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Epoxy Resin Monomers with Reduced Skin Sensitizing Potency

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Improvements in Epoxy Resin Polymer Systems: New Monomers with Reduced Skin Sensitizing Potency

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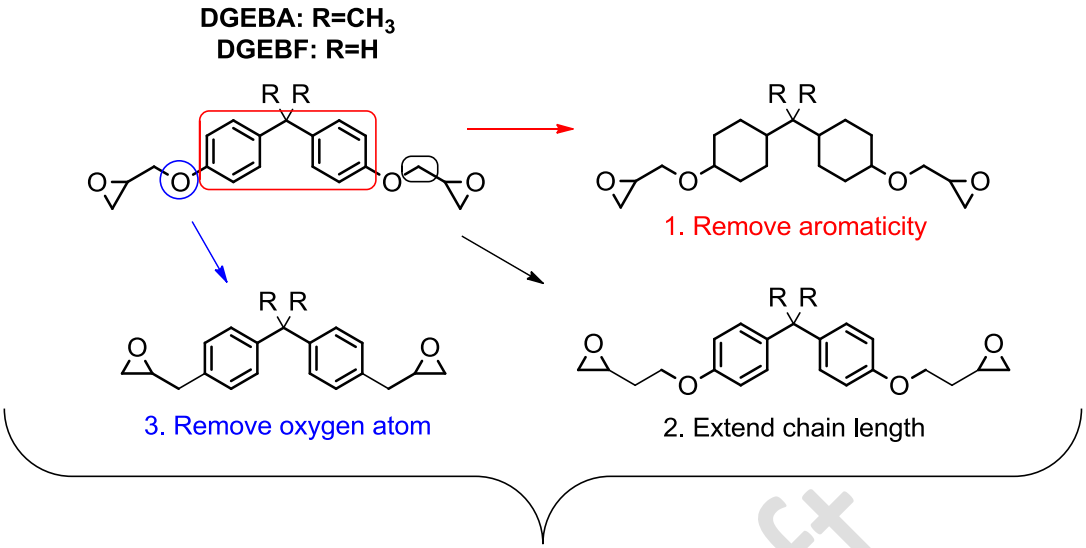
Table of Contents Graphic



Decreased skin sensitization potency whilst maintaining technical polymerisation properties

Abstract

Epoxy resin monomers, including diglycidyl ethers of bisphenol A and F (DGEBA and DGEBF), are extensively used as building blocks for thermosetting polymers. However, they are known to cause widespread contact allergy. This research describes a number of alternative epoxy resin monomers, designed with the aim of reducing the skin sensitizing potency whilst maintaining the ability to form thermosetting polymers. The compounds were designed, synthesized, assessed for skin sensitizing potency using the *in vivo* murine local lymph node assay, and tested for technical applicability using thermogravimetric analysis and differential scanning calorimetry. All the novel epoxy resin monomers had decreased skin sensitization potencies compared to DGEBA and DGEBF. With respect to EC3 values, which is the estimated concentration of a substance required to induce a 3-fold increase in sensitization compared to a control, the best of the new monomers had a value approximately 2.5 times higher than those of DGEBA and DGEBF. The diepoxides were reacted with triethylenetetramine and four out of the six novel monomers gave polymers with a thermal stability comparable to that obtained with DGEBA and DGEBF. The new epoxy resin monomers have the potential to replace DGEBA and DGEBF, leading to a decreased incidence of contact allergy due to epoxy resins, decreased healthcare costs, and an increased quality of life for those handling thermosetting materials.

Abbreviations

BPA	Bisphenol A
DGEBA	Diglycidyl ether of bisphenol A
DGEBF	Diglycidyl ether of bisphenol F
DSC	Differential scanning calorimetry
ERM	Epxoy resin monomer
ERS	Epoxy resin systems
LLNA	Local lymph node assay
mCPBA	3-Chloroperbenzoic acid
TETA	Triethylenetetramine
TGA	Thermogravimetric analysis

Introduction

Epoxy resin systems (ERS) are commercial thermosetting products used in applications where strong, flexible, and light-weight construction materials are required. The global epoxy resin market is projected to reach over 3 million tons in annual sales by 2017.[1] Traditionally used in paints, adhesives, coatings, industrial flooring and electrical laminates, they continually find new applications due to their excellent technical properties. Emerging usages include the relining of old pipes in buildings. ERS are multi-component systems comprised of epoxy resin monomers (ERMs), reactive diluents, hardeners and modifiers. ERMs are polymer precursor units which are reacted with hardeners to give the thermosetting product. The most commonly used ERMs are diglycidyl ethers based on bisphenol A (DGEBA) (also known as BADGE) and bisphenol F (DGEBF or BFDGE) (Figure 1).

ERMs are among the most common causative agents of occupational ACD.[2, 3] They are known to be extremely sensitizing to the skin and can sensitize upon first contact.[4] ACD has been reported from various epoxy resin system components,[5-13] most commonly from exposure to DGEBA and DGEBF.[14, 15] DGEBA is included in the European baseline series for diagnosis of ACD.[16] We are interested in ERS from a healthcare perspective as they are known to be extremely sensitizing to the skin. Contact allergy to epoxy resins is widespread in dermatitis patients with a reported prevalence ranging from 0.9 to 2.3%.[17-20] Reported prevalences in occupational settings are higher, with between 11.7 and 12.5% of cases of allergic contact dermatitis (ACD) attributable to epoxy chemicals.[21] Studies from workplaces found exceptionally high rates of ACD from ERS in aircraft manufacturing workers (56%)[7] and marble workers (45%)[22], amongst others. Skin sensitization is also common amongst construction workers (up to 9.7%) and is caused by ERS present in cement and other building materials,[18, 23] but is also frequent in newer settings such as the production of wind turbine rotor blades[15] and relining of old pipes.[13] It can also occur in unexpected settings such as microscopy of histological samples, due to the presence of ERS in the microscopy immersion oil.[24, 25] Epoxy chemicals are also implicated in non-occupational contact allergy.[17, 26] Skin sensitization potential has been investigated experimentally *in vivo* in mice and guinea pigs for DGEBA,[27, 28] DGEBF[28, 29] and others.[30, 31] DGEBA and DGEBF are classified as strong sensitizers in both

species according to regulatory guidelines.[32] It would be highly advantageous to replace these strongly sensitizing ERMs with less hazardous alternatives.

Our research aims to reduce the adverse skin sensitizing effects of ERMs whilst maintaining their excellent ability to form thermosetting polymers. This is a challenging task in which it is vital to keep a certain level of reactivity in order to enable polymerization. We have previously shown that the sensitizing effects of the epoxy resin DGEBF are directly related to the presence of the terminal epoxide groups.[33] In the present study, compounds that incorporate terminal epoxy groups with reduced reactivity have been designed by alteration of the total chemical structure of the ERMs (**1-6**, Figure 1). The polymerization potential of the novel ERMs **1-6** was evaluated using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The skin sensitizing potency was assessed using the *in vivo* murine local lymph node assay (LLNA).[34]

Experimental Procedures

Caution: This study involves skin sensitizing compounds which must be handled with care.

Instrumentation and Mode of Analysis. ^{1}H and ^{13}C NMR spectroscopy was performed on a Jeol Eclipse 400 spectrometer at 400 MHz and 100 MHz, respectively, using $CDCl_3$ (residual $CHCl_3$ δ 7.26 and δ 77.0 as internal standards) or DMSO-d_6 (residual $(CH_3)_2SO$ δ 2.54 and δ 40.45 as internal standards) solutions. Electron-ionization mass spectral analysis (70 eV) was performed on a Hewlett-Packard 5973 mass spectrometer connected to a gas chromatograph (Hewlett-Packard 6890). The GC was equipped with a cool on-column capillary inlet and an HP-5MSi fused silica capillary column (30 m×0.25 mm, 0.25 µm, Agilent Technologies, Palo Alto, CA). Helium was used as carrier gas, and the flow rate was 1.2 mL/min. The temperature program started at 70 °C for 1 min, increased by 10 °C/min for 20 min, and ended at 270 °C for 5 min. For mass spectral analysis, the mass spectrometer was used in the scan mode detecting ions with *m/z* values from 50 to 1500.

High performance liquid chromatography/mass spectrometry (LC/MS) analyses were performed using electrospray ionization (ESI) on a Hewlett-Packard 1100 HPLC/MS. The system included a vacuum degasser, a binary pump, an autoinjector, a column thermostat, a diode array detector,

and a single quadrupole mass spectrometer. The HPLC was equipped with a HyPURITY C18 column (150×3 mm i. d., particle size 3 µm, Thermo Hypersil-Keystone, Thermo Electron Corp., Bellafonte, PA). The mobile phase consisted of 0.005% pentafluoropropanoic acid, 0.1% acetic acid, and 5% acetonitrile in water (solvent A) and 0.005% pentafluoropropanoic acid, 0.1% acetic acid, and 50% water in acetonitrile (solvent B). A linear gradient from 0% to 100% B over 20 min, followed by 10 min of isocratic elution was used. The flow rate was 0.4 mL/min and the column temperature was 40 °C. The electrospray interface was used with the following spray chamber settings: nebulizer pressure, 40 psig; capillary voltage, 3500 V; drying gas temperature, 350 °C; and drying gas flow rate, 10 L/min. Fragmentor voltage was set to 120 V. The mass spectrometer was used in scan mode detecting molecular ions with *m/z* values ranging from 50 to 2000.

DGEBA and DGEBF were purchased from Sigma-Aldrich; DGEBF was obtained as a mixture of three isomers. Sodium hydride (60% dispersion in mineral oil) was washed twice with hexane and dried with N_2 prior to use. Acetone was purchased from Merck (Darmstadt, Germany) and olive oil from Apoteket AB (Goteborg, Sweden). Unless otherwise indicated, reagents were obtained from commercial suppliers and were used without further purification. TLC was performed using silica gel coated aluminum plates. The purity of all test compounds was >98% (GC/MS) before evaluation in biological assays.

Chemical Synthesis

Synthesis of bis[4-(2,3-epoxypropoxy)cyclohexyl]methane (2) (Scheme 1)

4,4'-Methylenedicyclohexanol (2a). A solution of 4,4'-methylenediphenol (0.05 M solution in isopropanol) was reacted in an H-cube® continuous flow hydrogenation reactor (ThalesNano©) at 100 °C, 100 bar at a flow rate of 1 mL/min and employing 5% Ru/C (30 mm CatCart™) as catalyst. The reaction was monitored by TLC until the starting material was consumed. The solvent was evaporated *in vacuo* and aqueous NaOH solution (50 mL, 10% w/v) was added. The mixture was stirred for 10 min and extracted twice with ethyl acetate (50 mL). The organic fraction was reduced *in vacuo* and the white residue was recrystallized from diethyl ether to give compound **2a** in 98% yield as a white powder (mixture of isomers).

^{1}H NMR (DMSO-d_6) δ 0.77-0.87 (m, 2H), 0.98-1.39 (m, 12H), 1.52-1.54 (m, 2H), 1.62 (m, 2H), 1.76-1.79 (m, 2H), 3.27-3.31 (m, 1H), 3.71 (m, 1H), 4.21 (d, 1H, J=2.9 Hz), 4.44 (d, 1H, J=4.4 Hz); ^{13}C NMR (DMSO-d_6) δ 27.7, 27.8, 31.9, 32.6, 33.2, 33.9, 34.1, 36.0, 40.6, 65.4, 69.8; EI-MS (70 eV), *m/z* (%) 194 (2.6), 176 (29), 165 (12), 147 (16), 135 (18), 94 (69), 81 (100)

Bis[4-(allyloxy)cyclohexyl]methane (2b). Sodium hydride (20.8 mmol, 5.2 equiv.) was washed with hexane (20 mL×2), suspended in anhydrous THF (40 mL) and cooled to 0 °C. Compound **2a** (4 mmol) was dissolved in anhydrous THF (20 mL) and added to the suspension. The mixture was stirred at 0 °C for 10 min. Allyl bromide (10.4 mmol, 2.6 equiv.) was added and the mixture was stirred at room temperature for 90 min before refluxing overnight. The reaction was continued until TLC indicated disappearance of the starting material. The mixture was cooled to 0 °C and saturated aqueous NH_4Cl (70 mL) was added slowly to quench the reaction. The aqueous layer was extracted with ethyl acetate (70 mL×3). The combined organic fractions were washed with brine (150 mL), dried over anhydrous Na_2SO_4 and reduced *in vacuo*. The product **2b** was isolated by column chromatography (9:1 hexane: ethyl acetate) and was obtained as a colorless oil in 93% yield.

^{1}H NMR ($CDCl_3$) δ 0.80-0.89 (m, 2H), 0.99-1.43 (m, 12H), 1.71-1.82 (m, 4H), 1.99-2.03 (m, 2H), 3.16-3.23 (m, 1H), 3.52 (m, 1H), 3.93 (d, 2H), 3.97-4.00 (m, 2H), 5.10-5.14 (m, 2H), 5.22-5.28 (m, 2H), 5.85-5.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.7, 29.5, 31.7, 32.4, 33.6, 33.9, 43.5, 44.1, 68.8, 69.1, 73.7, 73.9, 78.0, 78.1, 116.1, 116.4, 135.7, 135.9; EI-MS (70 eV), *m/z* (%) 291, 235 (3), 193 (10), 177 (100), 135 (23), 95 (79), 81 (80), 67 (31), 55 (38)

Bis[4-(2,3-epoxypropoxy)cyclohexyl]methane (2). Compound **2b** (1.4 mmol) was dissolved in chloroform (20 mL) and cooled to 0 °C. 3-Chloroperbenzoic acid (mCPBA) (≤77%, 2.6 mmol) was added and the mixture was stirred at 0 °C for 2 h. The mixture was then stirred at room temperature with addition of further mCPBA as necessary until complete on TLC. Aqueous NaOH (10% w/v) (40 mL) was added and extracted with CH_2Cl_2 (40 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and reduced *in vacuo*. The product **2** was isolated as a mixture of isomers by column chromatography (9:1 hexane: ethyl acetate) as a colorless oil in 76% yield.

^{1}H NMR ($CDCl_3$) δ 1.12 (t, 2H, J=6.6 Hz), 1.22-1.31 (m, 4H), 1.34-1.42 (m, 10H), 1.78-1.81 (m, 4H), 2.60 (dd, 2H, J=2.9, 5.1 Hz), 2.78 (dd, 2H, J=4.0, 5.1 Hz), 3.10-3.14 (m, 2H), 3.37-3.41 (m, 2H), 3.53 (m, 2H), 3.61 (d, 1H, J=3.3 Hz), 3.64 (d, 1H, J=3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 27.6, 29.3, 29.5, 33.2, 42.7, 44.7, 51.3, 68.6, 75.0; EI-MS (70 eV), *m/z* (%) 324 (M^+), 193 (10), 176 (33), 147 (10), 135 (21), 113 (15), 95 (83), 81 (100), 67 (29), 57 (24)

Synthesis of 2,2-bis[4-(2,3-epoxypropoxy)cyclohexyl]propane (1) (Scheme 1)

2,2-Bis[4-(allyloxy)cyclohexyl]propane (**1b**) was prepared from commercially available 2,2-bis(4-hydroxycyclohexyl)propane (**1a**) by the same method used to prepare **2b** from **2a**. The product **1b** was isolated a mixture of isomers by column chromatography (9:1 hexane: ethyl acetate) as a colorless oil in 93% yield.

^{1}H NMR ($CDCl_3$) δ 0.68 (s, 6H), 0.94-1.03 (m, 3H), 1.12-1.38 (m, 8H), 1.67-1.71 (m, 3H), 1.94-1.96 (m, 1H), 2.02-2.08 (m, 3H), 3.15-3.20 (m, 1.5H), 3.49-3.56 (m, 0.5H), 3.92-3.94 (m, 1H), 3.98-4.00 (m, 3H), 5.10-5.14 (m, 2H), 5.22-5.24 (m, 1H), 5.26-5.28 (m, 1H), 5.85-5.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.0, 25.1, 30.8, 32.9, 36.7, 36.9, 43.1, 43.4, 44.0, 68.7, 69.0, 72.6, 78.1, 78.2, 116.0, 116.5, 135.7, 135.9; EI-MS (70 eV), *m/z* (%) 204 (13), 181 (4), 139 (7), 123 (100), 109 (8), 95 (10), 81 (36), 67 (25)

2,2-Bis[4-(2,3-epoxypropoxy)cyclohexyl]propane (**1**) was prepared from **1b** by the same method used to prepare compound **2** from **2b**. The product **1** was isolated as a mixture of isomers by column chromatography (8:2 hexane: ethyl acetate) as a colorless oil in 82% yield.

^{1}H NMR ($CDCl_3$) δ 0.69 (d, 6H, J=4.7 Hz), 0.94-1.04 (m, 3H), 1.10-1.39 (m, 8H), 1.66-1.72 (m, 3H), 1.96 (m, 1H), 2.06-2.09 (m, 3H), 2.58-2.62 (m, 2H), 2.78 (t, 2H, J=4.8, 9.2 Hz), 3.10-3.15 (m, 2H), 3.18-3.24 (m, 1.5H), 3.36-3.46 (m, 2H), 3.59-3.64 (m, 1H), 3.38-3.72 (m, 1.5H); ^{13}C NMR ($CDCl_3$) δ 20.7, 20.9, 25.0, 30.5, 30.8, 32.7, 32.9, 36.7, 36.9, 43.1, 43.4, 44.6, 44.7, 51.3, 51.4, 68.5, 68.8, 73.8, 79.2, 79.3; EI-MS (70 eV), *m/z* (%) 204 (6), 197 (4), 155 (3), 123 (100), 109 (14), 95 (14), 81 (37), 67 (23)

Synthesis of bis[4-(3,4-epoxybutoxy)phenyl]methane (4) (Scheme 2)

Bis[4-(but-3-en-1-yloxy)phenyl]methane (4a). 4,4'-Methylenediphenol (5 mmol) was dissolved in DMF (20 mL) and K_2CO_3 (20 mmol, 4 equiv.) was added. 4-Bromo-1-butene (15 mmol, 3 equiv.) was added. The mixture was warmed to 40 ^oC and stirred overnight. Water was added to quench the reaction. After extraction with EtOAc, the organic phase was washed with 2M HCl, brine and dried over anhydrous Na_2SO_4. The product **4a** was isolated using column chromatography (5:2 hexane: EtOAc) (61%) and used in the next step without further characterization.

^1H NMR ($CDCl_3$) δ 2.49-2.54 (m, 4H), 3.84 (s, 2H), 3.98 (t, 4H, J=6.6 Hz) 5.07-5.17 (m, 4H), 5.84-5.92 (m, 2H), 6.80 (d, 4H, J=8.4 Hz), 7.06 (d, 4H, J=8.4 Hz); EI-MS (70 eV), *m/z* (%) 308 (100) (M^+), 254 (19), 200 (19), 107 (34), 55 (37)

Bis[4-(3,4-epoxybutoxy)phenyl]methane (4). Compound **4a** (1.4 mmol) was oxidized using mCPBA (≤77%, 2.6 mmol) as described above for **2b**. The product **4** was isolated by column chromatography (8:2 hexane: ethyl acetate) as a white powder in 52% yield.

^1H NMR ($CDCl_3$) δ 1.88-1.96 (2H, m), 2.03-2.12 (2H, m), 2.56-2.58 (m, 2H), 2.81 (t, 2H, J=4.6 Hz), 3.11-3.16 (m, 2H), 3.85 (s, 2H), 4.03-4.12 (m, 4H), 6.81 (d, 4H, J=8.8 Hz), 7.07 (d, 4H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 32.6, 40.2, 47.2, 49.9, 64.7, 114.5, 129.9, 133.9, 157.1; EI-MS (70 eV), *m/z* (%) 340 (100) (M^+), 269 (9), 199 (19), 107 (43), 71 (23)

Synthesis of 2,2-bis[4-(3,4-epoxybutoxy)phenyl]propane (3) (Scheme 2)

2,2-Bis(but-3-en-1-yloxy)phenyl]propane (3a) was prepared from 2,2-bis(4-hydroxyphenyl)propane by the same method used to prepare compound **4a**. The product **3a** was isolated using column chromatography (5:2 hexane: EtOAc) (19%).

^1H NMR ($CDCl_3$) δ 1.63 (s, 6H), 2.50-2.56 (m, 4H), 3.99 (t, 4H, J=6.6 Hz), 5.08-5.19 (m, 4H), 5.85-5.95 (m, 2H), 6.80 (d, 4H, J=8.8 Hz), 7.13 (d, 4H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 31.2, 33.8, 41.8, 67.2, 113.9, 117.0, 127.8, 134.7, 143.3, 156.8; EI-MS (70 eV), *m/z* (%) 336 (35) (M^+), 321 (100), 267 (20), 213 (26), 119 (8)

2,2-Bis[4-(3,4-epoxybutoxy)phenyl]propane (3) was prepared from compound **3a** by the same method used to prepare compound **4** from compound **4a**. The product **3** was isolated by column chromatography (8:2 hexane: ethyl acetate) as a white powder in 37% yield.

^{1}H NMR ($CDCl_3$) δ 1.63 (s, 6H), 1.91-1.97 (m, 2H), 2.04-2.12 (m, 2H), 2.57-2.59 (m, 2H), 2.81-2.83 (m, 2H), 3.13-3.17 (m, 2H), 4.06-4.12 (m, 4H), 6.81 (d, 4H, J=9.2 Hz), 7.14 (d, 4H, J=9.2 Hz); ^{13}C NMR ($CDCl_3$) δ 31.1, 32.6, 41.8, 47.2, 49.9, 64.6, 113.9, 127.8, 143.4, 156.6; EI-MS (70 eV), *m/z* (%) 368 (19) (M^+), 353 (100), 283 (5), 213 (8), 119 (5)

Synthesis of bis[4-(2,3-epoxypropyl)phenyl]methane (6) (Scheme 3)

Bis[(4-trifluoromethylsulfonyloxy)phenyl]methane (6a). 4,4'-Methylenediphenol (4.5 mmol) and anhydrous CH_2Cl_2 (50 mL) were added to a round-bottomed flask containing pyridine (18 mmol, 4 equiv.) under an inert atmosphere. Trifluoromethanesulfonic anhydride (10.8 mmol, 2.4 equiv.) dissolved in anhydrous CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with diethyl ether (40 mL), quenched with 10% aq. HCl (20 mL) and washed successively with saturated $NaHCO_3$ (40 mL) and brine (40 mL). It was dried over anhydrous Na_2SO_4, the solvent was removed *in vacuo* and the product **6a** was isolated using silica gel (95:5 hexane: ethyl acetate) as a white solid in 93% yield.

^{1}H NMR ($CDCl_3$) δ 4.03 (s, 2H), 7.22-7.23 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 40.5, 118.8 (q, 3F, *J*=320 Hz), 117.2, 120.4, 121.7, 130.7, 140.6, 148.3; EI-MS (70 eV), *m/z* (%) 464 (95) (M^+), 331 (100), 315 (28), 198 (25), 181 (13), 169 (37), 153 (59), 141 (41), 115 (23)

Bis(4-(2,3-epoxypropyl)phenyl)methane (6). A solution of **6a** (0.86 mmol), $Pd(PPh_3)_4$ (0.17 mmol, 0.2 equiv.) and $allylSnBu_3$ (2.75 mmol, 3.2 equiv.) in anhydrous DMF (2 mL) was reacted in a microwave cavity at 160 ˚C for 30 min. The mixture was filtered through Celite with ethyl acetate (50 mL). The filtrate was stirred with KF (aq.) (50 mL) for 1 h. The mixture was filtered. The organic phase was separated, washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was crudely purified by column chromatography (100% hexane) to yield bis(4-allylphenyl)methane (**6b**). Compound **6b** (1.4 mmol) was dissolved in chloroform (20 mL) and cooled to 0 °C. mCPBA (≤77%, 2.6 mmol) was added and the mixture was stirred at 0 °C for 2 h. The mixture was then stirred at room

temperature with addition of further mCPBA as necessary until complete on TLC. Aqueous NaOH (10% w/v) (40 mL) was added and extracted with CH_2Cl_2 (40 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and reduced *in vacuo*. The product **6** was isolated by column chromatography (8:2 hexane: ethyl acetate) as a white solid in 28% yield.

^{1}H NMR ($CDCl_3$) δ 2.53-2.55 (m, 2H), 2.75-2.80 (m, 4H), 2.86-2.91 (m, 2H), 3.12-3.15 (m, 2H), 3.94 (s, 2H), 7.13-7.18 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 38.5, 41.3, 47.0, 52.6, 129.1, 129.2, 134.9, 139.6; EI-MS (70 eV), *m/z* (%) 280 (100) (M^+), 249 (80), 237 (35), 223 (16), 207 (18), 193 (39), 178 (53), 165 (32)

Synthesis of 2,2-bis[4-(2,3-epoxypropyl)phenyl]propane (5) (Scheme 3)

2,2-Bis[(4-trifluoromethylsulfonyloxy)phenyl]propane (5a) was synthesized from 2,2-bis(4-hydroxyphenyl)propane in 94% yield by the same method used to obtain **6a**.

^{1}H NMR ($CDCl_3$) δ 1.68 (s, 6H), 7.17 (d, 4H, J=8 Hz), 7.26 (d, 4H, J=8 Hz); ^{13}C NMR ($CDCl_3$) δ 30.8, 42.9, 120.5 (q, 3F, *J*=282 Hz), 121.1, 128.7, 147.8, 150.2; EI-MS (70 eV), *m/z* (%) 492 (14) (M^+), 477 (100), 344 (11), 267 (7), 251 (13), 211 (22)

2,2-Bis[4-(2,3-epoxypropyl)phenyl]propane (5) was synthesized from **5a**, via intermediate **5b**, by the same method used to obtain **6** from **6a**. The product **5** was isolated by column chromatography (8:2 hexane: ethyl acetate) as a white solid in 31% yield.

^{1}H NMR ($CDCl_3$) δ 1.66 (s, 6H), 2.54-2.56 (m, 2H), 2.75-2.80 (m, 4H), 2.85-2.90 (m, 2H), 3.12-3.16 (m, 2H), 7.13-7.18 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 30.8 (CH_3), 38.4 (CH_2), 42.5 (CH_2), 47.1, 52.6, 127.0, 128.7, 134.5, 149.1; EI-MS (70 eV), *m/z* (%) 308 (15) (M^+), 293 (100), 249 (4), 205 (22), 191 (8), 115 (8), 91 (7)

Experimental Animals. Female CBA/Ca mice, 8 or 9 weeks of age, were purchased from NOVA SCB Charles River, Germany. The mice were housed in "hepa" filtered air flow cages and kept on standard laboratory diet and water ad lib. The study was approved by the local ethics committee in Gothenburg.

Skin Sensitizing Potential of ERMs in Mice. The local lymph node assay (LLNA)[35] was used to assess the sensitizing potential. Mice in six groups of three animals in each were treated by

topical application on the dorsum of both ears with the test compound (25 µL) dissolved in acetone: olive oil (AOO) (4:1 v/v) or with the vehicle control. All solutions were freshly prepared for each application. Each compound was tested at five different concentrations. The test concentrations used were as follows: **1**, **2**: 0.05, 0.5, 5.0, 10 and 30% (w/v); **4**, **6**: 0.05, 0.5, 5.0, 10 and 20% (w/v); Treatments were performed daily for three consecutive days (days 0, 1, and 2). Sham treated control animals received vehicle alone. On day 5, all mice were injected intravenously via the tail vein with [methyl-^{3}H]thymidine (2.0 Ci/mmol, Amersham Biosciences, UK) (20 µCi) in phosphate-buffered saline (PBS, containing 137 mM NaCl, 2.7 mM KCl and 10 mM phosphate buffer, pH 7.4) (250 µL). After 5 h the mice were sacrificed, the draining lymph nodes were excised and pooled for each group, and single cell suspensions of lymph-node cells in PBS were prepared using cell strainers (Falcon, BD labware, 70 µm pore size). Cell suspensions were washed twice with PBS, precipitated with TCA (5%) and left in the refrigerator overnight. The samples were then centrifuged, resuspended in TCA (5%) (1 mL) and transferred to scintillation cocktail (10 mL) (EcoLume, INC Radiochemicals, USA). The [methyl-^{3}H]thymidine incorporation into DNA was measured by β-scintillation counting on Beckman LS 6000TA Instruments. Results are expressed as mean dpm/lymph node for each experimental group and as stimulation index (SI), i.e., test group/control group ratio. Test materials that at one or more concentrations caused an SI greater than 3 were considered to be positive in the LLNA. EC3 values (the estimated concentration required to induce an SI of 3) were calculated by linear interpolation. The sensitizing potency was classified to the following: ≤0.2% w/v, extreme; >0.2 to ≤2% w/v, strong; >2% w/v moderate.[32] For registration in REACH, the LLNA is the preferred method for measuring skin sensitization potential in animals.[36, 37]

LLNA with non-pooled lymph nodes. Single-cell suspensions of the lymph nodes from individual mice were prepared and the [methyl-^{3}H]thymidine incorporation was measured to investigate if a statistically significant difference in the sensitizing potency at equimolar concentrations of DGEBA and **5** could be demonstrated. The test concentration (0.064 M) of each compound was selected on the basis of results from the LLNA experiments with pooled lymph nodes on DGEBA and **6**. The test compounds were dissolved in acetone:olive oil (AOO) (4:1 v/v), were topically applied (25 µL) on the dorsum of both ears to two groups of mice (n=12 per group). A sham treated control group of 12 mice received vehicle alone. All solutions were

freshly prepared before application. Procedures and measurements were performed according to the normal LLNA method described above, but the draining lymph nodes were not pooled and single-cell suspensions from the lymph nodes of each mouse were treated separately. Results are expressed as dpm/lymph node for each animal and as stimulation index (SI), i.e. the ratio of individual test animal/mean of the control group. The non-parametric Mann-Whitney *U* test was used for statistical comparison between the two compounds.

Polymerization procedure. The general polymerization reaction between ERMs and triethylenetetramine (TETA) is shown in Scheme 4. This reaction was used for DGEBA, DGEBF, and compounds **1**-**6**. The diepoxide and TETA were thoroughly mixed for 2 min at room temperature, always at a two-to-one ratio of amino-hydrogens to epoxy groups, and the mixture was transferred to cavities of silicon embedding mold and placed in a vacuum desiccator. The mixture was degassed under vacuum for 10 min to remove acetone and trapped air. The cast resin was then cured at room temperature for 24 h followed by postcuring in an oven at 120 °C for 2 h. After the postcure, the oven was switched off and allowed to cool slowly to room temperature to avoid crack formation.

Differential Scanning Calorimetry (DSC). DSC analyses were carried out on polymers prepared from DGEBA, DGEBF and compounds **2** and **4** using a Perkin–Elmer Model Pyris 1 instrument under nitrogen purge. The polymers were heated from 20 to 220 °C at a rate of 10 °C/min, then cooled to room temperature at a rate of 20 °C/min. The change in enthalpy (ΔH) was determined from the upward scan.

Thermogravimetric Analysis (TGA). The TGA analyses were performed on polymers prepared from DGEBA, DGEBF and all the new diepoxides using a Perkin–Elmer TGA 7 instrument under nitrogen purge. The polymers were heated from 20 to 600 °C at a rate of 10 °C/ min and the weight loss was determined for each sample as a function of temperature.

Results and Discussion

To the best of our knowledge, this is the first time that novel DGEBA and DGEBF analogs are described that maintain the excellent technical properties of currently available ERMs while reducing their harmful allergenic effects. By modifying the intrinsic reactivity of ERMs, we have addressed the underlying causes of contact allergy to ERS. We thereby hope to diminish the problem of ACD caused by ERS, especially in occupational settings. We have adopted a global approach incorporating medicinal chemistry and toxicology to design new ERMs.

ERM Design and Synthesis

The design was focused on alternatives to DGEBA and DGEBF as these are the most commonly used ERMs and are described as the main cause of epoxy allergy.[21] Six novel ERMs (three of DGEBA and three of DGEBF) were synthesized and evaluated (ERMs **1**-**6**, Figure 1). The new compounds were designed to reduce the reactivity of the terminal epoxide enough to decrease the skin sensitizing potency but without compromising the ability to polymerize. This functional group is necessary for the desirable polymerization properties of DGEBA and DGEBF but we have previously shown that the sensitizing effects of DGEBF are directly related to the presence of the terminal epoxide groups.[33] Hence, the terminal epoxide group was retained but its reactivity decreased by alteration of other molecular features. Each novel ERM had slight structural modifications compared to DGEBA and DBEBF, designed to give delicately balanced structures capable of polymerization without excessive reactivity causing skin sensitization. ERMs **1**-**6** were designed based on previous work on the epoxy reactive diluent phenylglycidyl ether (PGE).[31, 38] Structural modifications to PGE that were found to give reduced skin sensitization potency were incorporated into the new ERMs. ERMs **1** and **2** have cyclohexane rings instead of aromatic, compounds **3** and **4** have a 2-carbon aliphatic chain between the ether oxygen and the epoxide ring instead of a 1-carbon chain, and the ether oxygen is removed in compounds **5** and **6** (Figure 1).

ERM **2** was synthesized in three steps from bisphenol F (Scheme 1). After hydrogenation of the two aromatic rings at 100 °C and 100 bar (step *i*), alkylation with allyl bromide in the presence of sodium hydride (step *ii*) and subsequent epoxidation with 3-chloroperbenzoic acid (mCPBA) (step *iii*) yielded the final product **2** in 69% overall yield. Hydrogenation was found to proceed

faster in isopropanol compared to ethanol.[39] ERM **1** was synthesized from commercially available 4,4'-isopropylidenedicyclohexanol (hydrogenated bisphenol A, **1a**) in an analogous manner (76% overall yield) (Scheme 1). Both **1** and **2** were obtained as *cis*/*trans* isomeric mixtures.

ERMs **3** and **4** were synthesized in two steps from bisphenol A and bisphenol F, respectively (Scheme 2). Alkylation with 4-bromo-1-butene in the presence of base (step *i*) followed by epoxidation with mCPBA (step *ii*) gave the desired products **3** and **4** in overall yields of 7% and 32%, respectively. Potassium carbonate was found to be a suitable base, whereas neither triethylamine nor sodium hydride were appropriate. DMF was found to be a superior solvent to both THF and methanol.

It was initially intended to synthesize ERMs with a two-carbon aliphatic linker between the aromatic ring and the terminal epoxide group. 3-Butenyltributylstannane was synthesized from tri-*n*-butyltin chloride[40] but attempts to couple it with bisphenol F were unsuccessful. Instead, allyltributylstannane was used to give compounds with a one-carbon linker. ERMs **5** and **6** were prepared from bisphenol A and bisphenol F respectively in three steps (Scheme 3). Triflation of the phenolic groups (step *i*) was followed by microwave-assisted Stille coupling to allyltributylstannane (step *ii*).[41] Finally, **5** and **6** were obtained by epoxidation with mCPBA (step *iii*) in overall yields of 29% and 26%, respectively.

Skin Sensitizing Potency Studies

The murine local lymph node assay (LLNA) was used to assess the skin sensitizing potency of the compounds.[42] LLNA results are expressed as EC3 values, which is the estimated concentration of a compound required to induce a 3-fold increase in sensitizing potency compared to a control. Compounds with lower EC3 values are more sensitizing. Our group has previously reported EC3 values for DGEBA and DGEBF of 1.24 and 1.13% w/v (0.036 M and 0.036 M), respectively.[28] This EC3 value for DGEBA is comparable to an independently published value of 1.5% w/v (0.044 M).[43] Initially in this study, analogs of both DGEBA and DGEBF were assessed in the LLNA. However, as DGEBA and DGEBF have the same EC3 values and related compounds **1** and **2** were found to have similar EC3 values (2.3% and 2.4%

w/v, equivalent to 0.065 M and 0.074 M respectively, Figure 2), further *in vivo* testing was carried out only on analogs of DGEBF (ERMs **4** and **6**) due to ethical considerations.

All four of the novel ERMs tested had reduced *in vivo* sensitizing potencies compared to DGEBA and DGEBF (Figure 2 and Supporting Information Table S1). The difference in the EC3 values of the two commercial products (DGEBA and DGEBF) and our four ERMs is illustrated in Figure 2.B. The EC3 value of ERM **6** was the highest (2.56% w/v; 0.091 M) indicating that this is the least sensitizing compound. The EC3 values of the other ERMs tested were approximately twice those of DGEBA and DGEBF, indicating that they are also less sensitizing. The four new ERMs are classified as moderate sensitizers (EC3>2% w/v) in accordance with regulatory guidelines in comparison to the commercially available monomers DGEBA and DGEBF which are classified as strong sensitizers (0.2<EC3≤2% w/v) (Figure 2).[32]

To establish whether there was a statistically significant difference between the sensitizing potencies of the new ERMs and DGEBA, an extension of the LLNA using non-pooled lymph nodes was applied. This modified method was used in our previous work with epoxy resin analogs as well as in other studies by the group.[38, 44] For ethical reasons, we did not want to repeatedly perform LLNA experiments and therefore only ERM **5** was compared with DGEBA. We chose to use the DGEBA analogue **5**, structurally related to the least sensitizing DGEBF analogue **6**, for this experiment as the sensitizing potencies of the pairs of DGEBA/F analogues tested in the ordinary LLNA with pooled lymph nodes were similar. Statistical analysis revealed that DGEBA was significantly more potent in inducing lymph node cell proliferation than **5** at the chosen concentration of 0.064 M. ($P<0.0001$, Figure 3 and Table S2, Supporting Information), indicating that DGEBA is significantly more sensitizing than **5**.

Examining the results of all LLNA *in vivo* experiments indicates that the newer ERMs are less skin sensitizing than DGEBA and DGEBF. The new ERMs are classified as moderate skin sensitizers in comparison to DGEBA and DGEBF, which are strong skin sensitizers.[32] To our knowledge, these are the first reported ERMs that are only moderately sensitizing. This is also the first time that a combined medicinal chemistry/toxicology approach has been used to design ERMs specifically aimed at reducing contact allergy. A reduction in the incidence of ACD due to occupational and non-occupational contact with ERS could be obtained by use of alternative, less sensitizing ERMs such as these alternative compounds.

Polymers from the ERMs

The thermal properties and suitability for polymerisation of the new ERMs were investigated. Epoxy resins were prepared from the novel ERMs using triethylenetetramine (TETA) as the co-reactant (Scheme 4). TETA was chosen because it is commonly used as a curing agent for epoxy resins.[45] The thermal properties of the epoxy resins were assessed using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) and the results were compared to epoxy resins based on DGEBA and DGEBF, prepared with the same molar ratio of the components and under the same reaction conditions.

The DSC results showed that the polymers prepared from ERMs **2** and **4**, DGEBA and DGEBF had almost the same glass transition temperature (T_g), between 42 and 43.6 °C (Table S3, Supporting Information). A T_g value of 40-45 °C has previously been reported for an epoxy resin based on DGEBA/TETA with the same molar ratio. Thus, the DSC analyses demonstrated that the enthalpy involved in the phase transition was approximately the same for all the polymers, including the polymer based on the standard diepoxide DGEBA. Since the analyses did not reveal any differences in performance between the diepoxides, no more DSC experiments were performed. It should be noted that the T_g of the epoxy resin increases linearly and reaches a peak at a one-to-one ratio of amino-hydrogen to epoxy groups. At higher molar ratios of TETA to epoxy monomer, the T_g decreases linearly again.[46] This has been explained as a plasticization effect caused by an excess of curing agent, i.e., TETA.[47]

Figure 4 shows TGA thermograms of the epoxy resins investigated in this study. Thermal stability and degradation data of the epoxy resins (i.e. IDT, E_a, T_{max}, and R_{max}) are summarized in Table 1. Initial decomposition temperature (IDT) indicates the apparent thermal stability of the epoxy resin, i.e., the failure temperatures of the resin in processing and molding, and is determined from the onset of weight loss of the sample in the TGA thermogram. The activation energy (E_a) for the decomposition of the cured epoxy resins was calculated from the TGA thermogram through the integral method based on the Horwitz–Metzger equation.[48, 49] The maximum weight loss rate (R_{max}) and the temperature at maximum rate of weight loss (T_{max}) were taken from the peak values of the differential thermograms. Epoxy resins based on DGEBA and DGEBF were used as controls.

Epoxy resins based on ERMs **1**, **2**, **5** and **6** showed somehow higher IDT and T_{max} values and almost the same thermal stability profiles as the epoxy resins based on the control samples. This demonstrates that the reactivity with TETA was approximately the same for ERMs **1**, **2**, **5** and **6** as for DGEBA and DGEBF and also that the degree of cross-linking obtained with these six ERMs was almost the same. The IDT of the epoxy resins based on ERMs **3** and **4** was considerably lower than the IDT obtained for the other epoxy resins, indicating that these two compounds would be less suitable as commercial replacements for DGEBA and DGEBF. One possible reason for the lower decomposition temperature of the compound **3**- and **4**-based epoxy resins could be higher reactivity of these monomers against TETA, resulting in a lower degree of cross-linking. The activation energy (E_a) of the epoxy resins based on **5** and **6** was of the same magnitude as for resins based on DGEBA and DGEBF (Table 1). Taken together, the TGA data indicate that from a polymerization point of view **5** and **6** are the preferred ERMs, both giving polymers with TETA with a thermal stability close to that obtained with the commercial diepoxides DGEBA and DGEBF.

There has been much unresolved discussion about the health effects of bisphenol A (BPA), which is used in the production of DGEBA.[50] The focus of our work was not to replace BPA but to reduce the skin sensitizing potency and the cause of epidemics in the factories where the ERMs DGEBA and DGEBF are used. Nonetheless, it is worth noting that the new ERMs **1**, **2**, **5** and **6** do not contain a bisphenolic core in their structures. Further research would be required to investigate the effects of these structural differences on the hormonal imbalances associated with BPA.

All of the new monomers had higher EC3 values in the LLNA compared to DGEBA and DGEBF, indicating that they are less sensitizing. As a representative example, ERM **5** was shown to be significantly less sensitizing than DGEBA in vivo. ERMs **1**, **2**, **5** and **6** have excellent thermal properties comparable to DGEBA and DGEBF. Taking the toxicological results in combination with the study of their technical properties, ERMs **5** and **6** emerge as the best candidates for further development. The design and use of improved ERMs with lesser toxicological effects is an excellent way to tackle the problem of contact allergy to ERS, particularly in occupational settings. Other measures, such as legislation, education of workers and use of personal protective equipment, are important to minimize the risks of exposure, but

unfortunately these measures only address the effects of the problem rather than the cause. Our approach recognizes that the cause of the problem is the inherent reactivity of epoxy groups, and suggests a solution based on reducing the skin sensitization potencies of the occupational allergens used. Use of the novel ERMs reported in this paper, particularly ERMs **5** and **6**, has the potential to decrease the incidence of ACD due to ERS, decrease the healthcare costs involved with the diagnosis and treatment of such allergies, and increase the quality of life for persons handling ERS-containing thermosetting materials.

Conclusion

The aim of this research was to investigate structural modifications to existing ERMs, DGEBA and DGEBF, with a view to reducing their sensitizing potency. A series of six novel ERMs was synthesized and found to have reduced sensitizing potency in *in vivo* models. The reduction in skin sensitizing potency was demonstrated to be statistically significant for compound **5** compared to DGEBA. In a preliminary assessment of their technical polymerization properties, four of the six new monomers were found to be comparable to DGEBA and DGEBF. It is anticipated that these new ERMs, particularly compounds **5** and **6**, will be useful as replacements for DGEBA and DGEBF in many occupational applications, reducing the risk of allergic contact dermatitis to those working with epoxy resin systems.

Supporting Information: Complete LLNA information and DSC results are available free of charge via the internet at http://pubs.acs.org.

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Tables

Table 1. Thermal stability and degradation data of the ERMs from thermogravimetrtic analysis in nitrogen

Test compound	IDT[a] °C	T_{max}[b] °C	R_{max}[c] % / °C	E_a[d] KJ/mol
DGEBA	358	382	-1.58	96
DGEBF	336	389	-1.02	103
1	378	400	-1.94	78
2	381	395	-2.86	75
3	296	321	-1.42	49
4	291	312	-1.62	54
5	376	404	-0.77	115
6	373	431	-0.78	98

[a]**IDT=** Initial decomposition temperature which was determined with the temperature of onset weight loss of the sample

[b]**T_{max}=** Temperature at maximum rate of weight loss which was taken as the peak value of the differential thermogravimetric thermograms

[c]**R_{max}=** Maximum weight loss rate or the slope of weight loss at T_{max}

[d]**E_a=** Activation energy for the cured epoxy resins' decomposition

Figure Legends

Figure 1. Structures of bidentate ERMs DGEBA, DGEBF and compounds 1-6

Figure 2.A. Results from the LLNA for bidentate ERMs. B. Enlarged portion showing concentrations from 0 to 0.2 M. Dose-response curves for DGEBA (■), DGEBF (▲), 1 (▼), 2 (♦), 4 (●) and 6 (□). SI=stimulation index. EC3 values; DGEBA: 0.036 M; DGEBF: 0.036 M; 1: 0.065 M; 2: 0.074 M; 4: 0.065 M and 6: 0.091 M

Figure 3. Results from the modified LLNA experiment using single-cell suspensions of the local lymph nodes from individual mice. Statistical analysis using non-parametric Mann-Whitney *U* test showed that when using 0.064 M of either epoxide, DGEBA (□) was significantly more potent in inducing lymph node cell proliferation compared to 5 (○) (P<0.0001)

Figure 4. Thermogravimetric thermograms showing % weight loss at increasing temperatures of epoxy resins based on different ERMs in N_2. DGEBA and analogs: dashed lines; DGEBF and analogs: solid lines. DGEBA (---), DGEBF (—), 1 (---), 2 (—), 3 (---), 4 (—), 5 (---), 6 (—).

Figure 1.

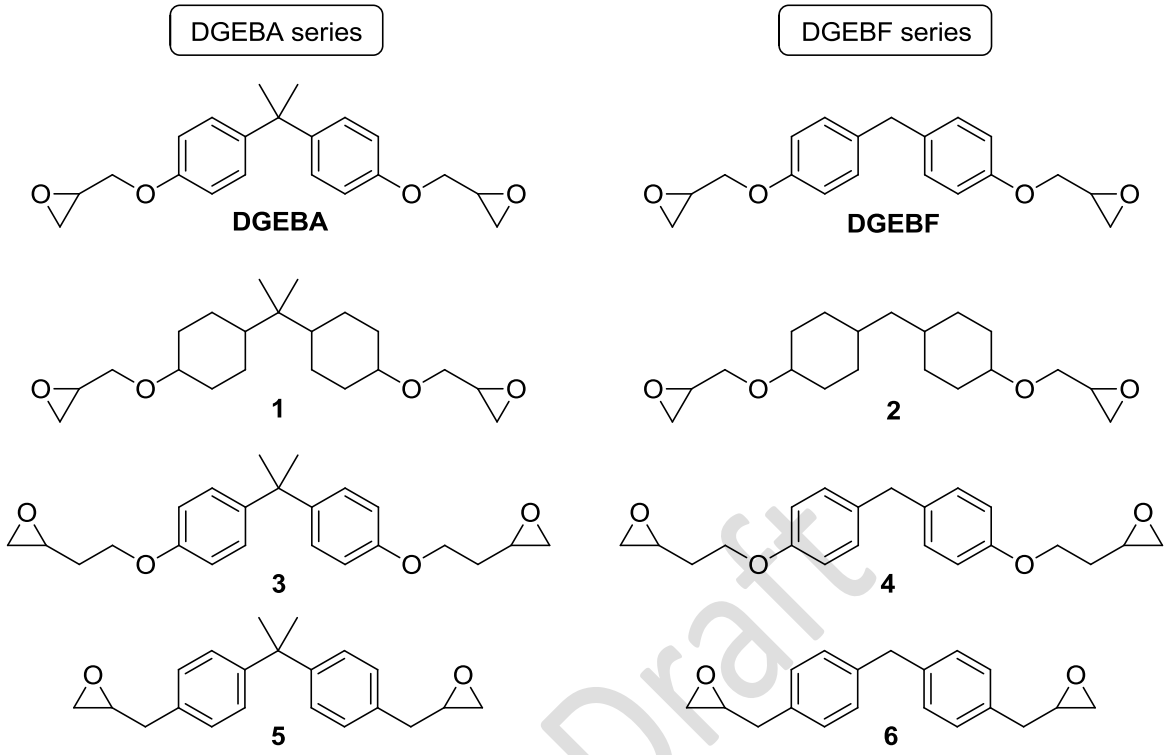


Figure 2.

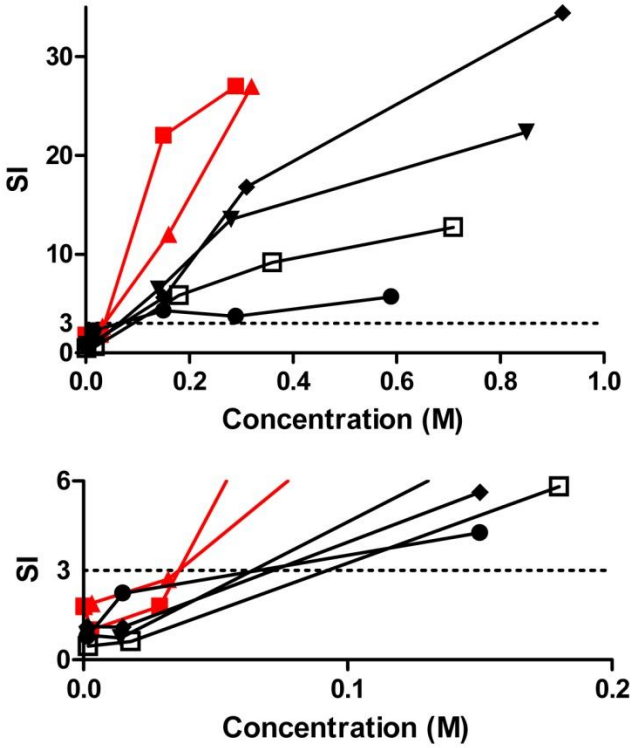


Figure 3.

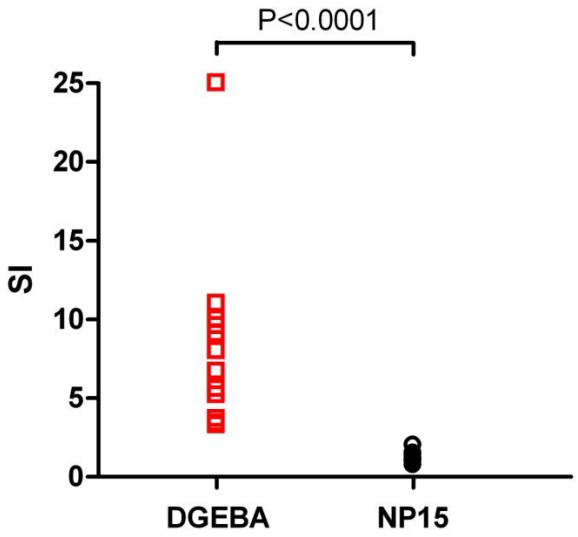
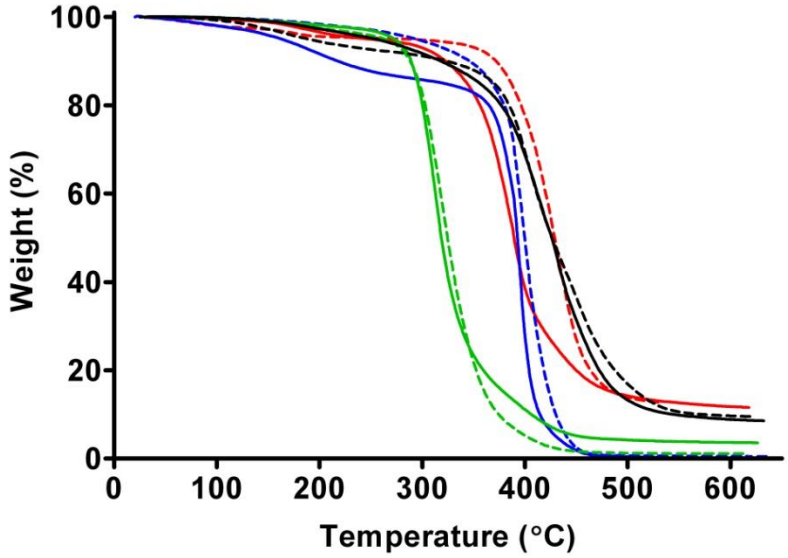


Figure 4.



Scheme Legends

Scheme 1. Synthesis of 1 and 2[a]

[a]Reagents and conditions: (*i*) H_2, 5% Ru/C, isopropanol, 100 ˚C, 100 bar, until complete on TLC; (*ii*) NaH, THF, 0 ˚C, 10 mins, then CH_2CHCH_2Br, rt, 90 min, then reflux until complete on TLC; (*iii*) mCPBA, $CHCl_3$, 0 ˚C then rt until complete on TLC

Scheme 2. Synthesis of 3 and 4[a]

[a]Reagents and conditions: (*i*) $CH_2CH(CH_2)_2Br$, DMF, K_2CO_3, 40 ˚C, overnight; *(ii)* mCPBA, $CHCl_3$, 0 ˚C then rt until complete on TLC

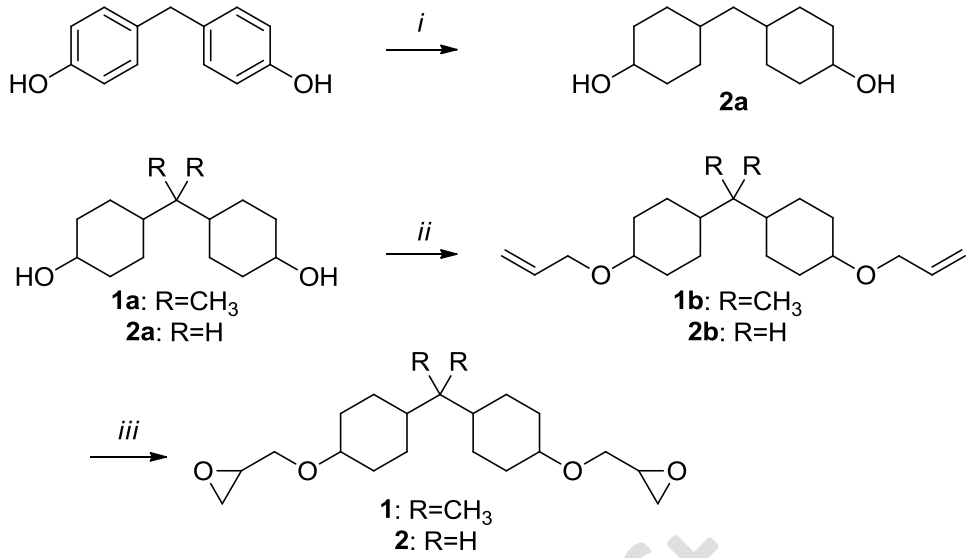
Scheme 3. Synthesis of 5 and 6[a]

[a]Reagents and conditions: (*i*) $O(SO_2CF_3)_2$ CH_2Cl_2, 0 ˚C then rt, 1 h; *(ii)* $Pd(PPh_3)_4$, $CH_2CHCH_2SnBu_3$, DMF, 160 ˚C, 30 min, microwaves; *(iii*) mCPBA, $CHCl_3$, 0 ˚C then rt until complete on TLC

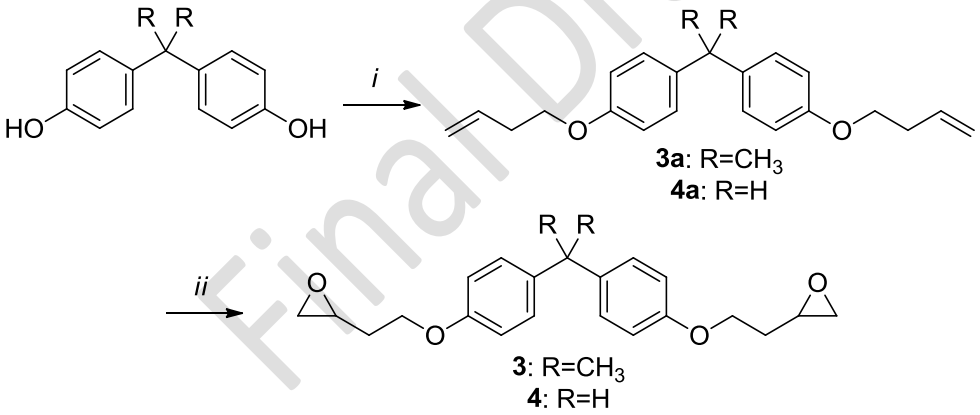
Scheme 4. Polymerization of ERMs with TETA[a]

[a]Reagents and conditions: Acetone (if solid), rt, 20 min; vacuum, 10 min; rt, 24 h; 120˚C, 2 h

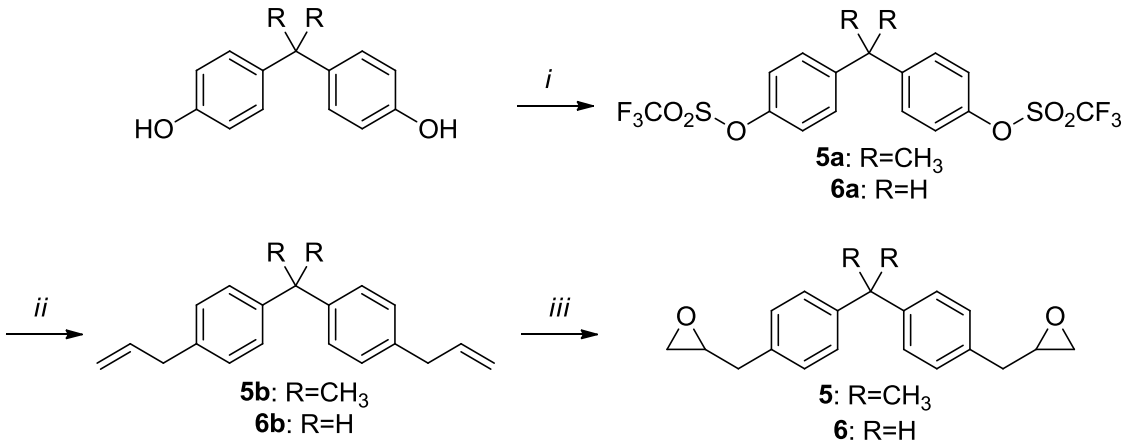
Scheme 1.



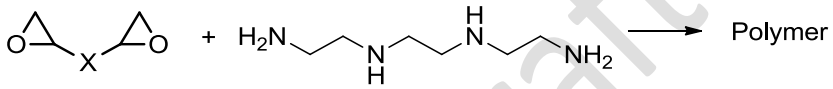
Scheme 2.



Scheme 3.



Scheme 4.



Supporting Information

Improvements in Epoxy Resin Polymer Systems: New Monomers with Reduced Skin Sensitizing Potency

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Table of Contents

Table S1. Detailed results from the LLNA of ERMs[a]

Compound Test Concentration		[^{3}H] Thymidine incorporation (dpm/lymph node)	SI	EC3 value	
(% w/v)	(M)			(% w/v)	(M)
1					
Control		340			
0.05	1.4 x 10^{-3}	283	0.83		
0.5	0.014	247	0.73	2.29	0.065
5	0.14	2188	6.43		
10	0.28	4597	13.51		
30	0.85	7605	22.35		
2					
Control		232			
0.05	1.5 x 10^{-3}	259	1.12		
0.5	0.015	254	1.10	2.39	0.074
5	0.15	1300	5.62		
10	0.31	3883	16.78		
30	0.92	7969	34.43		
4					
Control		531			
0.05	1.5 x 10^{-3}	413	0.78		
0.5	0.015	1186	2.23	2.21	0.065
5	0.15	2260	4.26		
10	0.29	1959	3.69		
20	0.59	3012	5.67		
6					
Control		477			
0.05	1.8 x 10^{-3}	217	0.46		
0.5	0.018	296	0.62	2.56	0.091
5	0.18	2768	5.81		
10	0.36	4360	9.15		
20	0.71	6089	12.69		

[a]Groups of mice were treated with the test substance in five different concentrations, on the dorsum of both ears for three consecutive days. Control animals received the vehicle alone. On day five, all mice were injected intravenously with PBS (250 μL) containing 20 μCi of [methyl-^{3}H]thymidine. After 5 h the mice were sacrificed, the draining lymph nodes were excised and pooled for each group, single cell suspensions of lymph-node cells were prepared, and the thymidine incorporation into DNA was measured by β-scintillation counting. The increase in thymidine incorporation relative to vehicle-treated controls was derived for each experimental group and recorded as stimulation index (SI). The EC3 values (the estimated concentration required to induce a SI of 3) were calculated using linear interpolation

Table S2. Detailed results from the modified LLNA of ERMs DGEBA and **5**[a]

Compound	Test concentrations (%)	(M)	dpm/ lymph node	SI	No. of animals
Control			**238**[b]	**1**	**12**
5	1.85	0.064	363	1.5	1
	1.85	0.064	182	0.76	1
	1.85	0.064	292	1.2	1
	1.85	0.064	236	0.99	1
	1.85	0.064	238	1.0	1
	1.85	0.064	249	1.1	1
	1.85	0.064	466	2.0	1
	1.85	0.064	344	1.4	1
	1.85	0.064	363	1.5	1
	1.85	0.064	356	1.5	1
	1.85	0.064	344	1.4	1
	1.85	0.064	483	2.0	1
DGEBA	2.18	0.064	1226	5.2	1
	2.18	0.064	1896	8.0	1
	2.18	0.064	2418	10	1
	2.18	0.064	2169	9.1	1
	2.18	0.064	5867	25	1
	2.18	0.064	1342	5.6	1
	2.18	0.064	1589	6.7	1
	2.18	0.064	2618	11	1
	2.18	0.064	2289	9.6	1
	2.18	0.064	880	3.7	1
	2.18	0.064	776	3.3	1
	2.18	0.064	815	3.4	1

[a]The local lymph node experiments were performed as described in the experimental procedures. The SI corresponds to the increase in [methyl-^{3}H]thymidine incorporation into DNA of treated animals relative to the mean dpm/lymph node of the vehicle-treated controls.

[b]Mean dpm/lymph node. Individual values from controls: 162, 181, 145, 334, 344, 221, 290, 102, 309, 100, 404, 264

Table S3. Polymerization parameters and characteristics of different epoxy resins from DSC

	Glass transition temperature T_g / °C	Decomposition temperature $T_{Decomposition}$ (50%) / °C
Epoxy resin based on DGEBA	43.3	427
Epoxy resin based on DGEBF	42.0	404
Epoxy resin based on 2	43.5	392
Epoxy resin based on 4	43.6	323