-triazinane (b)	(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	(b) Vancide-TH®; Forcide® 78[d]	7779-27-3 (b)
Formaldehyde (INCI, MI)	Formaldehyde	Formalin; Methanal; Methyl aldehyde; Oxymethylene		50-00-0
Glyoxalurea	4,5-Dihydroxyimidazolidin-2-one	Dihydroxyethyleneurea; Glyoxalmonoureine		3720-97-6
Imidazolidinyl urea (INCI, MI)	3-[3-(Hydroxymethyl)-2,5-dioxo-imidazolidin-4-yl]-1-[[[3-(hydroxymethyl)-2,5-dioxo-imidazolidin-4-yl] carbamoylamino]methyl]urea	Bis(methylolhydantoin urea) methane; Imidurea (MI)	Germall 115®; Liposerve IU®; Nipa Biopure 100®; Protacide U-13®; Unicide U-13®	39236-46-9

Table 2. (*Continued*)

Commonly used name	IUPAC name	Other synonyms	Current trade names[b]	CAS number
MDM hydantoin (INCI)	1-(Hydroxymethyl)-5,5-dimethyl-imidazolidine-2,4-dione	1-Hydroxymethyl-5,5-dimethyl hydantoin (MI); MDMH; Methylol dimethyl hydantoin; Monomethylol dimethyl hydantoin	Glycoserve®	116-25-6
Methenamine (INCI, MI)	Not available	Aminoform; Formamine; Hexamethylene tetramine; Hexamine; Methenamide	Cystamine®; Urotropine®; Vulkacit H30®	100-97-0
N,N'-Methylenebis(5-methyloxazolidine)	5-Methyl-3-[(5-methyloxazolidin-3-yl) methyl]oxazolidine		Grotan OX®	66204-44-2
4,4'-Methylenedimorpholine	4-(Morpholin-4-ylmethyl)morpholine	Bismorpholinomethane; Dimorpholinomethane; 4,4'-methylenebis-morpholine		5625-90-1
N-Methylol-chloracetamide	2-Chloro-*N*-(hydroxymethyl) acetamide	Chloroacetamide-*N*-methylol	Grotan DF-35®	2832-19-1
Methylol urea	Hydroxymethylurea	*N*-(hydroxymethyl)urea; Methyl hydroxyurea; Mono(hydroxymethyl)urea; Monomethylolurea;		1000-82-4
Paraformaldehyde	Formaldehyde	Paraform; Poly(oxymethylene)	Aldacide®; Formagene®	30525-89-4
Polyoxymethylene melamine (INCI)	Not available	Melamine, polymer with formaldehyde; Melamine/formaldehyde resin; Nanoplast		9003-08-1
Polyoxymethylene urea (INCI)	Formaldehyde; urea	Polynoxylin; Urea–formaldehyde resin; Urea, polymer with formaldehyde	Karbamol® (B/M); Kaurit® (285FL, 240); Uformite®	9011-05-6
Preventol D2®[f]	Phenylmethoxymethoxy-methylbenzene	Bis(benzyloxy)methane; Mixture of hydroxymethylene and polyhydroxymethylene monobenzylether; 1,1'-(Methylenebis(oxymethylene)) bis-benzene	Preventol D2®. This trade name is also often used for benzylhemiformal	2749-70-4
Propyleneglycol hemiformal	Not available			
Quaternium-15 (INCI, MI)		*N*-(3-Chloroallyl)hexaminium chloride; Chloroallylhexaminium chloride; 1-(3-Chloroallyl)-3,5,7-triaza-1-azonia-adamantane chloride; Hexamethylene tetramine chloroallyl chloride	Cosept 200®; Dowicide Q®; Dowicil® (75, 200)	4080-31-3

Table 2. (*Continued*)

Sodium hydroxymethyl-glycinate (INCI)	Not available	Glycine, *N*-(hydroxymethyl)-, sodium salt (1:1); *N*-hydroxymethylglycine (mono)sodium salt; Sodium *N*-(hydroxymethyl)glycinate	Suttocide A®	70161-44-3
Tetramethylol acetylenediurea	2,4,6,8-Tetrakis(hydroxymethyl)-2,4,6,8-tetraazabicyclo[3.3.0] octane-3,7-dione	Tetrakis(hydroxymethyl) glycoluril; Tetramethylolglycoluril	Fixapret 140®	5395-50-6
Tris(*N*-hydroxyethyl) hexahydrotriazine	2-[4,6-Bis(2-hydroxyethyl)1,3,5-triazinan-2-yl]ethanol	Hexahydro-1,3,5-tris(hydroxyethyl)triazine; Triazinetriethanol; Trihydroxyethylhexahydro s-triazine; 1,3,5-Trihydroxyethylhexa-hydrotriazine	Forcide 78® (see there); Grotan® (B, BK, HD); Onyxide 200®; Roksol T 1–7®	4719-04-4
Tris(hydroxymethyl)-nitromethane (INCI, MI)	2-(Hydroxymethyl)-2-nitropropane-1,3-diol	Nitromethylidynemethanol; Trimethylolnitromethane; Tris nitro	Tris Nitro®	126-11-4
(B) Chemicals for which adequate clinical data are lacking to identify them as formaldehyde-releasers beyond doubt				
5-Bromo-5-nitro-1,3-dioxane (INCI)	5-Bromo-5-nitro-1,3-dioxane	Bromonitrodioxane	Bronidox®; Dekasol® 5 & 10	30007-47-7
1,6-Dihydroxy-2,5- dioxahexane	2-(Hydroxymethoxy) ethoxymethanol	Dimethylol glycol; 2,5-Dioxahexane-1,6-diol; (Ethylenedioxy)dimethanol; Ethyleneglycoldiformal	Dascocide 9®; Nipacide FC®	3586-55-8

Table 2. (*Continued*)

Commonly used name	IUPAC name	Other synonyms	Current trade names[b]	CAS number
Hydantoin	Imidazolidine-2,4-dione	Glycolylurea; 2-Hydroxy-2-imidazolin-4 (or 5)-one		461-72-3
(Hydroxymethyl)-5,5-dimethyl-2-4-imidazolidinedione	Not available			27636-82-4
3-(Hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione	As in column 1	4,4-Dimethyl-2,5-dioxo-1-imidazolidenemethanol		16228-00-5
Methylal (INCI, MI)	Dimethoxymethane	2,4-dioxapentane; Formal; Formaldehyde dimethyl acetal	Anesthenyl®	109-87-5
N-Methylolethanolamine	2-(Hydroxymethylamino)ethanol		Troysan 174®	34375-28-5

INCI, INCI name (*CTFA Cosmetic Ingredient Dictionary and Handbook*, 11th edition. Washington, DC, USA, The Cosmetic, Toiletry and Fragrance Association, Inc., 2006. Available at: www.personalcarecouncil.org); MI, Merck Index name (*The Merck Index*, 14th edition. Whitehouse Station, NJ, USA, Merck & Co., Inc., 2006. Available at: www.merck.com).

[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:

(1) *The CTFA Cosmetic Ingredient Dictionary and Handbook*, 11th edition. Washington, DC, USA, The Cosmetic, Toiletry and Fragrance Association, Inc., 2006.

(2) *The Merck Index*, 14th edition. Whitehouse Station, NJ, USA, Merck & Co., Inc., 2006.

(3) The following databases:

(a) Chemical Name Synonym Finder (www.chemindustry.com);

(b) Comparative Toxicogenomics Database (http://ctd.mdibl.org/voc.go?type=chem);

(c) United States National Library of Medicine: ChemIDplus Advanced (http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp);

(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.

[c]Description of Forcide 78® as in Hamann (19) and the above-mentioned chemical databases.

[d]Forcide 78® is also used as a trade name by Redox Pty Ltd (www.redox.com/msds/data/TRIAZI80.html) for a preservative containing 75–80% triazinetriethanol.

[e]Description of Forcide 78® as in Andersen et al. (20).

[f]Preventol D2® is also used as a trade name for benzylhemiformal by Lanxess Energizing Chemistry (www.protectedbypreventol.com).

relationship to formaldehyde and other formaldehyde-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 miscellaneous releasers are reviewed.

Identification and Selection of Formaldehyde-releasers

Formaldehyde-releasers were defined as: (i) substances 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 textbooks (1–3), reviews (4–8), case reports and original articles. Exact identification of some substances described as formaldehyde-releasers has been problematic or even impossible, as a considerable number 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 incorrectly been identified as formaldehyde-releasers (Table 1).

Included in this article are only those formaldehyde-releasers that could unequivocally or with a high degree of certainty be identified, for instance, by their Chemical Abstract Service Registry Numbers (CAS numbers) or their chemical structure. Thus, a total of 42 formaldehyde-releasers were found in the literature. These are presented alphabetically in Table 2 with their (suggested) common 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 literature 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 testing (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, conversion and oxidization of ingested aspartame (an

Table 3. Formaldehyde-releasers commercially available for patch testing

Chemical	Chemotechnique[a]	Trolab[b]	Brial[c]
Benzylhemiformal		1% pet.	1% pet.
Bioban® CS 1135	1% pet.		1% pet.
Bioban® CS 1246	1% pet.	1% pet.	1% pet.
Bioban® P 1487	0.5% pet.	1% pet.	1% pet.
2-Bromo-2-nitropropane-1,3-diol	0.25% pet.	0.5% pet.	0.5% pet.
Diazolidinyl urea	2% pet.	2% pet.	2% pet.
1,3-Dimethyl-4,5-dihydroxyethyleneurea	4.5% aqua		
Dimethylol dihydroxyethyleneurea	4.5% aqua		
Dimethylol dihydroxyethylene urea, modified	5% aqua		
DMDM hydantoin	2% aqua	2% aqua	2% aqua
Ethylene urea	1% pet.		
Ethylene urea, melamine formaldehyde mix	5% pet.		
Formaldehyde	1% aqua	1% aqua	1% aqua
Imidazolidinyl urea	2% pet.	2% pet.	2% pet.
Melamine/formaldehyde resin	7% pet.		
Methenamine (hexamethylenetetramine)	2% pet.	1% pet.	1% pet.
N,N'-Methylenebis(5-methyloxazolidine)		1% pet.	1% pet.
N-Methylol-chloracetamide	0.1% pet.		
Polyoxymethylene urea (urea-formaldehyde resin)	10% pet.		
Quaternium−15	1% and 2% pet.	1% pet.	1% pet.
Tris(*N*-hydroxyethyl)hexahydrotriazine (triazinetriethanol, Grotan® BK)	1% aqua	1% pet.	1% pet.
Tris(hydroxymethyl)nitromethane (Tris Nitro)	1% pet.		1% pet.

[a]Available at: www.chemotechnique.se.
[b]Available at: www.hermal.com.
[c]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 oxidization 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]

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

[a]These 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.

product exceeds 0.05 wt% (500 p.p.m.) (44). However, as has been shown above, there are many 'hidden' or 'occult' sources of formaldehyde, and manufacturers may not be aware of such formaldehyde contamination.

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[a]

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

Table 5. (*Continued*)

Country	Years of study	Number of patients	Test concentrations and vehicle	Positive All (%)	Women (%)	Men (%)	Current relevance (%)	Comments/ setting	References
Germany	1993–1999	32 779	1% aqua	1.9			NS	Multicentre study, IVDK	Brasch et al. (70)
USA	1996–1998	3440	1% aqua	9.3			63[c]	Multicentre study, NACDG	Marks et al. (71)
USA	1988–1997	927	1% aqua	6.8			NS	One centre, Boston	Albert et al. (9)
Belgium	1995–1997	8521	1% aqua	0.9			NS	One centre, Leuven	Goossens et al. (72)
Denmark	1992–1996	3734	1% aqua	2.2			78[d]	One centre, Copenhagen	Trattner et al. (46)
Denmark	1992–1996	3734	2% aqua	2.6			78[d]	One centre, Copenhagen	Trattner et al. (46)
USA	1994–1996	3111	1% aqua	9.2			33/42[b]	Multicentre study, NACDG	Marks et al. (73)
Finland	1995–1996	9378	1% aqua	3.0			NS	Multicentre study	Hasan et al. (61)
People's Republic of China	1988–1996	1135	1% aqua	4.1			NS	One centre, Xuzhou	Liu et al. (74)
Germany, Austria	1990–1995	36 786		2.1	2.2	1.9	NS	Multicentre study, IVDK	Schnuch et al. (75)
USA	1992–1994	3526	1% aqua	7.8			64[c]	Multicentre study, NACDG	Marks et al. (76)
Austria	1992–1993	11 516	1% aqua	0.9	0.9	0.9	NS	Multicentre study	Kränke et al. (77)
Switzerland	1989–1990	2295	1% aqua/pet.	5.7			NS	Multicentre study	Perrenoud et al. (78)

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.

[a]Data provided back to approximately 1990. For pre-1990 literatures, see Fransway and Schmitz (11) and Fransway (29).

[b]Definite/probable relevance (first number)/possible relevance (second number).

[c]Percentage includes: 'possible relevance'.

[d]Percentage 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 discolouration. 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.*

Chemical	Number of registered products	Percentage of products in category	Volume Tonnes/year	Product category
Formaldehyde	**2363**		**26 152.95**	
	56	5.38	103.11	Adhesives
	63	10.59	8.31	Binding agents - for binding together the individual constituents in the product
	51	4.59	658.52	Biocides - pesticides for non agricultural uses
	222	5.37	0.53	Cleaning/washing agents
	46	7.67	0.01	Colouring agents
	46	8.42	21.04	Construction materials (building materials)
	7	2.27	0.00	Cooling agents for metal processing
	12	3.72	0.01	Cosmetics
	79	6.86	6.49	Filling agents
	11	31.43	1.22	Fixing agents - for fixing chemicals/particles to surfaces and fibres (not photo chemicals).
	18	10.34	0.08	Flooring materials (joint-less floors)
	10	7.04	0.00	Galvano-technical agents - for metal surface treatment
	59	76.62	0.01	Glazing materials, enamels etc.
	5	1.52	0.05	Hardeners
	18	9.18	3.04	Impregnation/ proofing - for protection from damp, fungus etc.
	3	2.46	0.00	Insulating materials - to protect from noise, cold, electricity, dust etc.
	41	10.00	2.49	Laboratory chemicals
	5	0.35	0.00	Lubricants
	12	2.44	4.99	Metal surface treatment remedies
	7	5.11	9.65	Moulding compounds
	3	1.57	0.00	Paint and varnish removers
	1306	22.53	2.97	Paint, lacquers and varnishes
	2	1.17	0.02	pH-regulating agents
	6	1.82	0.04	Plant protection - agricultural pesticides
	15	3.00	0.02	Polishing agents
	58	11.26	0.02	Printing inks
	6	1.01	0.04	Process regulators (synthesis regulators)
	14	2.36	25 967.47	Raw materials and intermediate products
	3	2.14	0.00	Rinsing agents
	22	4.31	0.08	Rust inhibitors
	3	2.22	0.12	Sanitation agents - for cleaning up liquids and other materials
	8	15.38	0.03	Sequestering agents
	4	5.56	0.06	Softeners (plastic-, rubber-, paint-, adhesive softeners)
	14	7.57	0.02	Surface treatment for paper, cardboard and other non-metals
	16	2.40	0.33	Surface-active agents - (surfactants, detergents)
	35	39.33	1.50	Toners
	8	10.67	0.01	Writing agents
Benzylhemiformal	**87**		**0.85**	
	3	0.97	0.03	Cooling agents for metal processing
	65	1.12	0.01	Paint, lacquers and varnishes
Bioban CS 1246®	**16**		**0.19**	
	7	2.27	0.18	Cooling agents for metal processing
2-Bromo-2-nitropropane-1,3-diol	**549**		**69.84**	
	27	2.59	0.10	Adhesives
	11	1.85	0.13	Binding agents - for binding together the individual constituents in the product
	22	1.98	43.34	Biocides - pesticides for non agricultural uses
	111	2.69	0.70	Cleaning/washing agents
	8	1.33	0.01	Colouring agents
	7	1.28	0.00	Construction materials (building materials)
	19	5.88	0.14	Cosmetics
	13	1.13	0.00	Filling agents
	15	7.65	0.10	Impregnation/ proofing - for protection from damp, fungus etc.

Table 6. (*Continued*)

Chemical	Number of registered products	Percentage of products in category	Volume Tonnes/year	Product category
	204	3.52	19.17	Paint, lacquers and varnishes
	18	3.60	0.02	Polishing agents
	18	3.50	0.10	Printing inks
	5	2.70	0.00	Surface treatment for paper, cardboard and other non-metals
	13	1.95	0.03	Surface-active agents - (surfactants, detergents)
	5	4.03	0.01	Viscosity adjustors
5-Bromo-5-nitro-1,3-dioxane	**62**		**0.47**	
	25	0.61	0.14	Cleaning/washing agents
	24	7.43	0.21	Cosmetics
	5	1.00	0.00	Polishing agents
Diazolidinyl urea	**4**		**0.10**	
1,6-Dihydroxy-2,5-dioxahexane	**289**		**26.13**	
	5	0.48	0.01	Adhesives
	10	0.90	24.85	Biocides - pesticides for non agricultural uses
	13	0.31	0.01	Cleaning/washing agents
	11	1.83	0.00	Colouring agents
	5	1.62	0.39	Cooling agents for metal processing
	8	0.69	0.01	Filling agents
	174	3.00	0.22	Paint, lacquers and varnishes
	15	2.91	0.50	Printing inks
	3	1.62	0.00	Surface treatment for paper, cardboard and other non-metals
	4	0.60	0.01	Surface-active agents - (surfactants, detergents)
Dimethylol urea	**78**		**7.50**	
	2	0.34	0.00	Binding agents - for binding together the individual constituents in the product
	3	0.27	7.36	Biocides - pesticides for non agricultural uses
	10	0.24	0.00	Cleaning/washing agents
	25	0.43	0.06	Paint, lacquers and varnishes
DMDM hydantoin	**16**		**0.14**	
Imidazolidinyl urea	**3**		**0.00**	
Melamine/formaldehyde resin	**98**		**162.29**	
	57	0.98	53.25	Paint, lacquers and varnishes
Methenamine	**117**		**99.27**	
	3	0.29	0.04	Adhesives
	17	1.53	0.28	Biocides - pesticides for non agricultural uses
	10	0.24	0.06	Cleaning/washing agents
	3	0.61	0.02	Metal surface treatment remedies
	49	0.85	0.08	Paint, lacquers and varnishes
	3	0.59	0.11	Rust inhibitors
Methylal	**91**		**35.44**	
	13	0.31	1.04	Cleaning/washing agents
	11	0.76	2.77	Lubricants
	3	1.57	1.77	Paint and varnish removers
N,N'-Methylenebis(5-methyloxazolidine)	**36**		**11.06**	
	5	0.45	8.45	Biocides - pesticides for non agricultural uses
	20	6.49	1.76	Cooling agents for metal processing
4,4'-Methylenedimorpholine	**18**		**5.13**	
	11	3.57	4.66	Cooling agents for metal processing
N-Methylolchloracetamide	**83**		**0.07**	
	4	0.67	0.00	Binding agents - for binding together the individual constituents in the product
	3	0.26	0.01	Filling agents
	47	0.81	0.01	Paint, lacquers and varnishes
	13	2.52	0.02	Printing inks

Table 6. (*Continued*)

Chemical	Number of registered products	Percentage of products in category	Volume Tonnes/year	Product category
N-Methylolethanolamine	**33**		**2.34**	
	8	2.60	2.08	Cooling agents for metal processing
	19	0.33	0.08	Paint, lacquers and varnishes
Paraformaldehyde	**8**		**1.50**	
Polyoxymethylene urea	**182**		**7 595.94**	
	13	1.25	1 122.75	Adhesives
	148	2.55	56.49	Paint, lacquers and varnishes
Quaternium-15	**30**		**0.05**	
	11	3.41	0.00	Cosmetics
Sodium hydroxymethylglycinate	**60**		**1.72**	
	48	1.16	0.90	Cleaning/washing agents
	4	2.86	0.03	Rinsing agents
Tetramethylol acetylene diurea	**100**		**1.70**	
	7	1.17	0.07	Colouring agents
	7	0.61	0.03	Filling agents
	66	1.14	1.58	Paint, lacquers and varnishes
	6	1.20	0.01	Polishing agents
	3	1.62	0.01	Surface treatment for paper, cardboard and other non-metals
Tris(hydroxymethyl)-nitromethane	**84**		**0.19**	
	13	0.31	0.08	Cleaning/washing agents
	40	0.69	0.08	Paint, lacquers and varnishes
	2	1.48	0.01	Sanitation agents - for cleaning up liquids and other materials
Tris(N-hydroxyethyl) hexahydrotriazine	**103**		**1 708.54**	
	7	0.63	1.02	Biocides - pesticides for non agricultural uses
	9	0.22	0.05	Cleaning/washing agents
	11	3.57	0.97	Cooling agents for metal processing
	5	0.35	3.10	Lubricants
	41	0.71	3.47	Paint, lacquers and varnishes
	4	0.78	0.02	Printing inks
	3	0.59	0.04	Rust inhibitors
Total	**3560**	12.10	**40 125.11**	

*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.

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

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 can 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.

*The Detergents Regulations 648/2004 of the European Union came into force in October 2005 and requires the listing of preservation agents irrespective of their concentration in products for domestic use. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:168:0005:0010:EN:PDF

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