

Identification and allergenic activity of hydroxyaldehydes – a new type of oxidation product from an ethoxylated non-ionic surfactant

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Ethoxylated alcohols, which are widely used as surfactants, are susceptible to oxidation on air exposure. A complex mixture of oxidation products is formed, among which alkylated aldehydes, alkylated formates, formaldehyde and peroxides have previously been identified by our group. In the present study, we have identified a new class of oxidation product from the nonionic ethoxylated surfactant $C_{12}E_5$. These oxidation products are highly water-soluble hydroxyaldehydes with the general formula $HO(CH_2CH_2O)_nCH_2CHO$, $n=1-4$. To facilitate the identification of the hydroxyaldehydes in oxidized $C_{12}E_5$, reference compounds were synthesized. The sensitizing potential of 1 of the identified hydroxyaldehydes, $HO(CH_2CH_2O)_3CH_2CHO$, was studied in guinea pigs and was found to be weak. A significant cross-reactivity between this aldehyde and the next shorter homologue, $HO(CH_2CH_2O)_2CH_2CHO$, was observed. Irritant components, present in the oxidation mixture, facilitate the skin penetration of allergens, which further accentuates the importance of controlling the conditions of storage and handling of ethoxylated surfactants, to reduce the formation of allergenic and irritant oxidation products.

Key words: ethoxylated surfactant; contact dermatitis; autooxidation; chemical analyses; guinea pigs; sensitization experiments. © Munksgaard, 2001.

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The ethoxylated surfactants have wide application in industrial and household cleaners, laundry products and pharmaceuticals. Non-ionic surfactants are often preferred to ionic surfactants since they are considered to cause less skin irritation (1). However, we have shown that the autooxidation of non-ionic alcohol ethoxylates generates products that are both skin irritating (2) and sensitizing (3). Oxidation products are formed from ethoxylated non-ionic surfactants during storage and handling. Formaldehyde and peroxides have been detected (4) and the structures of previously unidentified components in the oxidation mixture, alkylated aldehydes and formates (Fig. 1), elucidated (5, 6). Formaldehyde is a well-known contact allergen and the alkylated aldehydes were found to have a sensitizing capacity of the same magnitude as that of formaldehyde (5).

The aim of the present study was to identify and isolate potentially allergenic oxidation products from an air-exposed ethoxylated surfactant. In this paper, we present a new group of secondary oxidation products formed by cleavages of the poly-

ethyleneoxy chain, yielding a series of highly water-soluble homologous hydroxyaldehydes of various lengths. The products were identified in the oxidation mixture using synthesized authentic aldehydes as reference compounds. The sensitizing capacity of 1 of the aldehydes was determined, as well as the cross-reactivity between this aldehyde and the next smaller homologue.

Materials and Methods

Chemicals

Tetraethylene glycol (99%) was obtained from Aldrich (Steinheim, Germany). Triethylene glycol (99%), bromoacetaldehyde diethylacetal (99%) and sodium hydride (60% in mineral oil) were obtained from Acros Organics (Geel, Belgium). Ethylene glycol was obtained from Kebo Lab AB (Stockholm, Sweden). Pentaethylene glycol mono-*n*-dodecyl ether $C_{12}H_{25}(OCH_2CH_2)_5OH$ (CAS Reg No. [3055–95–6]) (referred to as $C_{12}E_5$) was purchased from Nikko Chemicals CO., Ltd (Tokyo, Japan). The purity was stated by the producer to be 98%.

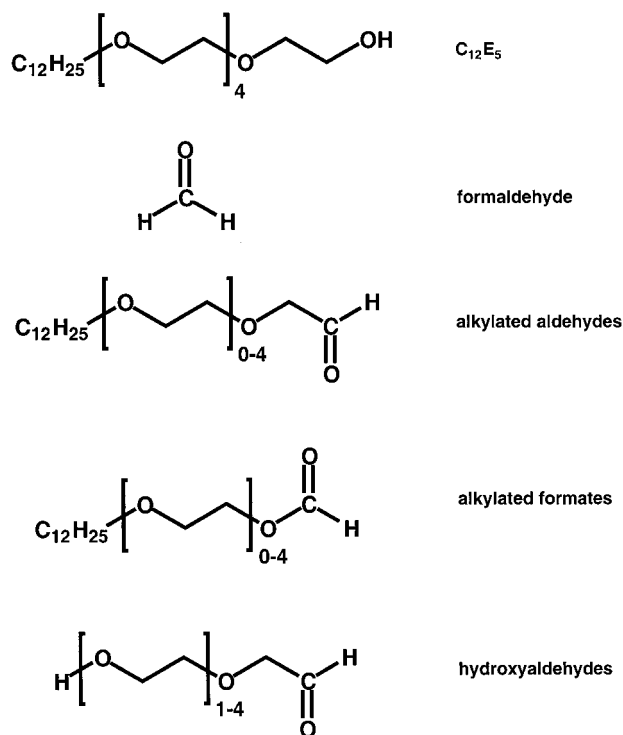


Fig. 1. $C_{12}E_5$ and identified oxidation products.

Freund's complete adjuvant (FCA) was obtained from Difco (Detroit, MI).

Instrumentation and mode of analysis

FT-IR spectra were recorded with a Perkin-Elmer 16 PC FT-IR instrument using a sealed liquid cell with KBr windows. NMR spectroscopy was performed at 270 MHz for ^1H and 67.5 MHz for ^{13}C , on a JEOL EX 270 instrument, using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Chemical shifts are expressed in ppm and the abbreviations used for signal multiplicity are s (singlet), t (triplet) and m (multiplet).

LC-MS analyses were performed using the atmospheric pressure electrospray ionization technique (API-ES) on an Hewlett Packard 1100 LC-MS instrument. Detection was made with a quadrupole analyzer and the samples were analyzed in the positive mode. The LC was equipped with a Zorbax SB-C18 column (150 mm $\times$ 3.0 mm i d) with a particle size of 3.5 μm (Hewlett Packard, USA). Water and acetonitrile, 65:35, were used as mobile phase and formic acid (5 mM) was added to promote the formation of positive ions.

GC-MS analyses were performed on a HP 6890 GC-system, coupled to a HP 5973 mass selective detector. The MS analyses were performed in the electron impact (EI) mode. Introduction of the sample into the ion source was made via GC using

on-column technique. The GC was equipped with a HP-1MS crosslinked methyl siloxane capillary column (25 m $\times$ 0.25 mm i d) with a film thickness of 0.25 μm (Hewlett Packard, USA) and helium was used as a carrier gas. The temperature programming of the GC-oven was as follows: 35°C for 1 min, followed by a temperature increase of 10°C/min up to 250°C. The GC-MS transferline was held at 280°C, the ion source was held at 230°C and the electron energy was 70 eV.

Synthesis

Tetraethylenoxyacetaldehyde diethylacetal 4. Sodium hydride (24 mg, 1.0 mmol) was added in small portions to tetraethylenoxyglycol (3.9 g, 20 mmol) at 25–40°C over 1.5 h. Bromoacetaldehyde diethylacetal (0.2 g, 1.2 mmol) was added and the reaction mixture was stirred at 100°C under nitrogen overnight. The reaction mixture was chromatographed on a silica gel column eluted with ethyl acetate containing increasing amounts of methanol (0–10%). The diethylacetal **4** was obtained in 44% yield (2.7 g). The diethylacetals **1–3** were prepared using the same method. Identification was performed using FT-IR, NMR and MS.

Tetraethylenoxyacetaldehyde 8. The acetal **4** (2.7 g, 8.8 mmol) was dissolved in 1N HCl (1 ml) and left at room temperature under nitrogen for 3 h. After chromatography on a silica gel column, eluted with ethyl acetate with increasing methanol content (15–25%), the aldehyde **8** was obtained in 41% yield (0.9 g) as a 65:35 mixture of the aldehyde and its hydrate, as shown by NMR. The other aldehydes were prepared from the corresponding diethylacetals, using the same method.

5-hydroxy ethyleneoxyacetaldehyde diethylacetal, $HO(CH_2CH_2O)_2CH_2CH(OCH_2CH_3)_2$, 1. Yield 35%. FT-IR (neat): 3444 cm^{-1} (O-H). ^1H -NMR ($CDCl_3$): δ 4.59 (1H, t, $CH(OR)_2$), 3.66–3.48 (8H, m, ($4 \times -CH_2O-$)), 3.36 (2H, t, CH_2OH), 2.67 (1H, s, OH), 1.18 (6H, t, $(OCH_2CH_3)_2$). ^{13}C -NMR ($CDCl_3$): δ 101.04 (1C, $CH(OR)_2$), 72.77, 71.42 (4C, $4 \times -CH_2O-$), 62.22 (2C, $CH(OCH_2CH_3)_2$), 61.50 (1C, OCH_2CH_2OH), 14.88 (2C, $CH(OCH_2CH_3)_2$). MS (API-ES) m/z : 196 ($M+18$) $^+$, 201 ($M+23$) $^+$. These spectral data are consistent with structure **1**.

8-hydroxy diethyleneoxyacetaldehyde diethylacetal, $HO(CH_2CH_2O)_2CH_2CH(OCH_2CH_3)_2$, 2. Yield 52%. FT-IR (neat): 3450 cm^{-1} (O-H). ^1H -NMR ($CDCl_3$): δ 4.60 (1H, t, $CH(OR)_2$), 3.49–3.66 (12H, m, $6 \times -CH_2O-$), 3.34 (2H, t, CH_2OH), 2.60 (1H, s, OH), 1.16 (6H, t, $(OCH_2CH_3)_2$). ^{13}C -NMR ($CDCl_3$): δ 101.25 (1C, $CH(OR)_2$), 72.41, 71.68, 70.82, 70.22 (4C, $4 \times -CH_2O-$), 62.14 (2C, $CH(OCH_2CH_3)_2$), 61.57

(1C, OCH₂CH₂OH), 14.91 (2C, CH(OCH₂CH₃)₂). MS (API-ES) m/z: 240 (M+18)⁺, 245 (M+23)⁺. These spectral data are consistent with structure **2**.

11-hydroxy triethyleneoxyacetaldehyde diethylacetal, HO(CH₂CH₂O)₃CH₂CH(OCH₂CH₃)₂, **3**. Yield 51%. FT-IR (neat): 3440 cm⁻¹ (O-H). ¹H-NMR (CDCl₃): δ 4.61 (1H, t, CH(OR)₂), 3.52–3.60 (16H, m, 8×–CH₂O–), 3.35 (2H, t, CH₂OH), 2.80 (1H, s, OH), 1.17 (6H, t, (OCH₂CH₃)₂). ¹³C-NMR (CDCl₃): δ 101.17 (1C, CH(OR)₂), 72.45, 71.73, 70.71, 70.49, 70.45, 70.24 (6C, 6×–CH₂O–), 62.12 (2C, CH(OCH₂CH₃)₂), 61.57 (1C, OCH₂CH₂OH), 14.92 (2C, CH(OCH₂CH₃)₂). MS (API-ES) m/z: 284 (M + 18)⁺, 289 (M + 23)⁺. These spectral data are consistent with structure **3**.

14-hydroxy tetraethyleneoxyacetaldehyde diethylacetal, HO(CH₂CH₂O)₄CH₂CH(OCH₂CH₃)₂, **4**. Yield 44%. FT-IR (neat): 3456 cm⁻¹ (O-H). ¹H-NMR (CDCl₃): δ 4.61 (1H, t, CH(OR)₂), 3.68–3.51 (20H, m, 10×–CH₂O–), 3.34 (2H, t, CH₂OH), 2.55 (1H, s, OH), 1.19 (6H, t, (OCH₂CH₃)₂). ¹³C-NMR (CDCl₃): δ 101.24 (1C, CH(OR)₂), 72.50, 71.78, 70.78, 70.52, 70.50, 70.48, 70.45, 70.22 (8C, 8×–CH₂O–), 62.20 (2C, CH(OCH₂CH₃)₂), 61.50 (1C, OCH₂CH₂OH), 14.96 (2C, CH(OCH₂CH₃)₂). MS (API-ES) m/z: 328 (M+18)⁺, 333 (M+23)⁺. These spectral data are consistent with structure **4**.

Ethyleneoxyacetaldehyde, HOCH₂CH₂OCH₂CHO+HOCH₂CH₂OCH₂CH(OH)₂, **5**. Yield 72%. FT-IR (neat): 3464 cm⁻¹ (O-H), 2976 and 2876 cm⁻¹ (C-H), 1448 cm⁻¹ (C-H in CH₂), 1374 cm⁻¹ (CH₂-OH), 1106 cm⁻¹ (C-O). ¹H-NMR (CDCl₃): δ 4.97 (1H, m, OCH₂CH(OH)₂), 3.73–3.53 (6H, m, 3×–CH₂O–), 3.36–3.38 (2H, m, CH₂CH₂OH), ¹³C-NMR (CDCl₃): δ 90.78 (1C, CH(OH)₂), 69.91 (1C, OCH₂CH(OH)₂), 65.94 (1C, CH₂O), 61.24 (1C, CH₂OH). MS (EI) m/z: 104 M⁺, 75 (M–29)⁺, 58 (M–46)⁺. These spectral data are consistent with structure **5**.

Diethyleneoxyacetaldehyde, HO(CH₂CH₂O)₂CH₂CHO+HO(CH₂CH₂O)₂CH₂CH(OH)₂, **6**. Yield 60%. FT-IR (neat): 3330 cm⁻¹ (O-H), 2904 and 2876 cm⁻¹ (C-H), 1732 cm⁻¹ (C=O). ¹H-NMR (CDCl₃): δ 9.70 (1H, s, CH₂CHO), 4.85 (1H, m, OCH₂CH(OH)₂), 4.17 (2H, s, OCH₂CHO), 3.73–3.53 (6H, m, 3×–CH₂O–), 3.36–3.38 (2H, m, CH₂CH₂OH). ¹³C-NMR (CDCl₃): δ 200.56 (1C, CHO), 96.37 (1C, CH(OH)₂), 76.53 (1C, OCH₂CHO), 73.33, 72.47, 70.78 (3C, 3×–OCH₂–), 61.44 (1C, CH₂OH). MS (API-ES) m/z: 149 (M+1)⁺, 166 (M+18)⁺. These spectral data are consistent with structure **6**.

Triethyleneoxyacetaldehyde, HO(CH₂CH₂O)₃CH₂CHO+HO(CH₂CH₂O)₃CH₂CH(OH)₂, **7**. Yield 50%. FT-IR (neat): 3334 cm⁻¹ (O-H), 2904 and 2878 cm⁻¹ (C-H), 1734 cm⁻¹ (C=O). ¹H-

NMR (CDCl₃): δ 9.70 (1H, s, CH₂CHO), 4.82 (1H, m, OCH₂CH(OH)₂), 4.16 (2H, s, OCH₂CHO), 3.75–3.44 (10H, m, 5×–CH₂O–), 3.36–3.38 (2H, m, CH₂CH₂OH). ¹³C-NMR (CDCl₃): δ 200.56 (1C, CHO), 96.37 (1C, CH(OH)₂), 76.53 (1C, OCH₂CHO), 73.49, 72.43, 71.12, 70.62, 70.17 (5C, 5×–OCH₂–), 61.60 (1C, CH₂OH). MS (API-ES) m/z: 193 (M+1)⁺, 210 (M+18)⁺. These spectral data are consistent with structure **7**.

Tetraethyleneoxyacetaldehyde, HO(CH₂CH₂O)₄CH₂CHO+HO(CH₂CH₂O)₄CH₂CH(OH)₂, **8**. Yield 41%. FT-IR (neat): 3334 cm⁻¹ (O-H), 2905 and 2878 cm⁻¹ (C-H), 1736 cm⁻¹ (C=O). ¹H-NMR (CDCl₃): δ 9.69 (1H, s, CH₂CHO), 4.80 (1H, m, OCH₂CH(OH)₂), 4.16 (2H, s, OCH₂CHO), 3.68–3.50 (14 H, m, 7×–CH₂O–), 3.38 (2H, m, CH₂CH₂OH). ¹³C-NMR (CDCl₃): δ 201.66 (1C, CHO), 96.50 (1C, CH(OH)₂), 76.54 (1C, OCH₂CHO), 73.51, 72.43, 71.09, 70.88, 70.60, 70.47, 70.18 (7C, 7×–OCH₂–), 61.52 (1C, CH₂OH). MS (API-ES) m/z: 237 (M+1)⁺, 254 (M+18)⁺. These spectral data are consistent with structure **8**.

Air oxidation of C₁₂E₅

A sample of neat C₁₂E₅ (10 g) was stored in an open Erlenmeyer flask in daylight at room temperature during 10 months. The top of the flask was covered with aluminium foil to prevent contamination and to diminish evaporation. The sample was stirred for 1 h, 4× daily.

The degree of oxidation after 10 months was determined by LC-MS. The amounts of the respective hydroxyaldehydes were determined by GC-MS or LC-MS, using the synthesized aldehydes **5–8** as references.

Studies on the sensitizing capacity of **7** and cross-reactivity with **6**

The sensitizing capacity of the hydroxyaldehyde **7** was determined using female Dunkin-Hartley guinea pigs (weight 320–400 g) from AB Sahlins Försöksdjursfarm (Malmö, Sweden). The guinea pigs were given a standard diet from Beekey (North Humberside, UK), and water *ad libitum*. The sensitization studies were performed according to a previously published protocol (7) of the cumulative contact enhancement test (CCET) (8). The guinea pigs, randomly divided into an exposed and a control group, received an occlusive epidermal application on their shaved upper back on days (D) 0, 2, 7 and 9 as induction. The exposed group was induced with 33% w/w **7** (1.7×10⁻³ mol/g) in water. The control group was induced with distilled water. At each of the 4 induction oc-

casions a filter paper (4×2 cm), wetted with about 200 mg of the induction material, was attached to the skin. All animals were given FCA (0.1 ml×2), intradermally on the upper back, on D 7. Challenge testing was performed on D 21 on the shaved left flank using small Finn Chambers (8 mm i. d., Epitest®, Helsinki, Finland). The guinea pigs were tested with **7** at the concentrations 3.3, 10 and 33% w/w (1.7×10^{-4} , 5.2×10^{-4} and 1.7×10^{-3} mM) in distilled water. 15 µg of the test solution was applied in each Finn Chamber. After 24 h the chambers were removed. Visual evaluation of the reactions was performed at 48 and 72 h after test application (Table 1). The minimum criterion for a positive reaction was a confluent erythema.

Rechallenge. Rechallenge was performed on D 41 (Table 2). A new control group ($n=15$) was used to exclude the possibility of sensitized control animals. Rechallenge was performed on the shaved right flank with hydroxyaldehydes **7** (10 and 33%) and **6** (25%, 1.7×10^{-3} mM) in distilled water. Distilled water was used as a vehicle control.

Table 1. Results from sensitization studies on hydroxyaldehyde **7** in guinea pigs using the CCET method with closed challenge testing

Guinea pigs	No. animals with positive reactions ^{a)}			
	33%	10%	3.3%	water
exposed ^{b)} ($n=15$)				
48 h	4 ^{c)}	6 ^{d)}	1	1
72 h	5 ^{c)}	5 ^{c)}	0	0
controls ($n=15$)				
48 h	0	0	2	0
72 h	0	0	1	0

^{a)}No. animals with confluent erythema 48 and 72 h after application of the test material.

^{b)}Induction: 33% of **7** in water.

^{c)}Significantly different from controls, $p<0.05$.

^{d)}Significantly different from controls, $p<0.01$.

Table 2. Results from rechallenge in the sensitization studies on hydroxyaldehyde **7**; cross-reactivity with hydroxyaldehyde **6**

Guinea pigs	No. of animals with positive reactions ^{a)}			
	aldehyde 7 33%	aldehyde 7 10%	aldehyde 6 25%	water
exposed ^{b)} ($n=15$)				
48 h	8 ^{d)}	5 ^{c)}	11 ^{c)}	0
72 h	4	6 ^{d)}	10 ^{c)}	0
new controls ($n=15$)				
48 h	1	0	0	0
72 h	1	0	0	0

^{a)}No. animals with confluent erythema 48 and 72 h after application of the test material.

^{b)}Induction: 33% of **7** in water.

^{c)}Significantly different from controls, $p<0.05$.

^{d)}Significantly different from controls, $p<0.01$.

^{e)}Significantly different from controls, $p<0.001$.

Preliminary study. Prior to the experiments, a preliminary study was performed in FCA-treated animals, to find the lowest irritating and the highest non-irritating concentrations. Hydroxyaldehyde **7** was tested in 3 guinea pigs at the concentrations 10, 15, 20, 25 and 30% w/w (5.2×10^{-4} , 7.8×10^{-4} , 1.0×10^{-3} , 1.3×10^{-3} and 1.6×10^{-3} mM) in distilled water. A concentration of 33% was chosen for induction, as no irritation was observed for 30%. For challenge testing concentrations of 33% and below were considered suitable.

The study was approved by the local ethics committee.

Statistical analysis

The results from the sensitization study were statistically evaluated using the Fisher exact test. The number of positive reactions in the exposed group was compared to the number of reactions in the control group. A p -value of <0.05 was considered statistically significant.

Log P values

The log P values were calculated manually by the Leo & Hansch method (9), using the Roberts modification (10) for oligoethoxylation.

Results

Spectral characteristics

FT-IR spectra of the synthesized hydroxyaldehydes **6–8** showed a specific carbonyl resonance at $1732\text{--}1736\text{ cm}^{-1}$. It is worth noting that the specific C=O vibration was not present for hydroxyaldehyde **5**. One interpretation is that this small aldehyde forms a favourable hemiacetal ring structure, which is predominant.

LC-MS analyses of **6–8** dissolved in water yielded the protonated molecular ions $(M+1)^+$, as well as $(M+18)^+$ (ammonium adduct) of high intensities.

GC-MS analyses of **5** dissolved in dichloromethane yielded the molecular ion M^+ . Intensive fragments from cleavage of the ethyleneoxide chain were also detected.

These MS-spectra, together with the FT-IR and NMR data, are consistent with the structures **5–8**.

Identification of oxidation products in $C_{12}E_5$ after air exposure

Air oxidation of $C_{12}E_5$ produced, among other compounds, a mixture of the hydroxyaldehydes **5–8**, with **8** as the dominating hydroxyaldehyde. Identi-

fication of these aldehydes was made with GC-MS (aldehyde **5**) or LC-MS (aldehydes **6–8**). Duplicate analyses were performed on each sample. The total amount of the identified hydroxyaldehydes in $C_{12}E_5$ after 10 months of air exposure was about 1.2%. The degree of oxidation of the sample was estimated using LC-MS; 58% $C_{12}E_5$ remained unoxidized and hence 42% had been converted to oxidation products. The identified aldehydes had identical retention times and identical mass spectra as the authentic synthesized samples.

Sensitizing capacity of **7**

A significant response was observed to the hydroxyaldehyde **7** at challenge and rechallenge (Tables 1 and 2). At rechallenge, the animals were also exposed to the hydroxyaldehyde **6**, which gave a significant response at the concentration tested (Table 2).

Discussion

This study is part of our investigation of the oxidative formation of potential contact allergens from ethoxylated surfactants (3). In the present study we have identified a new type of oxidation product formed on autoxidation of the pure ethoxylated dodecyl alcohol $C_{12}E_5$. The secondary oxidation products identified are hydroxyaldehydes, i. e., aldehydes that lack the C_{12} -chain (Fig. 1). In general, non-ionic ethoxylated surfactants have been regarded as stable products and are often stored at room temperature, since they become semisolid at lower temperatures (11). Previous studies from our group show, however, that storage and handling of the pure non-ionic ethoxylated alcohol $C_{12}E_5$ at room temperature result in oxidative degradation, producing a large number of degradation products, some of which have allergenic properties (3). One proposed pathway for this autoxidation is the free radical mechanism described by Decker & Marchal (12), according to which peroxides and hydroperoxides are the primary oxidation products. Carbonyl compounds are formed as secondary products.

The aldehydes identified in this study were predicted to have a sensitizing capacity, judging from their electrophilic properties. The sensitizing capacity of aldehyde **7** was studied experimentally in guinea pigs (Table 1). It was found to be a weak allergen, and showed a lower sensitizing capacity in guinea pig experiments, compared to the results from corresponding experiments with formaldehyde and alkylated aldehydes. Differences in skin penetration might be responsible for the difference in sensitizing potential between alkylated aldehydes and hydroxyaldehydes.

The permeability of chemicals through the skin has been shown to depend largely on a few key physicochemical characteristics, of which the octanol/water partition coefficient (P) is the most important. As can be seen in Table 3, the alkylated aldehydes have much higher log P values than the hydroxyaldehydes, which means that the alkylated aldehydes penetrate the skin more easily. It can be presumed that the hydroxyaldehydes **5**, **6** and **8** have sensitizing capacities analogous to **7**. A significant cross-reactivity was observed between the hydroxyaldehydes **7** and **6** (Table 2). Cross reactivity studies with the hydroxyaldehydes containing 1 and 4 ethyleneoxy groups (**5** and **8**) were not performed. Aldehydes **6** and **7** have effectively the same hapten, hence the smaller compound tends to give a stronger response. One explanation for this might be found by considering the partition coefficients; aldehyde **6** has a log P value of -1.50 , and the corresponding value for aldehyde **7** is -1.60 , which means that aldehyde **6** more easily penetrates the skin.

Chemically, the compounds identified in the present study are aldehydes of polyethylene glycols (PEG). Such compounds, with the general formula $H(OCH_2CH_2)_nOH$, are extensively used in topical pharmaceuticals, shampoos, detergents, cosmetics and a variety of foods. In industry the PEGs are used as solvents for nitrocellulose, as wetting agents in epoxy hardeners and as plasticizers for glue and casein. Although allergic contact dermatitis from PEG is uncommon, several cases have been reported (13–16). According to the literature, it is principally the low molecular weight (MW) PEGs from 200 to 400 that may evoke an allergic reaction, whereas those with higher MWs are not contact sensitizers (14). The compounds identified in this study have MWs between 104 and 236. Cross-reactivity appears to occur only between compounds of about the same MW (14). The purity and the presence of autoxidation products in the PEGs were not investigated in those studies.

Table 3. Log P values for the alkylated aldehydes and the hydroxyaldehydes

Compound	Log P
alkylated aldehydes	
$C_{12}H_{25}OCH_2CHO$	5.56
$C_{12}H_{25}OCH_2CH_2OCH_2CHO$	5.46
$C_{12}H_{25}(OCH_2CH_2)_2OCH_2CHO$	5.36
$C_{12}H_{25}(OCH_2CH_2)_3OCH_2CHO$	5.26
$C_{12}H_{25}(OCH_2CH_2)_4OCH_2CHO$	5.16
hydroxyaldehydes	
$HOCH_2CH_2OCH_2CHO$	-1.40
$H(OCH_2CH_2)_2OCH_2CHO$	-1.50
$H(OCH_2CH_2)_3OCH_2CHO$	-1.60
$H(OCH_2CH_2)_4OCH_2CHO$	-1.70

We conclude that, even if the hydroxyaldehydes identified here are less allergenic than the previously identified alkylated aldehydes, they do have a sensitizing capacity. Irritant components in the oxidation mixture make it easier for these allergens to penetrate the skin. This accentuates further the importance of controlling the storage, transportation and handling conditions of ethoxylated surfactants, to avoid the formation of allergenic and skin irritant oxidation products. Our work concerning identification of new oxidation products from ethoxylated surfactants, and subsequent investigation of their allergenic properties, continues. Suggested primary oxidation products, such as hydroperoxides, are of immediate interest, as their chemical structure might reveal the mechanisms of the autoxidation. To evaluate the clinical significance to man, diagnostic patch testing in humans is required, which is in progress.

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