

Preservatives in registered chemical products

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Preservatives are common causes of contact allergy and contact dermatitis. Exposure to cosmetics, personal care products, consumer products and occupationally used products often involve contact with the same range of preservatives. The aim of this study is to provide an overview on the occurrence of preservatives in registered chemical products. The studied preservatives included substances from standard patch test series and other preservatives relevant for registered chemical products. Data obtained from the Danish Product Register Database (PROBAS) in January 2005 were compared to similar data from January 2002. Paints/lacquers, cleaning agents and printing inks were the most frequently registered product categories, and the studied preservatives were registered in most of the product categories included in the study. For most product categories the total number of registered products was stable during the study period. Butylated hydroxytoluene, benzoic acid, isothiazolinones, Bronopol and formaldehyde showed an increase from 2002 to 2005. Most of these changes occurred in the product category paints/lacquers, for which a doubling mainly due to a change in registration practice was observed. The frequent registration of isothiazolinones (MCI/MI and benzisothiazolinone) in paints/lacquers may be a possible explanation for the relative high and stable frequency of positive patch test reactions to MCI/MI.

Key words: chemical products; contact allergy; contact dermatitis; isothiazolinones; occupational exposure; preservatives; prevention; product register database. © Blackwell Munksgaard, 2005.

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Preservatives are among the contact allergens most frequently causing contact allergy and contact dermatitis (1), and exposure to cosmetics, personal care products, consumer products and occupationally used products often involve contact with the same range of preservatives.

Data on the number of positive patch test reactions over a 10-year period (1991–2000) in European patch test clinics for seven commonly used preservatives showed that the frequency of positive patch test reactions were steady for most of the tested preservatives. Parabens had the lowest frequency of sensitization at 0.5–1%. Quaternium 15 and imidazolidinyl urea were a little higher at approximately 1%, and for diazolidinyl urea frequencies were at 0.5–1.5%. Formaldehyde and MCI/MI frequencies were stable but relative high at 2–2.5%. For MCI/MI this is remarkable, as the content in cosmetics has been regulated to a level at which the risk of sensitization is regarded as minimal (7.5 p.p.m. in leave-on products and 15 p.p.m. in wash-off products). For formaldehyde the high level is thought to be due to the frequent use of

formaldehyde-releasing preservatives. For methyl-dibromo glutaronitrile a significant increase was observed, from 0.7% in 1991 to 3.5% in 2000 (2).

Elucidation of exposure to contact allergens is central for the process of establishing the clinical relevance of positive patch test reactions and diagnosing allergic contact dermatitis. Information on sources of exposure to preservatives is important for prevention of contact allergy and contact dermatitis as the use of preservatives only seldom can be avoided in water-based products. Product databases offer possibilities for generating matrices on the occurrence of contact allergens divided into product categories, which in turn can be used for assessing the potential exposure from a product category or for tracing the sources of exposure to a specific contact allergen.

The aim of this study is to provide an updated overview on the occurrence of preservatives in registered chemical products for occupational use. Data were obtained from the Danish Product Register Database (PROBAS) in January 2005 and compared to similar data from January 2002 (3).

Materials and Methods

The selection of preservatives for this study was based on contact allergens included in the European standard series as recommended by the European Environmental Contact Dermatitis Research Group, the North American standard series or the lists of proposed allergens for a modified or an extended international standard series (4, 5). In addition, other preservatives relevant for registered chemical products were included.

The PROBAS was established in 1979 as a governmental database common for the authorities for the working environment and the external environment. The main part of the registered products is notified according to legal demands for providing information on hazardous chemical products for occupational use. Other product categories are included but often not covering all marketed products (e.g. cosmetics and toiletries). The registration includes information on chemical composition with components identified by Chemical Abstract Service Registry Number, product category, industrial area of use and quantities imported or manufactured. The registered data are kept confidential, and public access is not possible (6). The legislation on notification was changed in July 2004. In short, the products to notify 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 chemical composition a 1% limit has been introduced, thus only substances making up more than 1% of any given product has to be declared, although for certain groups of substances the limits are lower. These exceptions include, e.g. preservatives, which should 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 be declared (7). 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% (8). For further details on PROBAS please refer to references (6, 9).

The data obtained for this study include products registered by January 2005, which have been active on the market within the past 5 years and computerized with information on chemical composition and product category. All products containing the studied preservatives either directly or from raw materials were included. Data on substances registered in less than four products within a product category were excluded.

Results

Table 1 shows the occurrence of the studied preservatives in the registered chemical products. Overall, the most frequently registered preservatives were butylated hydroxytoluene (BHT), formaldehyde, MCI/MI, benzisothiazolinone and benzyl alcohol. Formaldehyde-releasing preservatives can be relevant for contact allergy to formaldehyde and are marked with FR in the table (10).

Paints/lacquers, cleaning agents, printing inks and hardeners were the most frequently registered product categories. The studied preservatives were registered in most of the product categories included in the study. Some preservatives, especially formaldehyde releasers, and some parabens were mainly registered in toiletries and cosmetics.

The total number of registered products increased by 16% during the study period from 2002 to 2005. For most product categories the total number of registered products was stable during the study period. Among the changes observed was a doubling for paints/lacquers, which may be explained by a change in registration practice, probably bringing the registration of products to reflect the actual occurrence of these product categories on the market (see below). The increase for printing inks, construction materials and polishes corresponded to the total increase. The registration for toiletries and cosmetics decreased with one third, mainly due to a decrease in hair care products (halved) and a more moderate decrease in skin care products. Thus, changes in the registration of the different preservatives in toiletries and cosmetics should not be interpreted as real change in the occurrence of preservatives in these products (see below).

For the different preservatives BHT, benzoic acid, isothiazolinones, Bronopol and formaldehyde an increase from 2002 to 2005 could be seen. Most of these changes occurred in the product category paints/lacquers. Other preservatives increased corresponding to the total number of registered products or decreased slightly. Diazolidinyl urea was only registered in toiletries and cosmetics and showed a major decrease to about 20% in 2005 compared with 2002.

The most frequently registered preservatives in adhesives/glues were formaldehyde and BHT followed by MCI/MI, benzyl alcohol, benzisothiazolinone, Bronopol and cresol. The registration of a few adhesives/glues containing benzoic acid in 2005 was new compared with the 2002 registration.

Table 1. Occurrence of preservatives in registered chemical products – divided into product categories. The table is based on 59,100 products registered in January 2002 and 68 800 in January 2005, all active on the market in the preceding 5 years and computerized with information on chemical composition and product category. Products can be registered in more than one product category and contain more than one of the allergens. Data on product categories with less than four products for each substance are not shown

Product categories		January 2002	January 2005	Adhesives/ Glues	Cleaning agents	Construction materials	Cutting fluids	Filling agents	Flooring agents	Hardeners	Impregnating agents	Paints/ lacquers	Polishes	Printing inks	Toiletries and cosmetics	Total number of products registered for each substance
Number of products registered for each product category	CAS R.N.	2002	2005	1775	6126	827	422	1913	370	3312	497	6250	771	3176	1774	
Substances (INCI-names)																
Benzalkonium chloride	8001-54-5	2002	2005	–	62	–	–	–	–	–	–	5	–	–	8	103
				–	70	–	–	–	–	–	–	11	6	–	–	116
Benzisothiazolinone	2634-33-5	2002	2005	15	52	–	9	8	7	8	75	253	55	110	–	788
				16	76	–	10	13	9	10	74	1084	84	112	–	1726
Benzoic acid	65-85-0	2002	2005	–	17	–	–	4	–	6	–	175	–	–	13	325
				4	22	–	–	–	–	15	–	484	–	–	–	668
Benzyl alcohol	100-51-6	2002	2005	16	86	9	–	44	92	471	–	195	21	78	37	1288
				19	103	6	–	40	114	513	4	412	28	79	37	1624
2-bromo-2-nitro-1,3-propanediol (FR)	52-51-7	2002	2005	10	97	5	–	–	6	–	62	177	14	–	60	514
(Bronopol)				10	117	4	–	6	6	–	63	388	33	–	36	773
Butylated hydroxytoluene (BHT)	128-37-0	2002	2005	58	69	24	15	110	54	107	20	1164	10	439	189	2815
Chloroalylhexaminium chloride (ST) (FR)	4080-31-3	2002	2005	56	80	54	23	125	76	103	16	5125	21	521	189	7105
(Quaternium 15)				–	5	–	–	–	–	–	–	–	5	–	16	33
Cresol	1319-77-3	2002	2005	9	–	–	–	–	–	–	–	–	5	–	13	28
				10	–	–	–	4	–	–	–	20	–	–	–	75
Diazolidinyl urea (ST) (FR)	78491-02-8	2002	2005	–	–	–	–	4	–	–	–	20	–	–	–	68
				–	–	–	–	–	–	–	–	–	–	–	35	38
Formaldehyde (ST)	50-00-0	2002	2005	–	–	–	–	–	–	–	–	–	–	–	6	8
				136	227	57	8	151	50	81	64	1157	28	311	31	3574
				129	261	65	18	123	75	66	66	2935	37	414	17	5372
Imidazolidinyl urea (ST) (FR)	39236-46-9	2002	2005	–	–	–	–	–	–	–	–	–	–	–	193	196
				–	–	–	–	–	–	–	–	–	–	–	184	190
Mercaptobenzothiazole (ST) (MBT)	149-30-4	2002	2005	–	5	–	4	–	–	7	–	22	–	20	–	84
				–	4	–	–	–	–	–	–	36	–	20	–	79
Methyltribromo glutaronitrile (ST)	35691-65-7	2002	2005	–	12	–	–	–	–	–	–	–	–	–	36	61
				–	11	–	–	–	–	–	–	–	–	–	–	69
Methylchloroisothiazolinone (ST)	26172-55-4	2002	2005	28	133	7	4	26	11	9	35	498	94	168	281	1907
the MCI part of MCI/MI				23	126	9	–	25	8	22	34	2032	107	162	218	3398
Methylisothiazolinone (ST)	2682-20-4	2002	2005	26	135	7	4	25	11	9	35	497	89	167	279	1872

Table 1. Continued

Product categories	Adhesives/ Glues	Cleaning agents	Construction materials	Cutting fluids	Filling agents	Flooring agents	Hardeners	Impregnating agents	Paints/ lacquers	Polishes	Printing inks	Toiletries and cosmetics	Total number of products registered for each substance
Number of products registered for each product category	January 2002 January 2005	6126 6378	827 965	422 430	1913 1922	370 400	3312 3304	497 519	6250 13753	771 887	3176 3804	1774 1170	
CAS RN													
the MI part of MCI/MI	23	142	11	–	28	8	25	39	2145	122	164	217	3563
Parabens:													
Butylparaben ^(ST)	–	–	–	–	–	–	–	–	–	–	–	82	101
2005	–	–	–	–	–	–	–	–	8	–	–	81	117
Ethylparaben ^(ST)	–	–	–	–	–	–	–	–	–	–	–	59	81
2002	–	–	–	–	–	–	–	–	–	–	–	58	98
2005	–	5	–	–	–	–	–	–	8	–	–	390	492
Methylparaben ^(ST)	–	26	–	–	–	–	–	–	–	9	–	335	443
2002	–	27	–	–	–	–	–	–	10	11	–	337	430
2005	–	24	–	18	–	–	–	–	–	7	–	288	386
Propylparaben ^(ST)	–	26	–	11	–	–	–	–	9	9	–	–	–
2002	–	–	–	–	–	–	–	–	–	–	–	–	–
2005	–	–	–	–	–	–	–	–	–	–	–	–	–

^(ST) Substances included in the European standard series as recommended by the EEC/DRG, the North American standard series or the list of proposed allergens for a modified or an extended international standard series (4, 5).
^(FR) Formaldehyde-releasing preservatives (10).

In cleaning agents, the most frequently registered preservatives were formaldehyde, MCI/MI, Bronopol and benzyl alcohol followed by BHT, benzisothiazolinone and benzalkonium chloride. Some parabens (methylparaben and propylparaben), benzoic acid and methyldibromo glutaronitrile were also registered in cleaning agents, although only in few products. Quaternium 15 was no longer registered in cleaning agents in 2005.

The number of construction materials containing the studied preservatives was relatively limited; formaldehyde and BHT were the most frequently registered, followed by MCI/MI, benzyl alcohol and Bronopol.

The number of cutting fluids containing the studied preservatives was also relatively limited; the most frequently registered were BHT and formaldehyde, followed by propylparaben and benzisothiazolinone. MCI/MI and mercaptobenzothiazole (MBT) were no longer registered in cutting fluids in 2005.

In filling agents, BHT and formaldehyde were the most frequently registered, followed by benzyl alcohol, MCI/MI, benzisothiazolinone and a few products containing Bronopol and cresol. The registration of Bronopol in filling agents was new in 2005 compared with the 2002 registration, and benzoic acid was no longer registered in filling agents in 2005.

In flooring agents, benzyl alcohol was the most frequently registered, followed by BHT and formaldehyde and to a lesser extent benzisothiazolinone, MCI/MI and Bronopol.

The most frequently registered preservatives in hardeners were benzyl alcohol, followed by BHT and formaldehyde and to a lesser extent MCI/MI, benzoic acid and benzisothiazolinone. In 2005, MBT was no longer registered in hardeners.

For impregnating materials the most frequently registered preservatives were benzisothiazolinone, formaldehyde and Bronopol, followed by MCI/MI and BHT. The registration of benzyl alcohol in impregnating materials in 2005 was new compared with the 2002 registration.

Paints/lacquers were the only product category for which the number of registered products increased markedly relative to the total number of registered products. This increase has taken place gradually over the past 7–10 years. Part of this change can be explained by a change in registration practice, as some of the major paint manufacturers have divided their notifications into single products instead of combined notifications for a number of different paints with equal toxicological characteristics. Thus, the current number of registered paints/lacquers can be

regarded as a better measure for the number of paints/lacquers marketed. The most frequently registered preservatives in paints/lacquers were BHT, formaldehyde, MCI/MI and benzisothiazolinone, followed by benzoic acid, benzyl alcohol and Bronopol. The most distinct increase was observed for paints/lacquers registered with isothiazolinones (MCI/MI and benzisothiazolinone). A few paints/lacquers contained MBT, cresol and benzalkonium chloride. The registration of parabens in 2005 was new compared with the 2002 registration.

The most frequently registered preservatives in polishes were MCI/MI and benzisothiazolinone, followed by formaldehyde, Bronopol, benzyl alcohol and BHT. Parabens (methyl and propyl) and Quaternium 15 were registered only in a few polishes. The registration of benzalkonium chloride in polishes in 2005 was new compared with the 2002 registration.

In printing inks, the most frequently registered preservatives were BHT and formaldehyde, followed by MCI/MI, benzisothiazolinone and benzyl alcohol and to a lesser extent MBT.

The registration of toiletries and cosmetics decreased from 2002 to 2005, probably because the registration of these products in PROBAS is not based on legal demands but originate from data occasionally transferred from other authorities. The most frequently registered preservatives in toiletries and cosmetics were parabens, MCI/MI, BHT and imidazolidinyl urea, followed by methyl dibromo glutaronitrile, benzyl alcohol, Bronopol and to a lesser extent formaldehyde, benzoic acid and Quaternium 15. Still, it should be underlined that the registration of toiletries and cosmetics does not cover all marketed products and could thus represent only examples of preservatives which can be expected to occur in toiletries and cosmetics.

Discussion

It is important to remember that the distribution of preservatives into product categories in a study as the present is highly influenced by the product categories covered by the registration, which in turn affects the preservatives available for investigation. Furthermore, product categories only registered as containing a few of the studied allergens may contain other preservatives.

An earlier study comparing the registration of contact allergens in chemical products in 1990 and 1998 also showed a considerable increase in the registration of isothiazolinones (11), and the same tendency was observed in the present study.

As mentioned above, the increased number of registered paints/lacquers was mainly caused by a change in registration practice. The current registration of paints/lacquers with content of isothiazolinones could probably be seen as an occurrence of isothiazolinones that has been hidden in earlier studies.

Isothiazolinones are ubiquitous contact allergens and the use in paints/lacquers may be an underestimated source of exposure. Although many factors affect the rate of positive patch test reactions (12), the occurrence of isothiazolinones in paints/lacquers (both benzisothiazolinone and MCI/MI according to the present study) may contribute to the relative high and stable frequency of positive patch test reactions to MCI/MI (2) in spite of the regulation of the content allowed in cosmetics. Further investigation is needed to elucidate whether exposure to paints contributing to sensitization or provocation of contact allergy to MCI/MI is of occupational origin. Another possible explanation could be the relative frequent habit of painting and redecorating private homes as leisure-time activity, which also may imply less careful protection against skin contact compared with occupational use. Plans for future PROBAS studies include further investigations on the concentration of preservatives in registered chemical products, the use of more than one preservative in the same products and the implications this may have for the concentrations used. If possible changes over time in these parameters will be included.

Information on the occurrence of preservatives in registered chemical products as presented in this study can be used for selecting preservatives to patch test in patients exposed to a specific product category or to reveal relevant sources of exposure in eczema patients with positive patch test reactions to the studied preservatives.

When advising individual patients, it is always important to consult the data sheets and labelling for the specific products used at home, during leisure time and at their workplace. Toiletries and cosmetics should be labelled with a list of ingredients including preservatives. The labelling of chemical products as sensitizing is impaired by the 1% default threshold for the majority of contact allergens and the 0.1% limit for listing the name of sensitizers on the label for products not classified as sensitizing. These are typically too high for sensitizers of normal potency, although a lower limit is set for some contact allergens. Furthermore, the limited number of allergens classified with R43 (may cause contact sensitization by skin contact) adds to the

limitations of data sheets and product labelling (7) compared with information obtained from product databases with registration of complete product composition.

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