

Sensitizing capacity of some trimers in *p*-tert-butylphenol-formaldehyde resin

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Contact allergy to *p*-tert-butylphenol formaldehyde resin (PTBP-F-R) is not rare. This resin consists of a large number of substances, most of which are still unknown. For diagnostic and preventive reasons the chemical identity of the sensitizers should be known, as well as their sensitizing capacities, cross-reaction patterns and presence in the environment. The aims of this study were to investigate the sensitizing capacities and potential cross-reacting patterns for 4-tert-butyl-2,6-bis-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIII), 4-tert-butyl-2-(5-tert-butyl-2-hydroxy-benzyloxymethyl)-6-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIVa) and 7,15,23-tri-tert-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix(3)arene (XVIII) by the guinea pig maximization test. 4-tert-Butyl-2,6-bis-hydroxymethyl-phenol, 4-tert-butylbenzene-1,2-diol, 4-tert-butyl-2-hydroxymethyl-phenol, 4-tert-butyl-phenol, 4-tert-butyl-2-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-hydroxymethyl-phenol, 4-tert-butyl-2-[5-tert-butyl-3-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-2-hydroxy-benzyloxymethyl]-6-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol and were used as potential cross-reacting substances. In this study it is strongly indicated that the linear trimer XIII has a sensitizing capacity in the guinea pig which was significant when compared to the controls ($p = 0.024$). No cross-reactions were detected in animals induced with the linear trimer XIII. The linear trimer XIVa and the cyclic trimer XVIII failed to induce sensitization.

Key words: 4-tert-butyl-2-(5-tert-butyl-2-hydroxy-benzyloxymethyl)-6-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol; 4-tert-butyl-2,6-bis-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol; 7,15,23-tri-tert-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix(3)arene; CAS no. 76543-12-9; cross-reactivity; guinea pig maximization test; PTBP-F-R, *p*-tert-butylphenol-formaldehyde resin. © Blackwell Munksgaard, 2002.

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p-tert-Butylphenol formaldehyde resin (PTBP-F-R) is used as a binder in many adhesive formulations which can cause contact allergy (1–4). The resin consists of a large number of substances of which the vast majority are not chemically defined. PTBP-F-R has been used since around 1950 but only a few allergens have been identified. For diagnostic and preventive reasons the chemical identity of the sensitizers should be known, as well as their sensitizing capacities, cross-reaction patterns and presence in the environment.

The substances described in this paper are designated by roman numerals, which are the same as in most of the previously published papers on PTBP-F-R allergens by our research group.

The raw materials for the resin are *p*-tert-butylphenol (VII) and formaldehyde. Monomeric constituents of the resin come from the reaction of formaldehyde with VII. Each molecule of form-

aldehyde, which reacts with VII, forms a hydroxymethyl (methylol) group. Reaction of 1 molecule of formaldehyde with VII yields 4-tert-butyl-2-hydroxymethyl-phenol (IV). Reaction with 1 more molecule of formaldehyde leads to the formation of 4-tert-butyl-2,6-bis-hydroxymethyl-phenol (II). These monomers can react with each other, forming dimers, trimers, tetramers and so on. The connecting bridge between the monomer units can be of the dimethylene ether ($\text{Ar-CH}_2\text{-O-CH}_2\text{-Ar}$) or methylene ($\text{Ar-CH}_2\text{-Ar}$) type. In recent studies we have isolated some dimers and trimers from the resin that have been patch tested in patients hypersensitive to PTBP-F-R.

The purpose of this study was to determine the sensitizing capacities of 3 PTBP-F-R trimers and to investigate the cross-reaction patterns using the guinea pig for sensitization. The isolation of the trimers from PTBP-F-R has recently been pub-

lished by our group (5). The substances are 4-*tert*-butyl-2,6-bis-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxy-methyl)-phenol (XIII), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-benzyloxymethyl)-6-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIVa) and 7,15,23-tri-*tert*-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix(3)arene (XVIII).

When 6 patients hypersensitive to PTBP-F-R were patch tested to XIII and XIVa all of them reacted positively (5). Among these patients, no positive patch test reactions were seen to XVIII. Agatha & Schubert have previously reported some positive patch test reactions to XVIII, which they explained as probably due to contamination with the monomer II (6).

Two of the trimers, XIII and XIVa, are linear with 2 and 1 free hydroxymethyl groups, respectively. They are chemically closely related to the dimers of PTBP-F-R but have a higher molecular weight. XVIII has a cyclic structure and belongs to a group of substances often referred to as calixarenes. Many different calixarenes have been synthesized with the aim of creating substances that mimic the active centre in certain metal binding enzymes (7).

Materials and Methods

Substances

The following substances were used: methanol, and acetone in *pro analysi* quality manufactured by Laboratory-Scan (Ireland); VII, *p*-*tert*-butylcatechol 99% (III) and 2-methylol phenol (2-MP) were manufactured by Acros Organics (Belgium); II and IV were synthesized at our department, according to a method described by Agatha & Schubert (6) but with some modification (8). 4-*tert*-Butyl-2-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-hydroxymethyl-phenol (IX), the linear trimer XIII, the linear trimer XIVa, 4-*tert*-butyl-2-[5-*tert*-butyl-3-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-2-hydroxy-benzyloxymethyl]-6-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XVa) and the cyclic trimer XVIII were synthesized at the department as described elsewhere (5, 9). All PTBP-F-R substances that are used in this investigation have been isolated from the resin by our group (5, 8, 9). The isolation of XVa, however, has not yet been published.

Analytical high pressure liquid chromatography (HPLC)

An HP 1100 HPLC system was used consisting of a G1312A binary pump, a G1314A variable wavelength UV-detector, a G1323A control module and

an HP 3396 Series III integrator (Hewlett Packard GmbH, Waldbronn, Germany). The injector was a Rheodyne 7010 injector (Rheodyne, Cotati, CA, USA) with a 20- μ L loop. The column (4.6 mm i. d. $\times$ 250 mm) was packed with 5 μ m Nucleosil C₁₈ 100 Å (Macherey-Nagel & Co., Düren, Germany). The UV detector was operated at a wavelength of 280 nm. Different mixtures of methanol and water were used as mobile phases and the flow rate was 1 mL/min.

Purity of test substances

Analytical HPLC was used to investigate the purity of the linear trimers XIII, XIVa and the cyclic trimer XVIII. The chromatographic conditions have been described elsewhere (5).

Guinea pig maximization test (GPMT)

The GPMT was performed in accordance with the original description (10), but with some modifications in order to increase the standardization of the test and also to create conditions for objective evaluation, including statistical calculations of the patch test reactions and the inclusion of a positive control group (11, 12). The test and control animals, as well as the animals in the positive control group, were randomly distributed to the cages.

Animals

Albino female guinea pigs of the Dunkin-Hartley strain (J.A. Sahlin, Sweden) weighing 300–400 g were used. For each one of the sensitization series, 42 animals were used, 36 animals participated in the actual sensitization study, 12 in the control group and 24 in the test group, while the remaining 6 or 7 animals made up an additional control group. These 6 or 7 guinea pigs were sensitized to and challenged with the known sensitizer 2-MP and used as a positive control group. The purpose of the positive control group is to eliminate the possible influence of expectations on the evaluation of test reactions that would result in underestimation of the test response, and to serve as an indicator of the accuracy of the induction procedure (12). The animals included in these procedures were not engaged in tests for topical irritancy.

Topical irritancy

The topical irritancy of the substances used for inductions and challenges was studied by means of a 48-h closed patch test in 4–8 animals for each compound (12). The compound was applied to each animal on 4 patches on the flank: 2 near the back, 2

Table 1. Concentrations and vehicles used for induction of guinea pigs with 4-tert-butyl-2,6-bis-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIII), 4-tert-butyl-2-(5-tert-butyl-2-hydroxy-benzyloxymethyl)-6-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIVa) and 7,15,23-tri-tert-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix(3)arene (XVIII) and challenge with 4-tert-butyl-2,6-bis-hydroxymethyl-phenol (II), 4-tert-butylbenzene-1,2-diol (III), 4-tert-butyl-2-hydroxymethyl-phenol (IV), 4-tert-butyl-phenol (VII), 4-tert-butyl-2-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-hydroxymethyl-phenol (IX), XIII, XIVa, 4-tert-butyl-2-[5-tert-butyl-3-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-2-hydroxy-benzyloxymethyl]-6-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XVa) and XVIII

Substance	Molecular weight	Procedure and vehicle					
		Intradermal induction acetone/FCA/pg		Topical induction acetone		Challenge acetone	
		% w/v	mol $\times 10^{-1}$	% w/v	mol $\times 10^{-1}$	% w/v	mol $\times 10^{-1}$
II	210					25	1.2
III	166					7.5	0.45
IV	180					22	1.2
VII	150					2.0	0.13
IX	402					3.2	0.079
XIII	594	2.3	0.038	5.7	0.096	4.6	0.077
						0.020	0.00030
XIVa	564	2.2	0.038	5.4	0.096	4.3	0.077
						0.050	0.00090
XVa	786					6.1	0.077
XVIII	576	2.2	0.038	5.5	0.096	4.4	0.077

pg, propylene glycol. FCA, Freund's complete adjuvant.

near the abdomen. The induction substances were also applied on the neck. Testing was performed 1 week after pretreatment with Freund's complete adjuvant (FCA) (Pierce, Rockford, USA).

Induction procedure

For intradermal sensitization, 3 injections were given in a row, on each side of the shoulder:

- I. 0.1 mL of FCA in water 40% w/v (corresponds to FCA/water 50/50 v/v).
- II. 0.1 mL of the test substance in propylene glycol.
- III. 0.1 mL of the preparation consisting of a mixture of the test substance and FCA in acetone/propylene glycol where the concentration for FCA was the same as in (I) and the concentration for the test substance was the same as in (II).

The topical sensitization was performed 7 days after the intradermal sensitization. 24 h before the topical sensitization all the animals were treated with 200 μ L of a preparation consisting of sodium lauryl sulphate (SLS) 10.0% w/v in dimethyl acetamide/acetone/ethanol 99.5% 4/3/3 by vol. in an area of 2 $\times$ 4 cm. Topical sensitization was then performed by transferring 200 μ L of a solution of the suspected sensitizer to a 2 $\times$ 4 cm patch of Munktel 1002 filter paper (Munktel Filter AB, Gryksbo, Sweden). The patch was covered with overlapping, impermeable plastic adhesive tape

(Acrylastic, Beiersdorf AG, Hamburg, Germany). This in turn was firmly secured by an adhesive bandage (Durapore, 3M Health Care, St. Paul, USA). The dressing was left in place for 48 h. To enable comparisons of the sensitizing capacities among the test compounds themselves and with those of the earlier investigated dimers in resins based on phenol and formaldehyde P-F-R and PTBP-F-R, concentrations equimolar to these were used (9, 13). Concentrations of substances used for inductions are given in Table 1.

Challenge procedure

Challenge I was performed 2 weeks after the second stage of sensitization and a 24-h occluded patch test was performed on the right flank with 25 μ L of the test solutions on each of 2 patches near the back. For patch testing Al-test (Astra Agency, Södertälje, Sweden) on Durapore was used, which was firmly secured by Acrylastic and an outer layer of Durapore. In each sensitization study, 12 test animals received the suspected sensitizer on both patches, 6 animals received the suspected sensitizer only on the cranially located patch, while the vehicle alone was applied to the other patch. The same number of test animals received the suspected sensitizer and the vehicle in the reverse way.

Challenge II was performed at the same time as challenge I but on the other, left, side of the flank. 6 patches were tested on 24 test and 12 control animals, 2 patches were near the back, 2 near the abdomen and 2 between these. The animals were

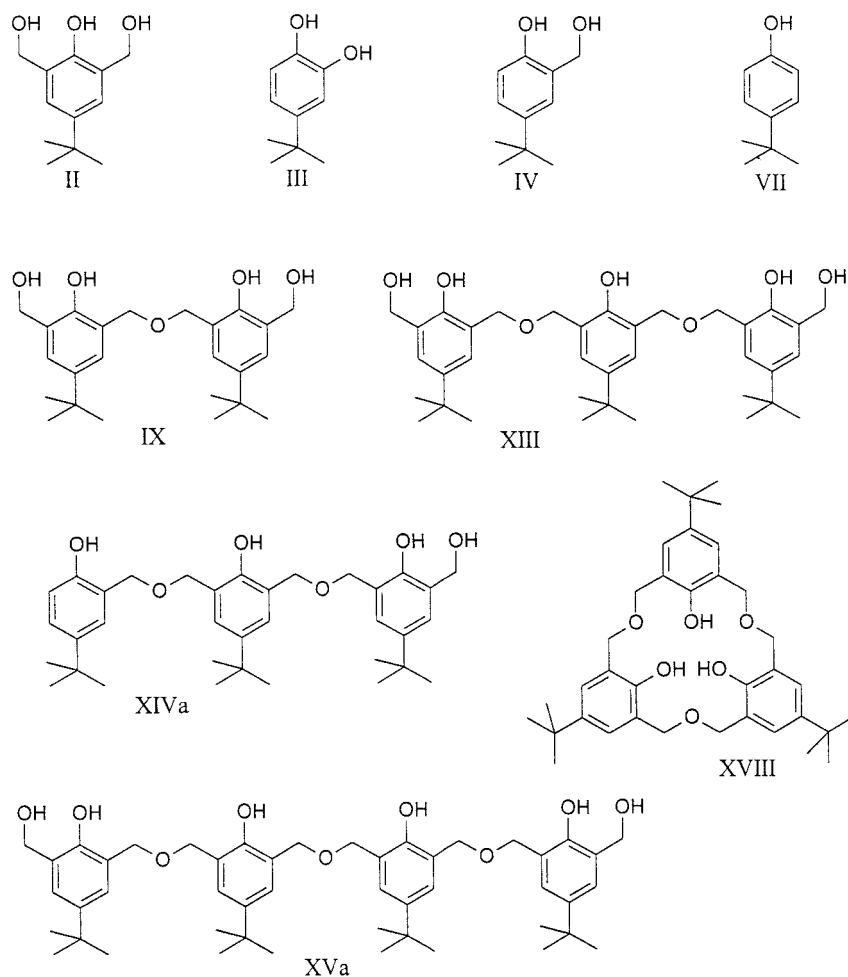


Fig. 1. Chemical structures of the substances used for induction and challenge: 4-*tert*-butyl-2,6-bis-hydroxymethyl-phenol (II), 4-*tert*-butylbenzene-1,2-diol (III), 4-*tert*-butyl-2-hydroxymethyl-phenol (IV), 4-*tert*-butyl-phenol (VII), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-hydroxymethyl-phenol (IX), 4-*tert*-butyl-2,6-bis-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIII), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIVa), 4-*tert*-butyl-2-[5-*tert*-butyl-3-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-2-hydroxy-benzyloxymethyl]-6-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XVa) and 7,15,23-tri-*tert*-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix(3)arene (XVIII).

challenged with the sensitizer and possible cross-reacting substances. A distribution pattern based on a Latin square table was used.

Challenge was performed with non-irritant solutions for all substances according to results from toxicity tests. The test concentrations in challenge I were equimolar to the ones used in earlier investigations of dimers in P-F-R. Test concentrations in challenge II were equimolar to the monomers of P-F-R when possible and equimolar to the dimers of P-F-R for the dimers and larger test compounds (13, 14). Test concentrations equimolar to the monomers in P-F-R could not be used for monomers III and VII because of the high topical irritancy of these compounds. Concentrations of substances used for challenge I and II are given in Table 1. The chemical structures of the test substances are shown in Fig. 1.

Controls

The induction and challenge procedures for the animals in each control group were carried out in the same way as the corresponding animals in the

test group, except that the suspected sensitizer was not administered during the induction.

For challenge I, 6 control animals received the suspected sensitizer on both patches. 3 others received the suspected sensitizer and the vehicle alone on the patches. The same number of animals received the suspected sensitizer and the vehicle in the reverse way.

For challenge II the 12 animals in the control group received the suspected cross-reacting substances in the same way and in the same concentrations as the animals in the test group.

The 6 or 7 animals in the particular positive control group were sensitized to and challenged with 2-MP according to procedures described in detail elsewhere (12).

Evaluation

The reactions were evaluated blind 24 h after the removal of the patches. First, the right flanks (challenge I), and with the left flanks shielded, of all animals were read and thereafter, still blind and without knowledge of the readings of the right

Table 2. Challenge I; test reactions after induction and challenge with 4-tert-butyl-2,6-bis-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIII), 4-tert-butyl-2-(5-tert-butyl-2-hydroxy-benzyloxymethyl)-6-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIVa) and 7,15,23-tri-tert-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix(3)arene (XVIII)

Induction substance	Number of positive animals			
	T/n	C/n	V/n	P/n
XIII	8/24 ^{a,b}	0/12 ^a	1/12 ^b	3/6
XIVa	3/24	2/12	2/12	3/7
XVIII	4/24	0/12	1/12	4/7

^a $p = 0.024$. ^b $p = 0.094$.

C, test reactions to the suspected sensitizer in control animals. T, test reactions to the suspected sensitizer in test animals. V, test reactions to the vehicle in test animals. P, test reactions in positive control animals after induction and challenge with 2-methylol-phenol. n, number of tested animals in the 4 groups C, T, V and P, respectively.

flanks, the left flanks (challenge II) were read. The minimum criterion of an allergic (positive) reaction was a confluent erythema. The number of positive animals in each test group was statistically compared to the number of positive animals in the corresponding control group and also to the number of positive test animals tested with the vehicle alone. The assessment of whether an animal was positive or not was based on the result for only one patch chosen in advance for those animals which had obtained the test solution on both patches (12 test animals and 6 control animals). When both comparisons yielded significant values the compound was considered to be a contact sensitizer.

For challenge II a comparison was made only between the number of positive animals in the test and control groups for each substance.

Statistical calculation

Fisher's exact test was used.

Results

Results of challenge I after induction with the linear trimers XIII, XIVa and the cyclic trimer XVIII, respectively, are given in Table 2. In the group of animals subjected to induction with the linear trimer XIII, 8 test animals showed positive test reactions. No control animals reacted positively to the linear trimer XIII. The difference in the numbers of positive animals to the linear trimer XIII in the test and control groups was significant ($p = 0.024$), but the comparison between test and vehicle groups yielded a non-significant difference ($p = 0.094$). In the group of animals subjected to induction with the linear trimer XIVa, only 3 test and 2 control animals showed positive test reactions. In the group of animals subjected to induction with the cyclic trimer XVIII, 4 test and no control animals showed positive test reactions, a non-significant difference.

Results from challenge II after induction with the linear trimers XIII, XIVa and the cyclic trimer XVIII, respectively, are given in Table 3. No statistically significant differences were found between test and control groups for the putative cross-reacting substances nor were there any non-significant but indicated cross-reactions.

Investigation of the purity of the linear trimers XIII, XIVa and the cyclic trimer XVIII showed that the test substances were of high purity. No impurities were seen over an estimated detection limit of 0.1% w/w.

Table 3. Challenge II; test reactions in animals after induction with 4-tert-butyl-2,6-bis-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIII), 4-tert-butyl-2-(5-tert-butyl-2-hydroxy-benzyloxymethyl)-6-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XIVa) and 7,15,23-tri-tert-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix(3)arene (XVIII) and challenge with 4-tert-butyl-2,6-bis-hydroxymethyl-phenol (II), 4-tert-butylbenzene-1,2-diol (III), 4-tert-butyl-2-hydroxymethyl-phenol (IV), 4-tert-butyl-phenol (VII), 4-tert-butyl-2-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-hydroxymethyl-phenol (IX), XIII, XIVa, 4-tert-butyl-2-[5-tert-butyl-3-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-2-hydroxy-benzyloxymethyl]-6-(5-tert-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (XVa) and XVIII

Induction substance	Group	n	No. of positive animals after challenge with									
			XIII		XIVa	XVIII	II	III	IV	VII	IX	XVa
			4.6%	0.02%	0.05%	4.4%	25%	7.5%	22%	2.0%	3.1%	6.1%
XIII	test	24	NT	2	NT	0	3	NT	7	NT	1	0
	control	12	NT	0	NT	0	0	NT	4	NT	1	0
XIVa	test	24	1	NT	0	1	1	NT	NT	NT	4	1
	control	12	1	NT	1	1	0	NT	NT	NT	1	2
XVIII	test	24	2	NT	NT	NT	2	8	7	2	3	NT
	control	12	1	NT	NT	NT	0	4	2	2	1	NT

n, number of animals in the different groups, respectively. NT, not tested.

Discussion

In our research on allergens in PTBP-F-R we have isolated several allergens in recent years and there are indications of more allergens to be isolated and identified. Among all these allergens it is important to distinguish between strong, moderate and weak sensitizers. The sensitizing capacities and cross-reaction patterns of these allergens can virtually only be investigated in animals.

Several of the monomers and dimers in PTBP-F-R are allergens. We have recently demonstrated that the linear trimers XIII and XIVa can also elicit contact allergic reactions in humans hypersensitive to PTBP-F-R, with reactions down to 0.0015 and 0.0014% w/v, respectively, in the most sensitive patients (5). In this study we wanted to investigate the sensitizing capacity of these 2 substances and an additional substance, the cyclic trimer XVIII.

In this study, it is strongly indicated that the linear trimer XIII has a sensitizing capacity in the guinea pig which was significant when compared to the controls ($p=0.024$) but non-significant when compared to the vehicle group. No cross-reactions to the monomers II and IV, the dimer IX, the linear tetramer XVa or the cyclic trimer XVIII were demonstrated or indicated. The linear trimer XIVa and the cyclic trimer XVIII did not induce sensitization or cross-reactivity to the tested substances. The test responses in the positive control groups indicate that this was not due to underestimation of the test reactions.

Hydroxymethyl phenols in P-F-R and PTBP-F-R are chemically closely related. To enable comparisons of the sensitizing capacities of monomers and dimers from the 2 resins the concentrations used for induction and challenge have been equimolar for the groups, respectively (13). Dimers in P-F-R and PTBP-F-R have been tested in the GPMT in this way and compared by classification. The significance levels $p<0.05$, $p<0.01$ and $p<0.001$ were used to designate the sensitizers as weak, moderate or strong, respectively (13).

It is strongly indicated that the linear trimer XIII is a weak sensitizer when compared to the dimers of P-F-R and PTBP-F-R. The linear trimer XIVa and the cyclic trimer XVIII did not show any sensitizing capacity in this investigation but this does not exclude that they are sensitizers. This could be investigated using higher concentrations for induction and challenge. However, our goal with this investigation was to compare the sensitizing capacities of these substances to the dimers of P-F-R and PTBP-F-R.

The molecular weight of the linear trimer XIII is 594; this is relatively high for a Type-IV sensitizer. This might indicate the involvement of degra-

dation products in the sensitization process. Degradation products were suggested as important sensitizers in PTBP-F-R allergy by Malten & Seutter in 1985 (15). Dimethylene ether bridges, the connecting bonds between the *p-tert* butylphenol units in the linear trimer XIII, can be broken by the addition of water under certain conditions. If this can happen to the linear trimer XIII on or in the skin, it would give rise to the monomer II and the dimer IX as degradation products. The animals that were induced with the linear trimer XIII were tested with both these substances and showed no cross-reactions. We can conclude that test reactions to the linear trimer XIII are caused by this substance and not by any of these degradation products.

This study also indicates a difference in sensitizing capacities for the linear trimers XIII and XIVa, with a lower sensitizing capacity for the linear trimer XIVa. The obvious difference between these 2 substances is the number of hydroxymethyl groups. When the sensitizing capacities of 2 P-F-R dimers were investigated, the dimer with 2 hydroxymethyl groups was classified as a strong sensitizer, while the corresponding dimer with 1 hydroxymethyl group was classified as a moderate sensitizer (13). The same difference in sensitizing capacities was found when the corresponding PTBP-F-R dimers with 2 and 1 hydroxymethyl groups, respectively, were investigated (9). By analogy with the dimers of P-F-R and PTBP-F-R it is not surprising that a lower degree of sensitizing capacity is indicated for the linear trimer XIVa with 1 hydroxymethyl group as compared to the linear trimer XIII with 2 hydroxymethyl groups. The hydroxymethyl groups in these hydroxymethyl phenols (methylol phenols) are reactive groups. Thus, it seems that an increase from 1 to 2 reactive groups in similar molecules enhances the sensitization capacity.

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