ACTA DERMATO-VENEREOLOGICA

SUPPLEMENTUM 159

OCCUPATIONAL SKIN DISEASES FROM EPOXY COMPOUNDS

Epoxy resin compounds, epoxy acrylates and 2,3-epoxypropyl trimethyl ammonium chloride

By
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Dissertation for the degree of Doctor of Technology to be presented with due permission for public examination and debate in Auditorium Kem 2 at Helsinki University of Technology (Espoo, Finland) on the 28 of June, 1991, at 12:00 noon.

HELSINKI 1991

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To Ilmo

3. INTRODUCTION

An occupational skin disease is a pathological skin condition for which occupational exposure can be shown to be a major or contributory factor. In Finland it is defined by the Occupational Disease Act (1343/88), supplemented by an ordinance (1347/88) (52). The Finnish Register of Occupational Diseases was established at the Institute of Occupational Health in 1964. Occupational skin diseases have been recorded in the Register as a separate category since 1975 (52, 178).

The first patents on epoxy resins were granted in the 1920s and early 1930s (80), and the first epoxy adhesive was demonstrated at the Swiss Industries Fair in 1946 (144). Large-scale production of epoxy resins began in 1952 (80). By the end of the 1960s at least 25 distinct types of epoxy resins were commercially available (116).

The development of dental materials based on epoxy resins began in the early 1950s. The first epoxy acrylate, known as BIS-GMA (2,2-bis(4-(2-hydroxy-3-methacryloxy-propoxy)phenyl)propane), was developed by Dr. R. L. Bowen in 1956 when he incorporated glycidyl methacrylate into bisphenol A. Dental composite resin products based on BIS-GMA have been used in dental restoration work since 1962 (27–29).

Occupational dermatitis caused by exposure to epoxy resin compounds was observed in the 1950s, shortly after epoxy resins were introduced (33, 73, 79, 122, 142, 143, 157).

The total world production of epoxy resins was about 500 000 tons a year in 1984. Thereafter epoxy resin consumption has probably been growing 2–4 % per year despite strong competition from materials which are less expensive, less laborious to process and less hazardous to work with (131).

Chemistry and properties of epoxy compounds

In this study, *epoxy compounds* consist of the following four categories: (i) any compound containing an epoxy group in its molecule, such as epoxy resins, reactive diluents and 2,3-epoxypropyl trimethyl ammonium chloride (EPTMAC); (ii) epichlorohydrin and bisphenol A, the primary raw materials of epoxy resins; (iii) hardeners used to cure epoxy resins; and (iv) epoxy acrylates. Epoxy resins are normally used in conjunction with other materials, in what is called an epoxy resin system, consisting of

2. ABBREVIATIONS

AGE	allyl glycidyl ether
BDDGE	1,4-butanediol diglycidyl ether
BGE	*n*-butyl glycidyl ether
BIS-GA	2,2-bis(4-(2-hydroxy-3-acryloxypropoxy)phenyl)propane
BIS-GMA	2,2-bis(4-(2-hydroxy-3-methacryloxypropoxy)phenyl)propane
BIS-EMA	2,2-bis(4-(2-methacryloxyethoxy)phenyl)propane
BIS-MA	2,2-bis(4-(methacryloxy)phenyl)propane
CGE	cresyl glycidyl ether
DETA	diethylene triamine
DGEBA	diglycidyl ether of bisphenol A
DGEHHPA	diglycidyl ester of hexahydrophthalic acid
EDA	ethylene diamine
EPTMAC	2,3-epoxypropyl trimethyl ammonium chloride
HDDGE	1,6-hexanediol diglycidyl ether
HHPA	hexahydrophthalic anhydride
HSA	human serum albumin
Ig	immunoglobulin
IPDA	isophorone diamine
MDA	4,4'-diaminodiphenyl methane
MHHPA	methyl hexahydrophthalic anhydride
MTHPA	methyl tetrahydrophthalic anhydride
MW	molecular weight(s)
no.	number(s)
NPGDGE	neopentyl glycol diglycidyl ether
PA	phthalic anhydride
pet.	petrolatum
PGE	phenyl glycidyl ether
TEPA	tetraethylene pentamine
TETA	triethylene tetramine
TMD	trimethyl hexamethylene diamine
tris-DMP	2,4,6-tris-(dimethylaminomethyl)phenol
UV	ultraviolet
w/w	weight/weight
XDA	xylylene diamine

1. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on investigations carried out at the Institute of Occupational Health. It summarized the following publications, which are referred to in the text by their Roman numerals.

I Jolanki R, Estlander T, Kanerva L. Occupational contact dermatitis and contact urticaria caused by epoxy resins. *Acta Derm Venerel (Stockh)* 1987; Suppl 134: 90–4.

II Jolanki R, Kanerva L, Estlander T, Tarvainen K, Keskinen H, Henriks-Eckerman M-L. Occupational dermatoses from epoxy resin compounds. *Contact Dermatitis* 1990; 23: 172–83.

III Kanerva L, Jolanki R, Tupasela O, Halmepuro L, Keskinen H, Estlander T, Sysilampi M-L. Immediate and delayed allergy from epoxy resins based on diglycidyl ether of bisphenol A. *Scand J Work Environ Health* 1991; 17: 208–15.

IV Kanerva L, Jolanki R, Estlander T. Allergic contact dermatitis from non-diglycidyl-ether-of-bisphenol-A epoxy resins. *Contact Dermatitis* 1991; 24: 293–300.

V Jolanki R, Sysilampi M-L, Kanerva L, Estlander T. Contact allergy to cycloaliphatic epoxy resins. In: Frosch PJ, Dooms-Goossens A, Lachapelle J-M, Rycroft RJG, Scheper RJ, ed. *Current topics in contact dermatitis*. Berlin, Heidelberg: Springer-Verlag, 1989: 360–7.

VI Jolanki R, Estlander T, Kanerva L. Contact allergy to an epoxy reactive diluent: 1,4-butanediol diglycidyl ether. *Contact Dermatitis* 1987; 16: 87–92.

VII Kanerva L, Jolanki R, Estlander T. Allergic contact dermatitis from epoxy resin hardeners. *Am J Contact Dermatitis* 1991; 2: (in press).

VIII Kanerva L, Jolanki R, Estlander T. Occupational dermatitis due to an epoxy acrylate. *Contact Dermatitis* 1986; 14: 80–4.

IX Kanerva L, Estlander T, Jolanki R. Allergic contact dermatitis from dental composite resins due to aromatic epoxy acrylates and aliphatic acrylates. *Contact Dermatitis* 1989; 20: 201–11.

X Estlander T, Jolanki R, Kanerva L. Occupational dermatitis to 2,3-epoxypropyl trimethyl ammonium chloride. *Contact Dermatitis* 1986; 14: 49–52.

In addition, some unpublished data (referred to as unpublished) have been included in the study.

CONTENTS

the epoxy resin and a hardener, reactive diluent, filler, or other additives (35). The compounds of the system are called epoxy resin compounds.

Epoxy resin compounds

Epoxy resins contain at least two epoxy groups, also called oxirane or epoxide groups, in their molecules. The term epoxy resin is commonly used to indicate the resins in both the thermoplastic (uncured) and thermoset (cured) state (116). The thermoplastic resins can be cross-linked through the use of a variety of curing agents (hardeners) to form thermoset plastics with insoluble three-dimensional structures.

Epoxy resins are generally prepared by the coupling of epichlorohydrin with compounds that possess at least two reactive hydrogen atoms (131). The reaction products of epichlorohydrin and bisphenol A resulted in the first commercial epoxy resins, which are generally mixtures of diglycidyl ether of bisphenol A (DGEBA), with a molecular weight (MW) of 340, and oligomers with higher MW. The average number of repetitive parts in the oligomers ranges from essentially 0 to approximately 25 (see Figure 1) (13). Resins with a low MW (the average value of the repetitive parts approaching 0 and the average MW being 350–400) and high yields of monomeric DGEBA (up to more than 90 %) are liquids with a relatively high viscosity. Resins with a high molecular mass (the average value of the repetitive parts being more than 2 and the average MW being more than 900) are solids (131). The amount of DGEBA in the solid resins may be more than 15 % (87).

DGEBA epoxy resins possess a rather unique combination of properties, for example, easy cure, low shrinkage, high adhesive strength, high mechanical properties, high electrical insulation, good chemical resistance and versatility (116). Special properties of non-DGEBA epoxy resins (Figure 2) have made the non-DGEBA epoxy resins competitive with the less expensive DGEBA resins for certain applications. However, the epoxy resin based on DGEBA still forms 75 % of the currently used epoxy resins (131).

Reactive diluents are used to modify epoxy resins, principally by reducing their viscosity. Reactive diluents are generally glycidyl ethers, sometimes glycidyl esters, of aliphatic or aromatic structure (Figure 3) which participate in the cross-linking reactions by their epoxy groups and become chemically linked to cured epoxy resins (23, 131). Aliphatic diluents include such compounds as *n*-butyl glycidyl ether (BGE) and 1,4-butanediol diglycidyl ether (BDDGE), whereas phenyl glycidyl ether (PGE) and cresyl glycidyl ether (CGE) are good examples of aromatic diluents.

When epoxy resins are used in two-component products, the hardeners are added to the resins immediately preceding the application, and the subsequent cross-linking occurs either at an ambient or elevated temperature. One-component products contain latent curing agents which are inactive at normal storage temperatures but which initiate the cross-linking when heated. Examples of one-component epoxy products include powder paints and special adhesives (23, 139).

Currently, a wide variety of curing agents is available. Primary and secondary polyamine hardeners are aliphatic, cycloaliphatic or aromatic amines. The molecules contain NH -groups in addition to two NH_2 -groups (Figure 4). Aliphatic amines include, for example, ethylene diamine (EDA), diethylene triamine (DETA) and triethylene tetramine (TETA); isophorone diamine (IPDA) is a cycloaliphatic amine; and 4,4'-diaminodiphenyl methane (MDA) belongs to the group of aromatic amines (131, 159). Aliphatic and cycloaliphatic amines are low-viscosity liquids that react readily with epoxy resins at ambient temperatures; less reactive aromatic amines require an elevated curing temperature (131).

The polyamines are often troublesome to work with because of their reactivity and volatility, and also because of their irritating and sensitizing properties to the skin and respiratory tract. To overcome these problems, less volatile and less reactive polyamides and amine-epoxy adducts have been developed. Polyamides are prepared by combining aliphatic amines (e.g., DETA or TETA) with fatty acids. Amine-epoxy adducts are formed in a reaction between epoxy resin and an excess of polyamine, mostly DETA, TETA or IPDA (13). In the amine-epoxy adducts used in metal paints, the content of free amine is about 5 %, but for those used in floor and concrete coatings the corresponding value is about 20 % (12). Free DGEBA is not found in amine-epoxy adducts (87).

When DGEBA epoxy resins are cured by polyamine-bearing hardeners at room temperature, the amounts of unreacted DGEBA and polyamine decrease rapidly within one to two days, but thereafter the decrease is slow. Nevertheless, after one week's cure 0.02–12 % of free DGEBA and 0.01–1 % of free DETA were found when six different epoxy resin products were experimentally cured by DETA (86).

Tertiary polyamines, for example, 2,4,6-tris-(dimethylaminomethyl)phenol (tris-DMP) (Figure 4), are catalyst-type curing agents used for epoxy resin homopolymerization (131).

Organic anhydride hardeners are used when good electrical properties are required. With the anhydrides the cross-linking reaction is catalyzed by tertiary amines, and an

elevated curing temperature (50–200°C) is used (84). The anhydrides include, for example, phthalic anhydride (PA) and phthalic anhydride derivatives, such as methyl hexahydrophthalic anhydride (MHHPA) (Figure 5) (131).

Typical latent curing agents in powder paints are composed of about 4 % hardeners, such as dicyandiamide or pyromellitic anhydride. The polymerization is achieved in a curing oven at about 200°C (139).

Epoxy acrylates

Epoxy acrylates, also called vinyl esters, are manufactured from epoxy resins and (meth)acrylic acids (9, 13). BIS-GMA (Figure 6) is manufactured from DGEBA and methacrylic acid or bisphenol A and glycidyl methacrylate (28, 127). Epoxy acrylates have desirable properties of both epoxy resins and polyacrylates, for example, a relatively low volumetric shrinkage during the curing process, as epoxy resins do, and an adequate polymerization rate (2–5 min at 37°C), as methacrylates of low molecular mass do (96, 154, 162).

The polymerization of epoxy acrylates is activated either chemically by peroxides and tertiary amines or by visible or ultraviolet (UV) light. Chemically cured dental restorative composite material is available in two BIS-GMA-based components. The tooth-colored base paste contains a tertiary amine (1–2 %), and the catalyst paste contains dibenzoyl peroxide (1–1.5 %). The light-cured composite material consists of only one BIS-GMA-based component (9, 96).

2,3-Epoxypropyl trimethyl ammonium chloride (EPTMAC)

EPTMAC is a quaternary ammonium compound with an MW of 152 and an epoxy group in its molecule (Figure 7). It is prepared from epichlorohydrin, trimethylamine and water (53).

Use of epoxy compounds

Epoxy resin compounds

Of the total world production of epoxy resins, more than 500 000 tons a year, about 45 % is used in coatings, and the remainder (55 %) in structural applications (13, 72, 131).

No epoxy resin production takes place in Finland. The import of epoxy resins is about 4000 tons, 60 % being solid and 40 % liquid resins (2, 84). Most epoxy resins (about 80 %) are used for coating purposes (12).

The scope of epoxy resin application is broad. Epoxy resins are used to provide good resistance against heat, water, and most chemicals and to form tough, high-strength adhesive bonds on metal and many other surfaces (e.g., plastics, rubber, wood, glass and ceramics). They are also used to insulate and encapsulate, as well as in the assembly of a wide variety of electrical and electronical devices and in the manufacture of plastic pieces, such as sporting goods (59, 84, 131).

The surface coatings are applied as reactive mixtures of epoxy resins, curing agents and a variety of possible solvents, reactive diluents, pigments and fillers. Most epoxy surface coatings are based upon DGEBA epoxy resins. Liquid epoxy resins are used in two-component solventless coatings. Water-borne epoxy coatings are prepared by the dispersion of epoxy resins modified with water-soluble functional groups or by the emulsification of DGEBA epoxy resins with surfactants (131). Both solventless and solvent-borne epoxy coatings have been employed mainly as anticorrosion protection for metals (e.g., marine and maintenance coatings), as waterproof protection for concrete, and as chemical-resistant protection for floors and walls (13, 131). Two-component coatings can be cured at ambient temperatures with polyamines, polyamides and amine-epoxy adducts. Tertiary amines (e.g., tris-DMP) are frequently used to accelerate the curing rates (116). Powder paints include solid DGEBA epoxy resins mixed with a curing agent and an accelerator (139).

Epoxy resins have structural applications in the use of bonding and adhesive materials, reinforced plastics or composites and in casting, moulding and tooling; they also have constructional applications in flooring, paving and aggregation (13, 72, 89, 131).

Epoxy adhesives are widely used as two-component, ambient cure, general adhesives in domestic applications, as in two-tube epoxy kits, and also in industrial applications. One-component, heat-cured epoxy adhesives are also available (23). Liquid DGEBA epoxy resins are used to formulate most of the one- and two-component epoxy adhesives. The curing agent generally consists of polyamides or aliphatic polyamines (e.g., DETA and TETA). Epoxy adhesives can be formulated with reactive diluents to give mixtures of low viscosity with improved wetting, spreading and penetrating action (158).

Reinforced plastics are combinations of strong, continuous glass and carbon fibres and polymeric binders. Glass fibres, the woven cloth, roving or chopped mat can be

impregnated with an epoxy resin-curing agent matrix. Epoxy composites made with glass fibres usually have a DGEBA epoxy resin-diamine matrix. Epoxy composites are used, for example, in sporting goods, such as tennis racquet frames, ski-sticks and fishing rods, automotive and aircraft industries, and in military and aerospace applications (32, 71, 111, 131).

Casting resins are liquid and solventless mixtures of low molecular mass epoxy resin, a curing agent and additives (e.g., fillers, reinforcements and catalysts). The mixture is poured into moulds and cured to solid structures. The casting resins are mainly used as electrical insulating material in the manufacture of transformers, switchgear, circuit breakers, conductors and insulators. Anhydride-cured cycloaliphatic epoxy resins are commonly used to improve arc-track resistance and weatherability (e.g., in outdoor electrical insulators) (131).

Epoxy moulding compounds are solid mixtures of epoxy resin (e.g., epoxy novolaks), a curing agent and catalyst, mould-release compounds, fillers, and other additives. The moulding compounds become liquid at relatively low temperatures (150–200°C) (3, 131). Epoxy moulding compounds are used, for example, in the manufacture of models and engine covers and in the encapsulation of electrical components (59).

Low viscosity liquids (e.g., vinyl cyclohexene diepoxide) are used in preparative work for electron microscopy (43, 99).

Epoxy acrylates

BIS-GMA is used in dental filling and coating materials, in dentin primers (105), and also when fissures in posterior teeth are sealed to protect them from caries (96). Epoxy acrylates also have many industrial applications. They are used in UV curable printing inks and coatings (18–20, 49), in corrosion resistant equipment, body and structural parts for land transportation equipment, electrical insulation for heavy electrical equipment, and in marine applications (9). Solventless epoxy acrylate coatings are cured by initiation with UV light (13).

2,3-Epoxypropyl trimethyl ammonium chloride (EPTMAC)

EPTMAC is used in the manufacture of cationic starch as a cationizing chemical and in the manufacture of ion-exchange resins (14, 53).

Literature review of health hazards due to epoxy compounds

Contact allergy

General

The first reports of sensitization to epoxy compounds were published in the 1950s in Switzerland, The Netherlands, the United States and Great Britain, where most of the epoxy resin development took place (33, 73, 79, 122, 142, 143, 157).

The highly alkaline amine hardeners were first considered to be responsible for most cases of dermatitis and sensitization observed during the handling of components of the epoxy system (16, 25, 26, 110), but later the resin was identified as the main cause. Gaul (73, 74) suspected that bisphenol A was the sensitizing structure in the resin, whereas Calnan (35) believed that the epoxy group of epichlorohydrin was more likely to be responsible for contact allergy. Thorgeirsson and Fregert (167) finally confirmed that the main sensitizer was DGEBA (i.e., DGEBA-based epoxy resin oligomer with an MW of 340). In the guinea pig maximization test the oligomer with an MW of 624 was also a sensitizer, but it had minor sensitizing capacity, whereas oligomers with an MW of more than 900 did not induce sensitivity (169).

Diglycidyl ether of bisphenol A (DGEBA) epoxy resins

Of 1690 patients who were not employed in the epoxy resin industry, 1.6 % developed allergic patch test reactions to DGEBA epoxy resin at the Department of Dermatology, Lund, up to 1964 (68). The DGEBA epoxy resin, because of being one of the top 20 contact allergens, was included in the European standard patch test series in 1966 (141).

Allergic contact dermatitis caused by epoxy resin is often due to exposure to two-component glues and bonding agents (17, 91, 138, 150). One patient, a floorlayer, became sensitized from a one-pack epoxy glue (41). Even small amounts in ready products are sufficient to cause sensitization, for example, contaminants in hand-applied eye lenses (81) and clothes (123).

There are also several reports of workers sensitized to epoxy resins used as binders in carbon or glass fibre reinforced plastics products (30, 32, 36, 38, 42, 93, 125, 164). Epoxy resins used in electron microscopy for tissue embedding have caused a few cases of allergic sensitization (43, 97).

Contact sensitivity from epoxy resin in medical equipment has been reported (7, 24, 62, 75, 124, 128, 148, 170, 181, 188). Allergic contact dermatitis has also been induced by unhardened epoxy resin in some other finished products (54, 63–65, 90, 121). Epoxy resins used as stabilizers and plasticizers for polyvinyl chloride have also been shown to be sensitizers (6, 67).

Non-diglycidyl ether of bisphenol A (non-DGEBA) epoxy resins

Most of the persons who have contact allergy to epoxy resins have been sensitized to DGEBA epoxy resins (3, 37, 55, 61). In the 1980s allergic contact dermatitis from non-DGEBA epoxy resins was also reported [i.e., from tetraglycidyl-4,4'-methylene dianiline and *ortho*-diglycidyl phthalate (32, 117), 4-glycidyloxy-N,N-diglycidylaniline (125), vinyl cyclohexene diepoxide (43), triglycidyl isocyanurate (126, 137), and a triglycidyl derivative of *para*-aminophenol (117)]. Many of the patients with allergic contact dermatitis from non-DGEBA epoxy resins did not have contact allergy to DGEBA epoxy resin.

Reactive diluents

Lea *et al.* (115) found that an epoxy reactive diluent (i.e., BGE) irritated and sensitized human volunteers. An investigation of Fregert and Rorsman (68) emphasised the occurrence of contact allergy to reactive diluents in patients allergic to epoxy resins. Epoxy reactive diluents have been revealed to be strong sensitizers in guinea pigs (165, 168), and, in a few sporadic cases, in humans (21, 39, 118, 152, 153).

Hardeners

In several investigations since the 1950s polyamine hardeners have been found to be contact irritants and sensitizers (25, 26, 33, 45, 122, 142). In the guinea pig maximization test polyamine hardeners with a low MW were found to be strong sensitizers. Polyamides and amine-epoxy adducts induced sensitization probably only due to the polyamine remnants (166).

Sporadic reports of contact allergy to non-amine hardeners have been published in the case of a latent curing agent, dicyandiamide (160), and an anhydride hardener, dodecenyl succinic anhydride (76).

Bisphenol A

Reports of contact allergy to bisphenol A are rather controversial. In a few studies a high incidence of bisphenol A allergy was found among those sensitized to epoxy resin (74, 112). These results have not been confirmed by other investigations (66, 145, 180).

Epichlorohydrin

A rather high risk of sensitization to epichlorohydrin has been reported for workers in plants manufacturing epoxy resins (145, 179, 180).

Epoxy acrylates

The guinea pig maximization test has shown that epoxy acrylates are weak to extreme sensitizers (18, 19). Despite increasing use of epoxy acrylates in industry, only a few reports of contact allergy have previously been published (18, 20, 49, 134).

2,3-Epoxypropyl trimethyl ammonium chloride (EPTMAC)

EPTMAC has been shown to be a sensitizer in guinea pigs and to cause allergic contact dermatitis in humans (14).

Other skin disorders

Irritative low molecular degradation products may be produced in the tooling of epoxy products and in heating processes (51). Amine and anhydride hardeners and epichlorohydrin irritate the skin and conjunctivae. In addition to causing irritant contact dermatitis epichlorohydrin, as a highly reactive compound, and aliphatic polyamines, as highly alkaline compounds (pH 13–14), can cause corrosive burns on the skin (3, 95). Ippen and Mathies (95) have described protracted chemical burns minutes or several hours after the exposure of five patients to epichlorohydrin.

Laurberg and Christiansen (114) have reported purpuric allergic contact dermatitis as a result of exposure to an epoxy resin paint. In the polymerization of epoxy resins, Yamakage *et al.* (189) described scleroderma-like disorders from vapours suspected of coming from a cycloaliphatic amine, and Bachurzewska and Borucka (11) reported Raynaud syndrome type ailments. Rycroft (155) reported the case of a patient whose epoxy resin sensitization was followed by atypical psoriasis.

Contact urticaria can be caused by aliphatic polyamine hardeners (55). In a report from 1974 (187), a patch test with an epoxy resin induced generalized urticaria. In 1983 Suhonen (164) reported on two patients who showed immediate urticarial reactions to a DGEBA epoxy resin of the workplace in a patch test, but the DGEBA epoxy resin in the patch test standard series did not give an immediate reaction. The causative agent was not further clarified.

Photosensitivity has been reported in relation to the heating of DGEBA epoxy resin (5) and the use of epoxy powder paints (77). Allen and Kaidbey (5) considered the photosensitivity to be probably due to bisphenol A contained in the resin. They observed persistent light reactivity among the patients. Similar persistent light reactivity has been found in mice photosensitized by bisphenol A (120).

Allergic rhinitis and asthma

The first detailed report of allergic rhinitis acquired during the processing of epoxy resins was reported by Morris (130). Allergy of the respiratory tract, rhinitis and asthma have been caused by polyamine or anhydride hardeners (15, 101, 106–109, 135, 185).

Genotoxicity and carcinogenicity

Glycidyl ethers have generally been shown to be direct-acting mutagens, in some but not all, *in vitro* assay systems (8, 82, 94, 132, 147, 184). According to the International Agency for Research on Cancer, epichlorohydrin is *probably* carcinogenic to humans (Group 2A), PGE is *possibly* carcinogenic to humans (Group 2B), and DGEBA (i.e., DGEBA epoxy resin with an MW of 340) and vinyl cyclohexene diepoxide are *unclassifiable* as to their carcinogenicity to humans (Group 3) (94).

Many aromatic amine hardeners, including MDA, have shown mutagenic activity in short-term assays (129, 161). From results of positive short-term tests for genotoxicity Vleminckx *et al.* (183) considered EPTMAC to be a potential carcinogen.

4. AIMS OF THE STUDY

The objectives of the present study were:

1. To analyse in detail occupational skin diseases caused by epoxy compounds. The period of 1974–1990 was chosen for the investigation. The purpose was to study in detail the epoxy compound materials having caused the dermatoses and to identify the allergenic epoxy compounds.

2. To determine in detail the methods to be used to examine patients suspected of having occupational dermatoses induced by epoxy compounds.

3. To gather information on the risks of occupational dermatoses induced by epoxy compounds and data on the means of preventing the dermatoses.

5. MATERIALS AND METHODS

In this section the patients who had occupational dermatoses due to epoxy compounds, the materials used for testing, and the chemical and clinical investigations used to identify the allergenic compounds and reveal the diagnosis are described.

The primary diagnosis, the main cause, the relevancy of an exposure and the exposure time were as defined in publication II.

Patients

The patients for the study were selected from the 3713 persons examined at the Section of Dermatology, Institute of Occupational Health, Helsinki, for suspected occupational skin disease during 1974–1990 (I–IV, VI–X) and from 18 patients investigated in 1985 at the Vaasa Central Hospital (V).

One hundred and thirty patients diagnosed at the Institute as having occupational skin disease due to epoxy compounds formed the backbone of the present study (I–IV, VI–X). Some unpublished data of the patients have been included. Twelve of 18 patients examined at the Vaasa Central Hospital were diagnosed as having occupational dermatitis due to exposure to epoxy resin compounds (V). These patients were also included in the study.

Chemicals

A list of the chemicals used to make the skin test substances follows. Available data on the purity of the chemicals are also given.

Epoxy resins (Figure 2)

Aracast CY 350 was provided by Ciba-Geigy, Switzerland. According to the manufacturer, it is an unmodified, solvent-free heterocyclic epoxy resin based on dimethyl hydantoin.

Araldit CY 184, a cycloaliphatic epoxy resin, was provided by Ciba-Geigy. The purity of diglycidyl ester of hexahydrophthalic acid (DGEHHPA) in this substance was about 50 % according to gas chromatography (III, V).

Epikote 827 was provided by Shell Chemie, The Netherlands. The purity of DGEBA in this substance was 89 % according to high-performance liquid chromatography (III).

Lekutherm X 100, a cycloaliphatic epoxy resin, was provided by Bayer AG, Germany. The purity of DGEHHPA in this substance was about 70 % according to gas chromatography (III, V).

Lekutherm X 287 was provided by Bayer AG. According to the manufacturer, it is a mixture of DGEBA epoxy resin (average MW lower than 700) and an epoxy resin based on aniline and a plasticizer. As determined by high-performance liquid chromatography, the amount of DGEBA was 43 % (III, V).

LX-112 Resin was provided by Ladd Research Industries, Inc., USA. According to the manufacturer, it is a mixture of diglycidyl and triglycidyl ether of glycerol. As determined by gas chromatography, the amounts of reactive diluents and DGEBA were below the detection limits (1–10 µg/mg) (99).

MCP primer, provided by Scanpol Oy, Finland, is a water-borne epoxy resin coating whose composition is unknown.

Rütapox 0451 was provided by Bakelite GmbH, Germany. According to the material safety data sheet, it contains 100 % epoxy resin based on the reaction product of bisphenol A and tetrabromo-bisphenol A. According to the high-performance liquid chromatography determinations, it contained 19 % DGEBA and 4.3 % DGEBA-based epoxy resin oligomer with an MW of 624. In addition, a 5 % content of an unspecified derivative of dibromophenol was detected (IV). The brominated epoxy oligomers could not be detected by the high-performance liquid chromatographic method used for DGEBA.

Samicatherm 366.28 tape was provided by Isola-Werke, Switzerland. According to the manufacturer, the tape contains phenol novolak epoxy resin and a latent catalyst of boron trifluoride complexed with an amine.

Reactive diluents (Figure 3)

Allyl glycidyl ether (AGE) was provided by Merck-Schuchardt, Germany. According to the manufacturer, the purity of AGE is 98 %.

1,4-Butanediol diglycidyl ether (BDDGE) of technical grade was provided by Aldrich-Chemie, Germany. The purity of BDDGE was 60 %, as determined by gas chromatography (VI).

Cardura E 10, glycidyl ester of synthetic fatty acids, was provided by Shell Chemie.

Epoxide 8, glycidyl ether of aliphatic alcohols, was provided by Procter & Gamble, Ltd., USA.

1,6-Hexanediol diglycidyl ether (HDDGE) (Grilonit RV 1812) and neopentyl glycol diglycidyl ether (NPGDGE) (Grilonit RV 1815) were provided by EMS-Chemie AG, Switzerland.

Polyamine hardeners (Figure 4)

Tetraethylene pentamine (TEPA) of technical grade was provided by Fluka Chemie AG, Switzerland. According to the manufacturer, the content of TEPA mixed with pentaethylene pentamine is about 85 %; the rest is TETA.

Trimethyl hexamethylene diamine (TMD), provided by Chemische Wirke Hüls AG, Germany, consists of equal parts of the isomers 2,2,4- and 2,4,4-TMD and has a purity of at least 99.7 % according to the manufacturer.

2,4,6-Tris-(dimethylaminomethyl)phenol (tris-DMP) (Curing Agent K 54) was provided by Shell Chemie. According to the manufacturer, Curing Agent K 54 is 100 % tris-DMP.

Xylylene diamine (XDA) (Euredur 14) was provided by Schering AG, Germany. According to the manufacturer Euredur 14 contains 30 % XDA.

Anhydride hardeners (Figure 5)

Methyl hexahydrophthalic anhydride (MHHPA) (Lekutherm-Härter M) was provided by Bayer AG. According to the material safety data sheet Lekutherm-Härter M is approximately 100 % MHHPA.

Methyl tetrahydrophthalic anhydride (MTHPA) (FW-750) was provided by Hitachi Chemical Co., Ltd., Japan. According to the material safety data sheet FW-750 is approximately 100 % MTHPA.

Hexahydrophthalic anhydride (HHPA) (HT 907) was provided by Ciba-Geigy. According to the manufacturer, HT 907 is mainly HHPA.

Phthalic anhydride (PA) was provided by Neste Oy, Finland. According to the material safety data sheet, it is 100 % PA.

2,3-Epoxypropyl trimethyl ammonium chloride (EPTMAC)

A technical product of EPTMAC, containing EPTMAC and water, about 50 % each, was provided by Raisio Group, Finland.

Vehicles

Yellow petrolatum (pet.) or acetone of pharmaceutical quality or distilled water was used as the vehicle for the skin test substances.

Methods

Chemical investigations (I–VIII)

The epoxy resin compounds handled by the patients were analysed by means of high-performance liquid chromatography or gas chromatography at the Turku Regional Institute of Occupational Health, Turku, Finland, as follows: DGEBA oligomers by high-performance liquid chromatography (I, III–VIII) (133) or gas chromatography (II) (83, 99), DGEHHPA by gas chromatography (II, III, V), reactive diluents by gas chromatography (I, III, V, VI), and polyamines by high-performance liquid chromatography (VII) (1, 85). The amounts of MTHPA present during the provocation challenges were determined by gas chromatography at the Institute of Occupational Health, Helsinki, Finland.

DGEBA (i.e., DGEBA-based epoxy resin with an MW of 340) was purified from Epikote 827 with the use of thin-layer chromatography (III) (69).

DGEHHPA was analysed in study V by mass spectrometry and nuclear magnetic resonance spectrometry at Åbo Akademi, Turku, Finland, and *para*-CGE in study II by mass spectrometry at the Turku Regional Institute of Occupational Health.

Patch tests (I–X)

Patch tests were carried out to diagnose contact allergy (type IV allergy). The test patches were applied on the upper back with Finn Chambers (Epitest Ltd. Oy, Finland) and Scanpor Surgical Tape (Norgesplaster A/S, Norway). The occlusion time used in 1974–1987 was 24 h, and thereafter it was 48 h (i.e., 24 h in studies I, V, VI and VIII–X, 48 h in study III, and either 24 h or 48 h in studies II, IV and VII). Solid materials, such as gloves (VI, IX, X), insulating tapes (II, IV) and cationic starch (X), were left on the skin for 48 h. The patch test reactions were assessed by dermatologists after at least two (V) or three (I–IV, VI–X) readings. The patch tests were scored as follows according to the recommendations of the Finnish Contact Dermatitis Group (see IX): – = negative; + = erythema, ++ = erythema and oedema; +++ = erythema, oedema and vesicles; ++++ = bullous or ulcerative reaction. The scores of ++ to ++++ were considered allergic reactions. When necessary, additional tests were performed, and uncertain results were confirmed by retestings.

All patients suspected of having contact dermatitis were tested with a standard series. (See reference 52). If the clinical and anamnestic data indicated the need, tests were also performed with other test series. In addition, practically all the patients were tested with their own epoxy compounds (i.e., the substances they had handled at work).

Details on the test substances, the test concentrations, the vehicles used and the control tests have been given in the corresponding reports (I–X).

Standard series

The standard series consisted of allergens recommended by the International Contact Dermatitis Research Group with the addition of some other compounds (52). The manufacturers of the test substances were Karen Trolle-Lassen (Denmark) during 1974–1981, Epikon Oy (Finland) from 1982 to September 1985, and thereafter Chemotechnique Diagnostics Ab (Sweden).

DGEBA epoxy resin, as a 1 % mixture in pet., was included in the standard series during the entire period from 1974 to 1990. EDA (1 % in pet.) was included first in the series of plastics and glue, but since September 1985 it has been a part of the standard series.

Plastics and glue series

The series of plastics and glues from the following manufacturers were used: Karen Trolle-Lassen in 1974–1980, Epikon Oy in 1981–1983, Epikon Oy and Chemotechnique Diagnostics Ab in 1984 and thereafter Chemotechnique Diagnostics Ab supplemented in September 1985 with additional compounds from Hermal-Chemie Kurt Herrmann (Germany) and Epikon Oy (see Table 1 in VII).

The following epoxy resin compounds were included in the plastics and glue series during 1974–1990: Bisphenol A (1 % in pet.), epichlorohydrin (1 % in pet. in 1981–1983, 0.3 % in pet. from 1984 to September 1985, and 0.1 % in pet. thereafter), EDA (1 % in pet. from 1974 to September 1985), DETA (1 % in pet. since 1984 when supplied by Chemotechnique Diagnostics Ab), IPDA (0.5 % in pet. since September 1985), MDA (0.5 % in pet.), TETA (0.5 % in pet. in 1974–1984, 0.5 % in water since 1984 when supplied by Chemotechnique Diagnostics Ab), and three reactive diluents (PGE, *ortho*-CGE and BGE at 0.25 % in pet. since September 1985) (I, II, VI, VII).

Dental and (meth)acrylate series

The patients exposed to epoxy acrylates and some of the patients exposed to epoxy compounds were also tested with two to four of the epoxy acrylates supplied by Chemotechnique Diagnostics Ab [i.e., BIS-GMA (2 % in pet.), 2,2-bis(4-(methacryloxy)phenyl)propane (BIS-MA, 2 % in pet.), 2,2-bis(4-(2-hydroxy-3-acryloxypropoxy)phenyl)propane (BIS-GA, 0.5 % in pet.) and 2,2-bis(4-(2-methacryloxyethoxy)phenyl)propane (BIS-EMA, 1 % in pet.)]. Two of the epoxy acrylates (i.e., BIS-GMA and BIS-MA) were tested from 1983 on, when a dental screening series of Chemotechnique Diagnostics Ab (10) was included in the patch testing. Since September 1985, an additional (meth)acrylate series, supplied by Chemotechnique Diagnostics Ab and containing 28 substances and including all four epoxy acrylates, has been used (IX).

Patient test substances

Substances brought in by the patients ("own substances") were routinely used for patch testing. However, testings were not performed with substances whose composition could not be clarified. In addition, individual components of the substances provided by manufacturers and "pure" chemicals were used for the testing. The amount of the known or hypothetical allergen used in the tests was as high as possible considering the irritancy of other components, but it did not exceed the previously recommended test concentrations for the individual allergens (44), because of the risk of active sensitization.

In most cases epoxy compounds were mixed in pet. up to the concentrations of 1–10 % (weight/weight, w/w). Then the test substance was diluted with a factor of $\sqrt{10}$ (e.g., 10 %, 3.2 %, 1 %, 0.32 %, etc.) (60). Positive patch test reactions caused by a patient's own substance were confirmed by sequel testings with pure components available from chemical suppliers or from the manufacturer of the substance. Controls were tested with the same test concentration that had given a clear (++) reaction in the patient.

Solid epoxy resin compound materials (e.g., insulating tapes) were tested with a drop of acetone or water in a test chamber. Other non-irritant solid materials (e.g., cationic starch and gloves) were tested with water.

The two cycloaliphatic epoxy resins, namely, Araldit CY 184 and Lekutherm X 100, and Lekutherm X 287 were patch tested at 1 % in pet. in 1985–1989 (II–IV) and at 0.5 % in pet. from 1990 on (VII); they were also tested in dilution series (1 %, 0.3 % and 0.1 % in pet.) at the Vaasa Central Hospital (VI). Since the beginning of 1990 Rütapox 0451 (0.5 % in pet.) has been included in the test series used for patients exposed to epoxy resin compounds. Other non-DGEBA epoxy resins have been tested for some patients from 1985 on, at either 1 % or 0.5 % in pet..

From September 1985 on, most of the patients exposed to epoxy resin compounds were also tested with six non-commercially available reactive diluents (i.e., AGE, BDDGE, HDDGE, NPGDGE, Cardura E 10, Epoxide 8) at 0.25 % in pet. (II–VII).

From December 1989 on, four amine hardeners (TEPA, TMD, XDA, tris-DMP) were tested either at 1 % in pet. or in a dilution series of 1 %, 0.32 %, 0.1 %, etc. in pet..

Open, scratch chamber and prick tests (I–V, VII–X)

Open, scratch chamber and prick tests were performed for the diagnosis of atopy, contact urticaria, rhinitis and asthma (type I allergy). The details have been given in the corresponding reports (I–V, VII–X).

Scratch tests and prick tests to 20–24 common environmental allergens were performed as described in detail elsewhere (52, 104).

An open test to detect contact urticaria to MHHPA was performed as described by Adams (3). Test substances including MHHPA at 100 % and 1 % were applied on the antecubital area (0.5 cm × 1.0 cm) of the arm. Small urticas on the test area were considered positive reactions. Control tests were performed on 12 unexposed persons

with undiluted MHHPA, and they were negative. Scratch chamber tests with 1 % MHHPA in ethanol and determinations of immunoglobulin (Ig) E antibodies were performed to reveal the nature of the reaction.

Specific immunoglobulin (Ig) E determinations (II–IV, VII)

Determinations of specific IgE antibodies to epoxy resins (III, IV, VII), polyamines (VII) and phthalic anhydrides (II, III) (Phadezym RAST®, Pharmacia, Sweden) and the inhibition of the assays (III) were performed with hapten-human serum albumin (HSA) conjugates. The details have been given in the corresponding reports.

Lung function and provocation tests (III, IV, VII)

Lung function and provocation tests were performed as described in study III to confirm the diagnosis of bronchial asthma.

6. RESULTS

Diagnoses and causative epoxy compounds (I–X)

Of the 3713 patients examined at the Institute of Occupational Health, Helsinki, 1832 patients (49.3 %) received a primary diagnosis of occupational skin disease and 1881 (50.7 %) were considered cases of non-occupational skin disease. Of all the occupational skin diseases, 901 (49.2 %) cases were allergic contact dermatitis, 843 (46.0 %) were irritant contact dermatitis, 36 (2.0 %) were contact urticaria, and 52 (2.8 %) were classified as "other".

One hundred and thirty patients were diagnosed in 1974–1990 at the Institute as *currently* having occupational skin disease due to occupational exposure to epoxy compounds (I–IV, VI–X). Epoxy resin compounds, epoxy acrylates and other epoxy compounds (i.e., EPTMAC) were involved for 120, 6 and 4 of the patients, respectively. One patient [patient number (no.) 5 in study IX] was first examined at the Institute in 1982 and was given a diagnosis of non-occupational skin disease at that time. Later, in 1986, she was given a diagnosis of occupational allergic contact dermatitis due to exposure to epoxy acrylates. Her case is included in the statistics from 1982.

Twelve of the 18 patients examined at the Vaasa Central Hospital were diagnosed in 1985 as having occupational allergic contact dermatitis due to epoxy resin compounds (V).

Thus, among 1844 patients with occupational skin diseases diagnosed in 1974–1990, 142 patients (7.7 %, 92 men and 50 women) were considered to have skin disorders from *current* occupational exposure to epoxy compounds (Table 1). In a total of 135 cases (95 %) the diagnosis was allergic contact dermatitis, for five it was irritant contact dermatitis, and for two it was contact urticaria (Table 2). In addition, 33 patients had developed contact allergy due to *previous occupational* or *non-occupational* exposure to epoxy compounds (see pages 35 and 36).

Of the 142 dermatoses caused by current occupational exposure to epoxy compounds, 132 cases (93 %) were due to epoxy resin compounds (i.e., epoxy resins, reactive diluents and hardeners), six were due to epoxy acrylates (or bisphenol A in epoxy acrylates), and four were due to other epoxy compounds, namely, EPTMAC (Table 2). In addition to the 125 cases due to epoxy resin compounds, allergic contact dermatitis was the diagnosis for all the cases due to epoxy acrylates and EPTMAC. All cases of

Table 1. Occupational skin diseases during 1974–1990 by main cause. Patients examined at the Vaasa Central Hospital in 1985 are included

Type of exposure	–74	–75	–76	–77	–78	–79	–80	–81	–82
Epoxy resin compounds	7	9	11	8	5	10	4	4	8
Epoxy acrylates	–	–	–	–	–	–	–	–	1
2,3-Epoxy-propyl trimethyl ammonium chloride (EPTMAC)	–	–	–	–	–	–	–	–	2
Other	116	129	129	118	77	80	76	88	106
Total	**123**	**138**	**140**	**126**	**82**	**90**	**80**	**92**	**117**

Table 1. Continues

Type of exposure	–83	–84	–85	–86	–87	–88	–89	–90	1974 –90
Epoxy resin compounds	9	4	21	6	7	6	7	6	132
Epoxy acrylates	–	–	1	1	1	–	–	2	6
2,3-Epoxy-propyl trimethyl ammonium chloride (EPTMAC)	2	–	–	–	–	–	–	–	4
Other	83	99	84	113	122	87	102	93	1702
Total	**94**	**103**	**106**	**120**	**130**	**93**	**109**	**101**	**1844**

Table 2. Occupational epoxy dermatoses by diagnosis and epoxy compound type (I–X)

Diagnosis	1974–83	1984–88	1989–90	1974–90
Allergic contact dermatitis	**76**	**44**	**15**	**135**
Epoxy resin compounds	71	41	13	125
Epoxy acrylates	1	3	2	6
2,3-Epoxypropyl trimethyl ammonium chloride (EPTMAC)	4	–	–	4
Irritant contact dermatitis	**3**	**2**	**–**	**5**
Epoxy resin compounds	3	2	–	5
Contact urticaria	**1**	**1**	**–**	**2**
Epoxy resin compounds	1	1	–	2
Total	**80**	**47**	**15**	**142**

irritant contact dermatitis and contact urticaria were caused by the epoxy resin compounds.

Causative exposure to epoxy compounds

The most frequent causative exposure for the 132 epoxy resin compound cases were paints and their raw materials (31 %), materials used in electrical insulation (29 %) and glues (18 %) (Table 3).

Table 3. Causative exposure in the 132 cases of occupational skin diseases caused by epoxy resin compounds (I–VII)

Causative exposure	1974–83	1984–88	1989–90	1974–90
Paints and their raw materials	25	13	3	41
Electrical insulation	17	18	3	38
Glues	13	7	4	24
Manufacture of epoxy objects	9	3	–	12
Surface coatings (paints excluded)	6	1	3	10
Construction applications	5	2	–	7
Total	**75**	**44**	**13**	**132**

Location of the dermatitis (I, II, IX, X)

For 37 (93 %) of the 40 patients diagnosed at the Institute of Occupational Health in 1984–1988 as having occupational skin dermatosis induced by *current* or *previous occupational* exposure to epoxy compounds (II), the skin symptoms were located on the patients' hands or arms, and for 21 patients (53 %) also on their face. Three patients had facial symptoms only. The fingers and interdigital spaces, forearms and wrists, and eyelids were typical areas affected by the skin disorders caused by exposure to epoxy resin compounds and epoxy acrylates (II, IX).

In all four patients with allergic contact dermatitis due to EPTMAC skin symptoms appeared on the hands (X). Two patients also had symptoms on their face, arms and feet. Irritant contact dermatitis was especially located in the interdigital space, on the backs of the hands and on other dust collecting areas. One of the patients (I) with contact urticaria had dermatitis on the face, neck, breast and arms, whereas the other such patient (II) had symptoms on the forehead.

Exposure time and hand protection (I–X)

Table 4 presents the length of exposure of the 135 patients who developed occupational allergic contact dermatitis due to current exposure to epoxy compounds. It was less than one month for 12 % of the patients, 1–12 months for 41 % and more than one year for 47 %. The exposure time was 1–12 months for both the patients who had contact urticaria and for four of the five patients who had irritant contact dermatitis. For the fifth patient with irritant contact dermatitis it was more than one year (I, II).

Table 4. *Length of exposure for the patients with occupational allergic contact dermatitis induced by epoxy compounds (I–X)*

Exposure time	1974–83	1984–88	1989–90	1974–90
< 1 month	11	5	–	16
1–12 months	26	20	9	55
> 12 months	39	19	6	64
Total	**76**	**44**	**15**	**135**

For the 40 patients with skin disease from *current* or *previous occupational* exposure to epoxy compounds, the mean exposure time was 31 months in 1984–1988. It was 35 months for 28 patients with allergic contact dermatitis from DGEBA epoxy resins, and 11 months for those with allergic contact dermatitis from reactive diluents (II). For all five patients with occupational irritant contact dermatitis from epoxy resin compounds, the average exposure time was eight months, and for two patients with contact urticaria it was six months (I, II).

Thirteen of the 40 patients who had been exposed to epoxy compounds had not used any protective gloves at all in their work before the onset of the skin symptoms. The other patients had used textile, leather, plastic or rubber gloves of the disposable, household or industrial type. None of the patients had used laminated multilayered plastic gloves especially developed for epoxy resin compound work (4H-glove, Safety 4 A/S, Denmark) (88). The mean exposure time before the onset of dermatitis was 22 months for patients who did not use protective gloves and 35 months for those who did.

Skin diseases due to epoxy resin compounds (I–VII)

Of the 125 patients diagnosed as having allergic contact dermatitis induced by current occupational exposure to epoxy resin compounds, 87 had isolated contact allergy – 68 (54 %) to DGEBA epoxy resins, 13 (10 %) to non-DGEBA epoxy resins, three to reactive diluents and three to hardeners (Table 5). Simultaneous contact allergy to different epoxy resin compound groups was found for 38 patients (30 %).

Table 5. *Contact allergy to different epoxy resin compounds revealed by patch testings of 125 patients with occupational allergic contact dermatitis induced by epoxy resin compounds (I–VII)*

Substance	1974–83	1984–88	1989–90	1974–90
DGEBA-ER	49	15	4	68
Non-DGEBA-ER	3	9	1	13
HA	–	1	2	3
RD	–	3	–	3
DGEBA-ER and non-DGEBA-ER	–	1	–	1
DGEBA-ER and HA	19	3	3	25
DGEBA-ER and RD	–	3	2	5
Non-DGEBA-ER and RD	–	3	–	3
DGEBA-ER, non-DGEBA-ER and RD	–	2	–	2
DGEBA-ER, HA and RD	–	–	1	1
Non-DGEBA-ER, HA and RD	–	1	–	1
Total	**71**	**41**	**13**	**125**

DGEBA = diglycidyl ether of bisphenol A
ER = epoxy resin(s)
HA = hardener(s)
RD = reactive diluent(s)

Of the 125 patients, 102 (82 %) were allergic to DGEBA epoxy resins, 20 (16 %) to non-DGEBA epoxy resins, 30 (24 %) to hardeners and 15 (12 %) to reactive diluents. In addition, five cases of irritant contact dermatitis and two cases of contact urticaria due to occupational exposure to epoxy resin compounds were diagnosed.

Contact allergy to diglycidyl ether of bisphenol A (DGEBA) epoxy resins (I–III, VII–IX)

Altogether 102 of the 125 patients with allergic contact dermatitis induced by *current occupational* exposure to epoxy resin compounds had contact allergy to DGEBA epoxy resins (Tables 5 and 6). In addition, for four patients (one patient from 1982, and three from 1984–1988) primary allergy to BIS-GMA was detected in the patch testing, but DGEBA epoxy resin allergies were also verified (Table 6) (VIII, IX). (See page 45.)

Table 6. *Allergic patch test reactions to epoxy resins based on diglycidyl ether of bisphenol A (DGEBA) by the relevance of the patient's exposure (I, II, VII–IX)*

Exposure	1974–83	1984–88	1989–90	1974–90
Current occupational exposure to epoxy resin compounds	68	24	10	102
Current occupational exposure to epoxy acrylates	1	3	–	4
Previous occupational or non-occupational exposure to epoxy resin compounds	17	9*	7**	33
Positive/ examined* **	**86/2484**	**36/909**	**17/338**	**139/3731**

* = five cases due to previous occupational exposure
** = two cases due to previous occupational exposure
*** = number of allergic reactions to DGEBA epoxy resin/number of patients examined

Thirty-three patients had contact allergy to DGEBA epoxy resin due to *previous occupational* or *non-occupational* exposure to epoxy resin compounds. Seventeen of the 33 patients had developed their allergy to DGEBA epoxy resin in 1974–1983, and the allergy was not shown to be the main reason for the dermatosis under investigation (I). In the present study the influence of previous occupational exposure was not clarified

in these cases. During 1984–1990 seven of the remaining 16 patients had developed their contact allergy to DGEBA epoxy resin from previous occupational exposure (Table 6). The current diagnoses for the 33 patients are occupational allergic contact dermatitis for 18 patients, occupational irritant contact dermatitis for eight patients, and non-occupational skin diseases for seven patients. A detailed analysis of these 33 patients has not been included in the present study.

Of all the 3731 patients investigated, 139 (3.7 %) proved to be allergic to the DGEBA epoxy resin of the standard series in the patch test (Table 6). The frequency of sensitivity was 7.2 % (132 of 1844 cases) for the patients diagnosed as having a primary occupational skin disease, namely, 13.6 % (124 of 913 cases) for the patients having allergic contact dermatitis and 0.9 % (8 of 843 cases) for those having irritant contact dermatitis. Only 0.4 % of those who had a primary non-occupational skin disease had an allergic patch test reaction to the DGEBA epoxy resin.

In 1974–1983 3.5 % of all the patients investigated had patch test results showing allergy to DGEBA epoxy resin. For 1984–1988 and 1989–1990 the corresponding figures were 4.0 % and 5.0 %, respectively. Of all the cases of contact allergy to the DGEBA epoxy resin, 76 % (106 of 139) was due to current occupational exposure.

Sensitization to diglycidyl ether of bisphenol A (DGEBA) epoxy resins with a high average molecular weight (MW) (I)

Among the 68 patients diagnosed as having allergic contact dermatitis due to DGEBA epoxy resins during 1974–1983, six (9 %) had been sensitized to the resins with an average MW above 700 (i.e., high average MW epoxy resins). The causative products contained from 6 to 100 % DGEBA epoxy resin, and the amounts of DGEBA were between 0.2 and 15.0 %. For five of the patients the products had been dissolved in organic solvents. All the patients were allergic to the standard epoxy resin. None of them had handled epoxy resins with an average MW below 700.

Allergic contact dermatitis and asthma due to diglycidyl ether of bisphenol A (DGEBA) epoxy resins (II, III)

In addition to allergic contact dermatitis due to DGEBA epoxy resins, specific bronchial asthma due to exposure to the resins was verified for two patients. These two patients in study III are the same as no. 32 and 34 in study II.

One of the patients had been working as a cleaner in a factory where sports articles were manufactured from DGEBA epoxy resin. The other one had been a connector in a factory manufacturing electronic devices and earlier had worked as an insulator in another factory. She had been exposed to epoxy resins in both of these jobs. In the patch testing both of the patients had clear positive reactions to the standard epoxy resin, and in the prick testing the reactions to the HSA conjugates of DGEBA epoxy resins were positive. Both of these patients had specific IgE antibodies to DGEBA and two epoxy resins containing DGEBA, but not to cycloaliphatic epoxy resins. The first-mentioned patient had also been occupationally exposed to MTHPA and had an allergic prick test reaction to the MTHPA-HSA conjugate. The specific IgE determinations to two anhydrides (MTHPA and MHHPA) were strongly positive, too.

The exposure times for the patients before the appearance of allergic contact dermatitis were two years and six months, and it was 7 and 21 years, respectively, before the bronchial asthma appeared.

Contact allergy to non-diglycidyl ether of bisphenol A (non-DGEBA) epoxy resins (I, III–V)

Of the 125 patients diagnosed as having allergic contact dermatitis due to epoxy resin compounds, 20 had contact allergy to non-DGEBA epoxy resins. Thirteen had an isolated contact allergy to non-DGEBA epoxy resins (nine to cycloaliphatic epoxy resins, i.e., Araldit CY 184 and/or Lekutherm X 100, and four to other non-DGEBA epoxy resins). In addition to contact allergy to cycloaliphatic epoxy resins, two patients developed cross-allergy to reactive diluents after having been exposed to the cycloaliphatic and DGEBA epoxy resins, and one developed contact allergy to DGEBA epoxy resins (V). In addition to contact allergy to reactive diluents after exposure to DGEBA epoxy resin materials, four patients developed cross-allergy to cycloaliphatic epoxy resins. (See page 42.)

Twelve of the 18 patients investigated at the Vaasa Central Hospital because of skin symptoms (V) had acquired an occupational contact allergy to cycloaliphatic epoxy resins based on DGEHHPA (Araldit CY 184 and Lekutherm X 100). Ten were women and two were men. Their ages ranged from 19 to 59 years, the average being 45 years. All of the 12 patients had hand dermatitis, seven also had dermatitis on their face or neck. The remaining 62 workers from the same department manufacturing insulators of epoxy resins had no skin symptoms.

Nine of the 12 patients were casting workers, and the rest worked in repair, finishing and maintenance. The mean exposure time before the appearance of symptoms was 14 months. In addition to exposure to cycloaliphatic epoxy resins, nine of the patients were also exposed to a diglycidyl aniline epoxy resin (Lekutherm X 287) containing 43 % DGEBA (III, V).

Of the 12 patients who showed allergic patch test reactions to the cycloaliphatic epoxy resins, seven also had allergic patch test reactions to the aniline-based epoxy resin, but only one patient was allergic to the DGEBA epoxy resin in the standard series. Five of the patients were able to continue their work with the cycloaliphatic epoxy resins, and three others with the aniline-based epoxy resin. Two had to change jobs, becoming coil winders in the same department. Two had to retire.

Of the same 80 workers, five who complained of respiratory symptoms which could have been caused by epoxy resins or their anhydride hardeners were studied with the same prick tests and specific IgE determinations as the patients diagnosed as having specific asthma due to DGEBA epoxy resins (III). None of the patients had a specific immediate allergy to the epoxy resins or anhydrides.

In addition, *four* patients investigated at the Institute of Occupational Health, Helsinki, were diagnosed as having allergic contact dermatitis caused by products containing a non-DGEBA epoxy resin (I, IV). None of the four patients were allergic to the standard epoxy resin. One of the causative products was a brominated epoxy resin (Riitapox 0451), one was a heterocyclic dimethyl hydantoin-based epoxy resin (Aracast CY 350), one was an insulating tape containing a novolak epoxy resin (Samicatherm 366.28 tape), and one was an epoxy primer containing an epoxy resin (MCP primer), the type of which remained unknown.

Contact allergy to reactive diluents (II, V, VI)

Reactive diluents caused allergic reactions in 15 patients diagnosed as having allergic contact dermatitis (Tables 5 and 7). Twelve of the cases were detected in 1984–1988 (II, V, VI; patients no. 1–12 in Table 7), and the remaining three were diagnosed in 1989–1990 (unpublished). Seven patients (no. 1–7) showed no concomitant allergic reaction to the DGEBA epoxy resin in the standard series, and one of them (patient no. 3) reacted to polyamine hardeners. Twelve of the 15 patients had been exposed only to products with a DGEBA epoxy resin base (II, unpublished; patients no. 1–5, 8–10 and 12–15 in Table 7); the other three had been exposed to products with a DGEBA epoxy resin base and also to those with a non-DGEBA epoxy resin base (II, V).

Thirteen patients reacted to PGE and 10 to *ortho*-CGE (Table 7). Two of the patients (no. 12–13) reacted only to PGE. None of the patients reacted to Epoxide 8 or to Cardura E 10, and only two to BGE (patients no. 2 and 8). The two patients (no. 1 and 7) who did not react to PGE reacted only to aliphatic reactive diluents (patient no. 1 to BDDGE and HDDGE and patient no. 7 to HDDGE and NPGDGE).

Contact allergy to reactive diluents without contact allergy to diglycidyl ether of bisphenol A (DGEBA) epoxy resins (II, V, VI)

Of the seven patients (no. 1–7 in Table 7) who had contact allergy to reactive diluents without contact allergy to DGEBA epoxy resins, three (patients no. 1–3) had been exposed to DGEBA-based epoxy resins which contained BDDGE as the main reactive diluent, and two (patients no. 4–5) to *ortho*-CGE contained in the resinous part of a epoxy paint (II). Two patients (no. 1–2) were female workers in a brush factory. When gluing with the help of a machine, their hands and arms constantly came into contact with a two-component epoxy glue containing 3 % BDDGE. Both of the patients had allergic reactions in patch tests to BDDGE, the resin component of the glue, and one to five of the eight other reactive diluents tested. Patient no. 2 (Table 7) even reacted to 0.03 % (w/w) technical grade BDDGE. One other patient (no. 8 in Table 7) from the same workplace was allergic to BDDGE, but also to the standard epoxy resin (II, VI). While making moulds, the third patient (no. 3 in Table 7), who had isolated allergy to reactive diluents from BDDGE, was exposed to DGEBA epoxy resin containing 10–15 % BDDGE. BDDGE and four other reactive diluents gave allergic reactions in the patch tests (II).

Two patients (no. 4–5) had acquired isolated allergies to reactive diluents from epoxy paints containing *ortho*-CGE without a concomitant reaction to the standard epoxy resin. They had been exposed to the *ortho*-CGE contained in the resinous part of one epoxy paint (11 % w/w). Contact allergy to PGE was also revealed in the patch testing (II).

The remaining two patients (no. 6–7) had been exposed to both DGEBA and non-DGEBA epoxy resins, containing traces of reactive diluents (0.06-0.4 %). They were shown to have contact allergy to cycloaliphatic epoxy resins (see page 37) and positive patch test reactions to two to three of the eight diluents tested. Neither of the patients was allergic to DGEBA epoxy resin in the patch tests. BGE, AGE, *ortho*-CGE, Cardura E 10, and Epoxide 8 produced no allergic reactions. BDDGE was not tested (Table 7) (V).

Table 7. Patch test results of 15 patients who were allergic to reactive diluents

Compound	Patient no.							
	$1^{II/18, VI/C}$	$2^{II/14, VI/A}$	$3^{II/23}$	$4^{II/21}$	$5^{II/22}$	$6^{V/2}$	$7^{V/11}$	$8^{II/15, VI/B}$
Standard ER based on DGEBA	–	–	–	–	–	–	–	AR
CA-ER	–	AR	AR	–	–	AR	AR	AR
BGE	–	AR	–	–	–	–	–	AR
BDDGE	AR	AR	AR	–	–	NT	NT	AR
HDDGE	AR	AR	AR	–	–	AR	AR	AR
NPGDGE	–	–	–	–	–	AR	AR	AR
AGE	–	AR	AR	–	–	–	–	AR
PGE	–	AR	AR	AR	AR	AR	–	AR
ortho-CGE	–	AR	AR	AR	AR	–	–	AR
Epoxide 8	–	–	–	–	–	–	–	–
Cardura E 10	–	–	–	–	–	–	–	–

II, V, VI = corresponding patients in II, V and VI
UP = unpublished, patient from the years 1989 and 1990
* = number of allergic reactions/number of patients tested
AR, –, NT = allergic reaction, negative result, not tested
DGEBA = diglycidyl ether of bisphenol A
CA = cycloaliphatic
ER = epoxy resin(s)
BGE, AGE, PGE, CGE = *n*-butyl, allyl, phenyl, cresyl glycidyl ether
BDDGE, HDDGE, NPGDGE = 1,4-butanediol, 1,6-hexanediol, neopentyl glycol diglycidyl ether

Contact allergy to reactive diluents and epoxy resins (II, IV, V)

Eight patients were diagnosed with simultaneous contact allergy to reactive diluents and DGEBA epoxy resins (patients no. 8–15 in Table 7). Patient no. 8 was a worker in the same factory as patients no. 1 and 2. (See page 39.) A paint handled by patient no. 12 contained 0.4 % *para*-CGE (II). Patient no. 10 was a laminate worker who had been exposed to a DGEBA epoxy resin and to fibre glass pre-impregnated with an epoxy resin. According to the Finnish importer, two reactive diluents, namely, NPGDGE and 2-ethylhexyl diglycidyl ether, had been added to the DGEBA epoxy resin. *para*-CGE and 2-ethylhexyl diglycidyl ether were not tested, but, of the reactive diluents tested,

Table 7. Continues

Compound	Patient no.							AR/ tested*
	$9^{II/16}$	$10^{II/17}$	$11^{II/20}$	$12^{II/27}$	13^{UP}	14^{UP}	15^{UP}	
Standard ER based on DGEBA	AR	AR	AR	AR	AR	AR	AR	8/15
CA-ER	AR	–	–	–	–	NT	–	6/14
BGE	–	–	–	–	–	–	–	2/15
BDDGE	AR	–	–	–	–	–	–	5/13
HDDGE	AR	–	–	–	–	–	–	7/15
NPGDGE	–	–	–	–	–	–	–	3/15
AGE	AR	–	–	–	–	–	–	4/15
PGE	AR	AR	AR	AR	AR	AR	AR	13/15
ortho-CGE	AR	AR	AR	–	–	AR	AR	10/15
Epoxide 8	–	–	–	–	–	–	–	0/15
Cardura E 10	–	–	–	–	–	–	–	0/15

PGE and *ortho*-CGE produced allergic reactions in these patients. Powdered fibre glass produced a clear allergic reaction in patient no. 10. The fibre glass was not analysed.

For five patients (no. 9, 11, 13–15) who had contact allergy to reactive diluents, occupational exposure to the diluents could not be verified; however, contact allergy due to occupational exposure to DGEBA epoxy resins was determined. One of them (patient no. 9) was a spray painter and another one (patient no. 13) was a floorlayer. By means of gas chromatography of the nine reactive diluents investigated only trace amounts (less than 0.01 %) of PGE could be determined in the paints and floor coatings handled by the patients (II). Two of the patients were workers in the electrical industry, one, patient no. 11, having handled insulating tapes which contained an unknown cycloaliphatic epoxy resin and the other, patient no. 14, having used a DGEBA epoxy resin which contained only traces of reactive diluents (less than 0.1 %). Patient no. 15 had been a painter for years in a zipper factory. In addition to DGEBA epoxy resin and reactive diluents, he reacted to polyamine hardeners in the patch tests. The exposure to epoxy resin compounds was clear, but exposure to reactive diluents was not traced.

Four patients (no. 2, 3, 8–9) who were allergic to reactive diluents concomitantly reacted to cycloaliphatic epoxy resins, though they were not exposed to these resins. Two of these four patients (no. 8–9) had simultaneous allergy to DGEBA epoxy resin in the patch tests, and two (no. 2–3) did not. Patient no. 2, who had primarily acquired allergic contact dermatitis from BDDGE, was also allergic to an epoxy resin based on glycerol (LX-112 Resin) (II, IV).

Contact allergy to polyamine hardeners (I, II, VII)

Of the 125 patients diagnosed as having allergic contact dermatitis due to current occupational exposure to epoxy resin compounds, 30 were allergic to epoxy resin hardeners in the patch testing (Table 5). Nineteen of the patients were diagnosed in 1974–1983 (I) and five in 1984–1988 (II). Of the six patients diagnosed in 1988–1990, four have been described in detail in study VII. Twenty-one patients reacted to at least one of the nine polyamine hardeners tested, and nine reacted only to the hardener they themselves brought in for testing (Table 8). Contact allergy to eight different polyamine hardeners was detected.

Two patients had simultaneous contact allergy to IPDA and DGEBA epoxy resin. One of them was a process man (patient no. 4 in VII) in the manufacture of two-component floor coatings, and the other was a floorlayer (patient no. 5 in VII) who coated concrete floors with two-component epoxy and polyurethane products. After four months of work, the process man started to show dermatitis on the backs of both hands, in the interdigital areas and on the wrists; he developed allergic reactions in the patch testing for IPDA (at 0.5, 0.32 and 0.1 % in pet.) and tris-DMP (at 1 and 0.32 % in pet.). One hardener was analysed, and it contained 80 % IPDA, but no tris-DMP. The exposure to tris-DMP could not be verified. After five years of work the floorlayer developed acute itching and erythematous face dermatitis, and a few months later a new, more widespread dermatitis appeared. Eight different components of the four hardeners he had handled were supplied by the manufacturer for patch testing. Three of the components gave positive allergic reactions, namely, IPDA, Euredur 14 containing 30 % XDA, and TMD. The patients could not continue their work with epoxy resin products because of a relapse of the dermatitis.

Isolated contact allergy to polyamine hardeners (II, VII)

Isolated contact allergy to polyamine hardeners without contact allergy to epoxy resins or reactive diluents was revealed for three patients (Table 5) (II, VII). Two of the patients had isolated contact allergy to DETA, the third to IPDA and tris-DMP. The

Table 8. *Number of allergic patch test reactions to individual hardener compounds for 30 patients with contact allergy to epoxy hardeners (I, II, VII)*

Hardener	1974–83	1984–88	1989–90	1974–90
Ethylene diamine (EDA)	1	–	–	1
Diethylene triamine (DETA)	NT	3	3	6
Triethylene tetramine (TETA)	3	1	1	5
Tetraethylene pentamine (TEPA)	NT	NT	–	–
Trimethyl hexamethylene diamine (TMD)	NT	NT	1	1
Isophorone diamine (IPDA)	NT	–	3	3
4,4'-Diaminodiphenyl methane (MDA)	6	3	–	9
Xylylene diamine (XDA)	NT	NT	1	1
2,4,6-Tris-(dimethyl-aminomethyl)phenol (tris-DMP)	NT	NT	2	2
Patient's own hardener only	9	–	–	9

NT = not tested

first patient (patient no. 1 in VII), a spray painter, developed dermatitis on his hands, the second (patient no. 2 in VII), a tiler, on his lower arms and eyelids, and the third (patient no. 3 in VII), a painter, only on his eyelids. The exposure times were two years, two months and one year, respectively. The standard series was negative for all these patients. The spray painter and the tiler developed strong allergic reactions to DETA, but the results for the other polyamine hardeners tested (EDA, TETA, MDA and, for the tiler, also IPDA) were negative. The spray painter had mainly been exposed to a two-component paint. The hardener of this paint was an amine-epoxy adduct containing 3.8 % free DETA determined by gas chromatography. The tiler had used a two-component mortar adhesive. According to the material safety data sheet, the hardener was 98.5 % DETA. The painter had used six different hardeners. One of the

hardeners contained 88 % IPDA, and four others included 1.6–9 % tris-DMP, according to chemical analyses (gas chromatography and high-performance liquid chromatography). In the patch testing he developed allergic reactions to both IPDA (at 0.5 and 0.32 % in pet.) and tris-DMP (at 1 and 0.32 % in pet.). (See table 2 in VII.)

Irritant contact dermatitis due to epoxy resin compounds (I, II)

Five cases of occupational irritant contact dermatitis were detected that were due to epoxy resin compounds. The diagnosis was based on the following clinical findings: location and course of the dermatitis (see page 32), negative patch tests (i.e., the standard series, the plastics and glue series, and the epoxy resin materials used at work), and occupational exposure to epoxy resin compounds.

For four patients irritant contact dermatitis was caused by solid DGEBA epoxy resins with a high average MW in paints or paint raw materials, and for one patient it was due to a mixture of a DGEBA epoxy resin with a low average MW and its anhydride hardener, used in electrical insulation.

Contact urticaria due to methyl hexahydrophthalic anhydride (MHHPA) (I, II)

Two patients were diagnosed, one in 1978 and the other in 1985, as having contact urticaria due to epoxy resin compounds, namely, MHHPA, an epoxy hardener. They worked in the same factory where condensers were manufactured and developed symptoms of contact urticaria after two and ten months of work at the factory. (See page 32.) One of them also had symptoms of rhinitis.

Patch tests with the standard series, the plastics and glue series, and the patients' own epoxy resin compounds produced no allergic reactions. Open tests with undiluted MHHPA caused urticarial reactions in both of the patients, as did also the concentration of 1 % (w/w) MHHPA in the second patient who had rhinitis. A scratch chamber test with MHHPA at a test concentration of 1 % caused a strong positive reaction in the second patient, and specific IgE antibodies to MHHPA were detected.

Both of the patients were obliged to change jobs, whereupon the symptoms of contact urticaria, and the rhinitis of the second patient, disappeared.

Allergic contact dermatitis due to epoxy acrylates and bisphenol A (VIII, IX)

Six patients were diagnosed as having contact allergy due to products containing epoxy acrylate. Five were allergic to epoxy acrylates (i.e., BIS-GA, BIS-GMA or BIS-EMA) and the sixth to bisphenol A (Table 9). Patient no. 1 had acquired the allergy in paint manufacturing, and the others (patients no. 2–6) had done dental restoration work (VIII, IX). Patients no. 3–6 in Table 9 correspond to the same patient numbers in study IX and patient no. 3 is the patient of study VIII.

Table 9. *Patch test results of six patients with contact allergy induced by epoxy acrylate products*

Compound	% (w/w) in pet.	Patient no.					
		1	2	$3^{IX/3, VIII}$	$4^{IX/4}$	$5^{IX/5}$	$6^{IX/6}$
BIS-GMA	2	–	–	AR	AR	AR	AR
BIS-GA	0.5	AR	–	AR	AR	AR	AR
BIS-EMA	1	–	–	–	AR	–	–
BIS-MA	2	–	–	–	–	–	–
Standard epoxy resin based on DGEBA	1	–	–	AR	AR	AR	AR
Bisphenol A	1	–	AR	–	–	–	–

VIII, IX = corresponding patients in VIII and IX
BIS-GMA = 2,2-bis(4-(2-hydroxy-3-methacryloxypropoxy)phenyl)propane
BIS-GA = 2,2-bis(4-(2-hydroxy-3-acryloxypropoxy)phenyl)propane
BIS-EMA = 2,2-bis(4-(2-methacryloxyethoxy)phenyl)propane
BIS-MA = 2,2-bis(4-(methacryloxy)phenyl)propane
AR, – = allergic reaction, negative result
DGEBA = diglycidyl ether of bisphenol A

For two patients (no. 1–2) contact allergy to epoxy acrylates was diagnosed in 1990 (unpublished). After two months of work in the manufacture of UV curable epoxy acrylate paints, patient no. 1 developed dermatitis on his hands, the lateral aspects of both brachia and his neck. In the patch testing he reacted to BIS-GA, but to none of the three other epoxy acrylates tested or to the epoxy resin in the standard series. In addition, he had contact allergy to a few aliphatic acrylates of the (meth)acrylate series.

Two raw materials of the paints producing allergic reactions at 1 % (w/w) in pet. were analysed, and 75 and 72 % BIS-GA and 0.02 and 0.07 % DGEBA were detected.

For patient no. 2, a dental nurse with mild periodic dermatitis on her hands, dermatitis began to worsen after 12 years of handling products of dental composite resin. In the patch testing, contact allergy was found for formaldehyde, but not for the products of dental composite resin. After two more years of work, the dermatitis became persistent, and contact allergy to bisphenol A was detected, but not to epoxy acrylates or the nurse's own dental composite resins (1 % in pet.) or the standard epoxy resin. Two of the products of dental composite resin (Delton Universal and Delton Catalyst, Johnson & Johnson, Dental Products Co., NJ, USA) were analysed by gas chromatography, and the bisphenol A content was 0.015 and 0.014 %.

Patient no. 3 had acquired dermatitis within three months after beginning work as a dental assistant (VIII). The dermatitis appeared on her hands and eyelids. She did not wear gloves. In the patch tests all BIS-GMA-based restorative materials brought in by the patient gave a 2+ allergic test reaction, down to the lowest concentration tested, 0.2 % (w/w) in pet. The lowest concentrations giving a positive patch test with BIS-GMA and the standard epoxy resin were 0.0002 % (w/w) and 0.033 % (w/w), respectively. The restorative materials were analysed by high-performance liquid chromatography, and the amount of DGEBA epoxy resin oligomer with an MW of 340 was below the detection limit (0.008–0.03 %). Of the other epoxy acrylates tested, BIS-GA caused a reaction.

Patients no. 4–6 were dental nurses who had been exposed for one to nine years to dental composite resins before sensitization. They had hand dermatitis, particularly on their fingers, despite the regular use of protective gloves. They also had intermittent dermatitis on their face. All the nurses were patch test positive to BIS-GMA, BIS-GA and to the standard epoxy resin, and one of them (patient no. 4) was also allergic to BIS-EMA.

None of the six patients could continue their work with epoxy acrylate materials.

Allergic contact dermatitis due to 2,3-epoxypropyl trimethyl ammonium chloride (EPTMAC) (X)

Four of eight workers in the manufacture of cationic starch developed dermatitis within three months of their commencing work. EPTMAC (50 %) was used as the cationizing

chemical. Three were process men, and the fourth was a female laboratory technician. Two of the process men had used rubber gloves almost regularly and the laboratory technician used gloves occasionally. One process man had never worn gloves. All three of the process men took daily samples from the process liquid and measured the pH values, while the technician measured the amount of EPTMAC in the samples.

All four of the patients reacted to EPTMAC at a 0.2 % (w/w) concentration (Table 10). The patients' tests with the standard epoxy resin and epichlorohydrin were negative.

Table 10. *Patch test results of four patients allergic to 2,3-epoxypropyl trimethyl ammonium chloride (EPTMAC) (X)*

		Patient no.*			
Compound	**% (w/w) in pet.**	**1**	**2**	**3**	**4**
EPTMAC	1	AR	AR	AR	NT
EPTMAC	0.5	NT	NT	NT	AR
EPTMAC	0.2	AR	AR	AR	AR
EPTMAC	0.1	NT	NT	NT	AR
EPTMAC	0.05	NT	–	NT	NT
Standard epoxy resin based on DGEBA	1	–	–	–	–
Epichlorohydrin	1	–	–	–	–

* = corresponding to the same patient no. in X
AR, –, NT = allergic reaction, negative result, not tested

After a short sick leave, all four patients were symptomless. Despite the regular use of protective gloves, two of the three process men had to stop working in the factory. The laboratory technician could continue her work as long as she did not make EPTMAC measurements.

An industrial hygiene project was carried out in the factory, and no new cases of allergic dermatitis have appeared during the last six years.

7. DISCUSSION

General

The first case of occupational allergic contact dermatitis due to DGEBA epoxy resins to be diagnosed at the Institute of Occupational Health, Helsinki, was seen in 1960 (unpublished), less than 10 years after the resins had come into general use and six years after the first cases of contact sensitization due to epoxy resin compounds were published (142, 143). In 1946–1956 synthetic resins caused only about 1 % of all occupational dermatoses, but already for 1965–1972 the figure was 9 %. Most of the resin allergies were caused by phenol formaldehyde resins. However, by the beginning of the 1970s, epoxy resins and their hardeners began to induce increasing numbers of cases of occupational dermatoses (56). During 1974–1983 epoxy resins were clearly more frequent causes of occupational skin diseases than phenol formaldehyde resins (102).

The present study covers 17.9 % (119 of 664) of all the cases of occupational dermatosis that were induced by epoxy resin compounds and reported to the Finnish Register of Occupational Diseases in 1975–1989 (Table 1). The proportion of dermatoses due to epoxy resin compounds among all the cases reported to the Register was less (3.3 %, 664 of 20 271) than the proportion of cases induced by epoxy resin compounds (7.3 %, 119 of 1620) in the present study (84, 102, 172–178).

Only a few other clinics in the world are devoted exclusively to the investigation of occupational diseases. Comparison of the present results with those of other occupational clinics is difficult because of the variations in the definition of occupational diseases from country to country (52). The proportion of cases induced by epoxy resin compounds (7.2 %, 132 of 1844 cases, Table 1) seems to be higher than found elsewhere. Wilkinson *et al.* (186) detected contact allergy to epoxy resin in 2.9 % (12 of 410) of their tested patients with occupational skin diseases, and Fregert (58) found epoxy resin allergy in 5.1 % (59 of 1157) of his male patients with occupational dermatoses.

The preponderance of cases induced by epoxy resin compounds in the present study, compared not only with the cases found in the whole of Finland, but also with the cases found at other occupational dermatology clinics, is probably due to two main reasons. Firstly, the relative number of industrial and construction workers exposed to epoxy resin compounds and seen at the Institute may have been greater than that of other clinics. Secondly, the causative agents have been clarified very carefully in the

present study on the basis of detailed data on the patients' exposure and extensive patch test series for epoxy resin compound allergens, including substances brought in by the patients. These procedures have revealed allergy cases that would have been undetected in routine examinations.

Contact allergy to epoxy resin compounds

Diglycidyl ether of bisphenol A (DGEBA) epoxy resins (I, II)

After chromium and rubber chemicals, epoxy resin compounds are the third most frequent cause of occupational allergic dermatoses (100, 102); they induced primary occupational allergic contact dermatitis in 12.5 % of the patients (113 of 901). The North American Contact Dermatitis Group studied about 9000 patients (119, 151, 163) and found that 2-3 % were allergic to the standard epoxy resin. Edman (48) found a lower frequency of 1 % among 3562 patients patch tested during 1982–1987 in the Malmö General Hospital. The frequency of 3.7 % (139 of 3731, Table 6) found for the patients in the present study proved to be higher than that determined in the other dermatological clinics.

A few cases of allergic contact dermatitis due to DGEBA epoxy resins with a high average MW have previously been reported (22, 41, 164). In the present study, six patients who had not handled epoxy resins with an average MW below 700 had an allergic patch test reaction to the standard epoxy resin. Thus the patients had become sensitized to DGEBA (i.e., DGEBA-based epoxy resin with an MW of 340). The sensitivity was due to DGEBA in the epoxy resins with a high average MW. Organic solvents probably promoted sensitization to the DGEBA by increasing skin penetration, even though the amount of DGEBA was as low as 0.2 % in the causative products (I).

The present study showed that epoxy resins with a high average MW are sensitizers, and accordingly they should be labelled as required by the Finnish Identification and Labelling System for Hazardous Chemicals (1214/88; 738/90). The Finnish system requires that packages of chemical mixes containing "reactive epoxy resin" be labelled with the name of the resin and warnings of the risk of sensitization. They must also be supplemented, without concentration limits, with material safety data sheets giving information on the epoxy resin as a hazardous ingredient in the product. The Finnish labelling system offers better possibilities to protect workers from unintentional exposure to epoxy resins with a high average MW than the European Economic Community directive (81/957/EEC, 23 October 1981), which does not require labelling of epoxy resins with a high average MW (I).

Non-diglycidyl ether of bisphenol A (non-DGEBA) epoxy resins (I, IV, V)

Contact allergy to epoxy resins is mostly caused by DGEBA epoxy resins (3, 37, 55, 61). The present study indicates that also cycloaliphatic epoxy resins based on DGEHHPA are strong sensitizers in humans (V). In addition, heterocyclic dimethyl hydantoin epoxy resins, phenol novolak epoxy resins and brominated epoxy resins were found to be causes of allergic contact dermatitis (I, IV). Allergy to these non-DGEBA epoxy resins was not revealed by testing with the standard epoxy resin based on DGEBA. A patch test concentration of 0.5 % in pet. for non-DGEBA epoxy resins is probably preferable to 1 % when low viscosity resins are tested because 1 % non-DGEBA may irritate (V).

Most of the 12 patients sensitized to cycloaliphatic epoxy resins in the present study were able to continue their work. One reason may be that, as casting workers, they were not heavily exposed, as they did not handle liquid resins, but instead worked with "oven-fresh", heat-cured insulators made of epoxy resins that still contained some uncured monomers. Another reason may be the minimization of exposure that took place after the cause of the contact dermatitis was identified (V).

Reactive diluents (II, VI)

Reactive diluents were found to be as common contact allergens as hardeners among patients exposed to an epoxy resin system (II). Three reactive diluents (BGE, *ortho*-CGE and PGE) were available from the test substance suppliers. Aromatic compounds, especially PGE, were found to give an allergic patch test reaction in most of the patients who were allergic to reactive diluents. Of the aliphatic compounds, BDDGE was found to screen contact allergy to reactive diluents better than BGE. Thus PGE and BDDGE are recommended for patch testing to detect contact allergy due to reactive diluents.

Seven of the patients who reacted to reactive diluents in the patch testing did not react to the standard epoxy resin based on DGEBA, even though they were exposed to the DGEBA epoxy resin. This finding indicates that reactive diluents do not produce cross-allergy with DGEBA epoxy resins, and contact allergy to reactive diluents is not revealed by the standard epoxy resin. However, an allergic patch test reaction to reactive diluents may indicate allergy to cycloaliphatic epoxy resins because of cross-allergy (V).

Reactive diluents are used mainly to reduce the viscosity of epoxy resins, and in products made of epoxy resin compounds they are mixed with the resins. Thus patch testing with the resinous part of a two-component epoxy product does not exclude contact allergy to reactive diluents if the patient is also sensitive to the resin. The test concentration of 0.25 % in pet. was found suitable for testing reactive diluents.

The occurrence of isolated contact allergy to reactive diluents in patients exposed to both reactive diluents and DGEBA epoxy resins indicates that reactive diluents may be even more potent allergens than DGEBA epoxy resins. The fact that the mean exposure time was significantly shorter (11 months) for patients with contact allergy due to reactive diluents than for patients with contact allergy due to DGEBA epoxy resins (35 months) also supports this observation (II).

Polyamine hardeners (I, II, VII)

In the present material, 30 (24 %) of 125 the patients who currently had occupational allergic contact dermatitis from epoxy resin compounds reacted to hardeners. During 1974–1983 nine patients were found who were sensitive only to the hardeners (with unknown composition) they had handled at work, but not to the EDA, TETA and MDA included in the patch test series (I). By including DETA and IPDA in the patch testing, at least one individual hardener compound was identified as responsible for the hardener allergy in every case (II). Most of the patients in the study reacted to MDA, DETA and TETA.

Isolated contact allergy to epoxy hardeners was unusual, but was detected in three of the patients studied (VII). In addition, rare cases of contact allergy to IPDA, TMD, XDA or tris-DMP were found (VII). Contact allergy to polyamines in patients who were exposed to amine-epoxy adduct type hardeners supported the results of Thorgeirsson (166), who found that polyamine remnants in the amine-epoxy adducts can induce sensitization.

Allergic patch test reactions to MDA or EDA are not necessarily an indication of sensitivity from exposure to epoxy resin hardeners. As a matter of fact during 1984–1988 only four of 13 reactions to MDA and neither of two reactions to EDA were found to be relevant to current or previous exposure to epoxy resin compounds (II). The relevancy of MDA allergy is sometimes difficult to detect. For example, a positive patch test reaction to MDA may represent allergy to *para*-amino compounds (e.g., *para*-phenylene diamine) (47, 70) or exposure to diphenyl methane diisocyanate

(II). EDA allergy may be due to exposure, for example, to rubber, synthetic coolants or topical creams (55).

The cycloaliphatic polyamine IPDA has been included in the plastics and glue series since 1985. (See Table 1 in VII.) Three of the patients were allergic to IPDA. The test concentration of 0.5 % was found to induce neither irritation nor active sensitization in the patch testing, as was the case when the testing was performed with a test concentration of 5 % (113). Thus an 0.5 % concentration is recommended.

Three previous reports on contact allergy to XDA have been published (78, 146, 182). The only patient of the present study who was allergic to both IPDA and XDA also had an allergic patch test reaction to TMD (VII). In the guinea pig maximization test this amine proved to be a strong sensitizer (166), but allergic contact dermatitis caused by TMD had earlier not been reported. The positive patch test reactions to IPDA, XDA and TMD in the patient probably represented concomitant sensitization to the compounds because he had been exposed to each of the compounds at work. Two other patients with contact allergy to IPDA had negative patch tests to TMD and XDA. (See Table 2 in VII.) This finding also suggests that the aforementioned patient had concomitant sensitization to IPDA, XDA and IPDA. A test concentration of between 0.1 % and 0.5 % seems to be suitable for patch testing for XDA and TMD.

The textbooks of Cronin (37), Foussereau *et al.* (57) and Adams (3) mention tris-DMP as an allergen, but the source of the information on sensitivity could not be traced. Two of the patients of the present study were allergic to tris-DMP; this finding indicates that this compound may be a more common allergen than expected (VII). The recommended test concentration for tris-DMP is 1 % in pet..

The present study indicates that patch testing with DETA, TETA, MDA, IPDA and tris-DMP should be performed when allergy to epoxy hardeners is suspected. Because of the vast variety of hardeners used, it is highly recommendable to test patients also with the hardeners they have been exposed to; then test concentrations of up to 10 % should be used for the amine-epoxy adducts. A test concentration of about 1 % is the most suitable for polyamine type hardeners.

Sporadic reports of contact allergy to non-amine hardeners have previously been published (76, 160). In the present study no cases of allergic contact dermatitis due to the non-amine hardeners were detected.

Bisphenol A and epichlorohydrin (II)

Occupational contact dermatitis due to epichlorohydrin and bisphenol A, the two main raw materials in the production of DGEBA epoxy resins, is uncommon. In epoxy resin plants, despite closed manufacturing systems, workers can be exposed to these compounds enough to develop contact allergy (145, 179, 180). In the finished resin, the amount of free epichlorohydrin is less than 0.001 % (145). The amount of bisphenol A is even less (140), because in the manufacturing process epichlorohydrin is always present in excess to ensure that the molecules terminate in epoxy groups (37).

Two patients had an allergic patch test reaction to bisphenol A. In neither of the patients had the sensitivity developed due to DGEBA epoxy resins. One of the patients was probably sensitized to bisphenol A from dental composite resins that were based on BIS-GMA and contained 0.014–0.015 % bisphenol A (unpublished). This percentage is markedly higher than the amounts of bisphenol A in epoxy resins.

The other patient with an allergic reaction to bisphenol A had probably acquired her dermatitis from phenol formaldehyde resin and had not been exposed to epoxy resin compounds (II). The contact allergy to bisphenol A was probably a cross-reaction with compounds responsible for phenol formaldehyde resin allergy, such as dihydroxydiphenyl methanes (bisphenol F) (31).

None of the patients studied during 1974–1990 had an allergic patch test reaction to epichlorohydrin in the first patch test session. However, one patient was actively sensitized due to patch testing performed with epichlorohydrin at 1 % in pet. (unpublished). The patient showed a mild irritant reaction on the test readings after 24–48 h, but after 21 days a more severe eruption was seen on the test site. On retesting two months later, she had a clear allergic reaction to epichlorohydrin.

This patient is possibly the only one who was actively sensitized by patch testing with epoxy compounds during 1974–1990. Previously, rare cases of active sensitization due to epoxy compounds have been reported (34, 35, 68, 113). Active sensitization is generally believed to occur in patch testing with unknown materials provided by the patient or employers (4). At the Institute of Occupational Health no patient has thus far been found to have developed contact allergy due to patch tests performed by the patients' own materials. Apart from epichlorohydrin, the aliphatic acrylate patch test substances available from the test substance suppliers have especially been sensitizers (103).

In the present study the test concentration of epichlorohydrin was lowered two times because of active sensitization and the frequent irritant reactions, the first time in the beginning of 1984 from 1 % to 0.3 % and then in September 1985 from 0.3 % to 0.1 %. Neither irritant reaction nor active sensitization has been observed with epichlorohydrin at 0.1 % in pet. It has not been established whether false-negative tests occur.

Contact allergy to epoxy acrylates (VIII, IX)

Despite the increasing use of epoxy acrylates in dental care and industry, only a few reports on contact allergy due to these compounds have previously been published (18, 20, 49, 134).

All four patients who had acquired their epoxy acrylate allergy from dental composite resins containing BIS-GMA as the main monomer were concomitantly allergic to both BIS-GMA and the standard epoxy resin (VIII, IX). The fifth patient was sensitized to BIS-GA, but neither to BIS-GMA nor to the standard epoxy resin (unpublished). He had worked in paint processing and had handled raw materials based on BIS-GA. Contact allergy to epoxy acrylates was also found in patients who had been exposed to DGEBA epoxy resins, but who had no known exposure to the epoxy acrylates (II, III, VII).

The accurate reason for the concomitant sensitization to epoxy acrylates (BIS-GMA) and the standard epoxy resin is not known. It may, for example, result from an impurity present in some compounds. Traces of DGEBA (i.e., DGEBA-based epoxy resin with an MW of 340) have been found in the dental composite resin material Concise (3M Company, MN, USA) (136). Thus BIS-GMA in dental composite resin materials probably contains impurities. Furthermore, depending on the type of manufacture of BIS-GMA, differences may occur. BIS-GMA based on a reaction between DGEBA and a methacrylic acid may contain more DGEBA than that based on bisphenol A and a glycidyl methacrylate. The latter BIS-GMA probably contains more bisphenol A than the former. (See page 13.) In the present study, DGEBA was not found in Miradapt (Johnson & Johnson), Delton (Johnson & Johnson) or Bonding Agent Universal Resin (Johnson & Johnson) (VIII), but about 0.001 % was found in one Concise batch (IX). The role of glycidyl methacrylates in BIS-GMA contact allergy is also unknown. When two raw materials of preparations of commercial standard epoxy resin were analysed, small amounts of PGE (up to 0.035 %) and some undetermined impurities were detected in addition to epoxy oligomers (II). Cross-allergy between epoxy acrylates (or their impurity) and DGEBA-based epoxy resin (or

its impurity) would explain why the patients reacted to both the standard epoxy resin and the epoxy acrylates.

According to the present patch test results, BIS-GMA and BIS-GA are recommendable for use in the detection of contact allergy due to epoxy acrylates. An allergic reaction produced by the standard epoxy resin may indicate contact allergy to epoxy acrylates, and this possibility should be clarified by additional patch tests.

Contact allergy to other epoxy compounds (X)

The manufacturing process of cationic starch was believed to be safe by both the employer and the workers because it was automatic and new. The regular handling of the process liquid was thought to be of short duration and thus without risk, and protective measures were not regularly used.

In the patients who were revealed to be allergic to EPTMAC, neither allergy to the standard epoxy resin nor to epichlorohydrin was found. EPTMAC and epoxy resin contain a similar epoxide group, but the compounds are not otherwise chemically closely related. However, the sensitizing capacity of both chemicals probably depends on their reactive epoxide structure and their ability to react with proteins (47). The end product of the modification process, cationic starch, gave a negative patch test result when tested undiluted. Though the test was performed only on one sensitized patient, it seems obvious that cationic starch is free from the allergenic EPTMAC, as it should be. This finding is important because the starch is used in the production of paper handled in everyday practice.

The development of contact allergy to EPTMAC might have been promoted by warm alkaline conditions during the process and the surface active nature of the compound. Sensitization took place after a short period of contact with EPTMAC as in the cases of Bergquist-Karlsson (14). This finding indicates that EPTMAC is probably a strong human sensitizer, although it was considered moderate in the guinea pig maximization test (14).

An industrial hygiene project was initiated in the starch modification factory to prevent new cases. It showed that there were many possibilities for skin contact with the process liquids during the manufacturing process, even though it was automated. Improvements in the work environment were versatile. Their costs (present value) were estimated at FIM 430 000 (USD 120 000) (98). As a consequence no new cases of

allergic dermatitis have appeared for six years, a finding indicating that the investment was even financially beneficial.

Immediate allergy to epoxy resin compounds (I–III)

Prick tests and specific IgE determinations indicated that two patients had IgE-mediated allergy to DGEBA epoxy resins. Bronchial asthma (187), rhinitis (149) and urticaria (164, 187) from the epoxy resins have earlier been reported. Tests to demonstrate that these symptoms could be IgE-mediated have not been performed earlier.

The observations from a patient group from an insulator factory indicated that immediate allergy from epoxy resins is possibly rare even if the patients have strong exposure to epoxy resins (III). The specific IgE antibodies to DGEBA (i.e., purified DGEBA-based epoxy resin monomer with an MW of 340) indicated that the DGEBA was the specific allergen in the two asthma patients.

The present study indicates that epoxy resins can cause both immediate and delayed allergic reactions (III). It remains to be seen whether more cases with immediate allergy from the resins will be detected when the specific IgE determinations and prick tests are used to investigate patients exposed to epoxy resins.

Though organic phthalic anhydride hardeners are well known occupational respiratory allergens (15), the two cases presented are the first cases of contact urticaria reported due to MHHPA (I, II).

Irritant contact dermatitis due to epoxy compounds (I, II)

Only five (0.6 %) of all the 843 occupational cases of irritant contact dermatitis were revealed to be due to epoxy compounds (I, II). DGEBA epoxy resins are not severe irritants, and the irritability decreases with an increasing MW of the oligomer (92). Curing agents in powder paints, such as dicyandiamide and organic anhydrides, are potentially irritant (108, 139). The role of such compounds may have been crucial in the development of irritant contact dermatitis in four of the patients who had handled powder paints or their raw material in the present study, and probably also in the fifth patient who had handled a mixture of a DGEBA epoxy resin with a low MW and an organic anhydride (MHHPA).

Exposure

Roughly 3000–5000 (0.1–0.2 %) of all workers are occupationally exposed to an epoxy resin system in Finland (84). During a period of 15 years (1975–1989) altogether 664 cases of skin disease induced by epoxy resin compounds (mainly allergic contact dermatitis) were reported to the Finnish Register of Occupational Diseases. Thus 1 % of the workers exposed to epoxy resin compounds (about 40 persons) developed an occupational dermatosis due to the agents every year.

Even higher risks of dermatitis from exposure to epoxy resin compounds were found for individual groups of workers constantly exposed to epoxy resin compounds. In a department manufacturing insulators from epoxy resins, 12 of 80 (15 %) exposed workers developed contact allergy to the resins (V), and in a brush factory three of four workers became sensitized by glue containing DGEBA epoxy resin and reactive diluents.

Dermatitis induced by epoxy resin compounds was also found often among patients who were referred to dermatological investigations for suspected occupational skin disease and who had a current or previous occupational exposure to epoxy resin compounds. The epoxy resin compounds were revealed to be the main cause for the current dermatosis in 41 % (32 of 79) of the cases (II).

Epoxy resin compounds were found to be allergens, especially in painting and paint processing, electrical insulation, gluing and the manufacture of epoxy objects (Table 3). Paints, the raw materials of paints and other surface coatings were the most frequent causative agents (31 %) for the dermatoses induced by epoxy resin compounds. This finding reflects the fact that most (about 80 %) of the epoxy resins imported to Finland are used for coating purposes (12). Nevertheless, a larger part of the patients than expected had developed their dermatosis due to epoxy resin compounds while working with electrical insulation (29 %) and gluing (18 %). It may be due to the fact that, in addition to the amount of epoxy resin compounds used, many other aspects may be important for the development of dermatitis induced by epoxy resin compounds, for example, the frequency of skin contacts with the causative agent, the concentration of the epoxy compound, the size of the contaminated skin area and possibilities to use protective gloves.

Most (65 %) of the patients having an epoxy compound dermatosis were men, as also was the case in previous studies (50, 58, 119, 186). The difference between the two genders probably represents differences in exposure.

Location of skin diseases due to epoxy compounds

Epoxy resins can induce direct or airborne contact dermatitis (46). The study covering the years from 1984 to 1988 (II) indicates that the skin symptoms are located mainly on the patients' hands or arms. Facial dermatitis was common (60 %) among the patients, but it was not especially common among patients allergic to reactive diluents or hardeners. Reactive diluents and hardeners have been considered the most probable causes of airborne epoxy resin compound dermatitis because the substances are more volatile than DGEBA epoxy resins (40). Nevertheless, they are not highly volatile at room temperatures. Dermatitis due to airborne epoxy resin compounds may also be due to other, unknown, volatile sensitizers contained in epoxy resin compounds. Even a minimal amount of an allergen (e.g., 1 µg) may be enough to evoke the symptoms on exposed skin in a patient highly sensitive to the allergen. Such a minimal amount of allergen may come into contact with the skin from dust particles and possibly via contaminated hands or gloves (156, 171).

Practical conclusions

The identification of specific allergens is important in occupational dermatology. Firstly, great economic aspects are connected with occupational disease legislation. Secondly, prevention of occupational allergic contact dermatitis is possible only when the allergen has been identified. It has been found necessary to combine chemical and dermatological experience for the optimal investigation of occupational skin diseases induced by epoxy compounds, for example, patch testing, clarification of the causative agents and planning of preventive measures for the patient and still healthy fellow workers. Since 1976 almost every investigation of patients suspected of having an occupational skin disease due to epoxy compounds has also included a consultation with the chemist in the Section of Dermatology at the Institute of Occupational Health. The present author has acted as the chemist since 1979. Between 1986 and 1989 the chemist personally interviewed every patient. In problematic cases, consultations with industrial hygienists, visits to the patients' worksite, and analyses of the material handled by the patients were found to be important. In a few cases, occupational hygiene measurements were used.

Of the chemical analyses, thin-layer chromatography was found to be suitable for isolating different fractions of epoxy resins for the preparation of specific DGEBA-HSA conjugates (III) or for patch testing (IV). Other chromatographic methods (gas chromatography and high-performance liquid chromatography) were used to demonstrate the presence or absence of particular allergens. To identify unknown

allergens more expensive mass spectrometry and nuclear magnetic resonance spectrometry (II, V) were necessary.

Most of the chemical analyses in the present study were connected with investigations of suspected occupational skin diseases, and the costs were paid by the insurance company of the patient, in accordance with Finnish legislation (Accident Insurance Act, 608/1984).

The present study also revealed problems encountered with the samples brought in by the patients. They may be wrongly labelled so that analyses of the samples indicate a substance different from that stated by the label. The amounts of the ingredients according to the chemical analyses may also differ from those given by the manufacturer, especially in cases in which small samples of solvent-borne substances have been packed in jars with loosely fitting lids that allow part of the solvent to evaporate before the analyses, and consequently also before the patch testing (VII).

No chemical can be used alone to screen for sensitization to several different contact allergens of epoxy compounds. Individual contact allergies to hardeners, reactive diluents and non-DGEBA epoxy resins were common among patients who also had simultaneous exposure to DGEBA epoxy resins (I, II, IV–VII). On patch testing, cross-allergy was found to chemically closely related compounds, especially to reactive diluents, and to epoxy acrylates. In addition, patients who were allergic to cycloaliphatic epoxy resins often reacted to reactive diluents, and vice versa.

The investigator must not be satisfied after having found one relevant contact allergen in the product because even the main allergen might have remained undetected. For instance, of the patients who had developed contact allergy to epoxy resin compounds, 30 % (Table 5) was sensitive to more than one of the three main epoxy resin compound groups (i.e., resins, hardeners and reactive diluents).

Thus it is highly recommendable that patients who have contact dermatitis suspected to be caused by exposure to epoxy resin compounds be tested not only with the standard epoxy resin but also with the individual allergenic compounds, hardeners, reactive diluents and non-DGEBA epoxy resins according to the contents of the epoxy resin compounds used by the patients. Despite the use of an extensive patch test series, testing with all materials to which patients have been exposed is important. Because of common cross-reactivity, a couple of reactive diluents and epoxy acrylates are probably enough to screen contact allergy also to other related compounds (Tables 7 and 9).

Testing only with the patients' own materials is not always completely reliable because the allergens may become too diluted and produce negative patch test results. But in initial patch testings, it was not uncommon to get the only positive reaction with the patient's own material. In subsequent testings the specific allergens may be identified.

In general, pet. seems to be a good vehicle for epoxy resin compounds. For solid materials containing uncured epoxy resins, it is preferable to use acetone instead of water to soften the material in the Finn Chamber (II).

According to the findings of the present study, the epoxy compound series is recommended as presented in Table 11.

Table 11. *Epoxy compound series including epoxy resin and ethylenediamine from the standard patch test series*

Test substance	% (w/w) in pet.
Standard epoxy resin	1
Cycloaliphatic epoxy resin	0.5
1,4-Butanediol diglycidyl ether (BDDGE)	0.25
Phenyl glycidyl ether (PGE)	0.25
Ethylene diamine (EDA)	1
Diethylene triamine (DETA)	1
Triethylene tetramine (TETA)	0.5
4,4'-Diaminodiphenyl methane (MDA)	0.5
Isophorone diamine (IPDA)	0.5
2,4,6-Tris-(dimethylaminomethyl)phenol (tris-DMP)	1
2,2-Bis(4-(2-hydroxy-3-methacryloxypropoxy)phenyl)propane (BIS-GMA)	2
2,2-Bis(4-(2-hydroxy-3-acryloxypropoxy)phenyl)propane (BIS-GA)	0.5

Gloves of laminated multilayered plastic (4H-glove), containing ethylene-vinyl alcohol copolymer, have been developed especially for the handling of epoxy compounds (88). None of the patients of the study had used such gloves because they were not

commercially available until recently. Nevertheless, the mean exposure time to epoxy resin compounds was more than one third longer for patients using protective gloves than for those not using them. Thus the use of any type of gloves seems to reduce exposure to epoxy resin compounds and helps to protect against sensitization, although the use of protective gloves may in some individual cases encourage contact allergens to come into contact with the skin (II). Unhealthy skin, even small wounds and abrasions, should be protected from epoxy compound exposure because of increased skin penetration.

8. SUMMARY AND CONCLUSIONS

Of a total of 3731 patients investigated between 1974 and 1990, 1844 (49.4 %) had an occupational skin disease. Of them 142 (7.7 %) had an occupational skin disease caused by epoxy compounds – 135 patients (95 %) had allergic contact dermatitis, five had irritant contact dermatitis, and two had contact urticaria. Apart from dermatoses, two patients had IgE-mediated asthma from exposure to DGEBA epoxy resins. Thus epoxy compounds are one of the main causes of occupational allergic contact dermatoses and can be considered potential causes of occupational asthma.

The most frequent causes were epoxy resin compounds, which together induced 93 % (132 cases) of all epoxy compound dermatoses. The three most common causative products were epoxy paints and their raw materials (31 %, 41 cases), epoxy resin compounds used in electrical insulation (29 %, 38 cases) and epoxy glues (18 %, 24 cases). Fewer cases were caused by products containing epoxy acrylate and EPTMAC.

The present study found that, in addition to contact allergy to DGEBA epoxy resins, contact allergy to epoxy hardeners, non-DGEBA resins and reactive diluents is common. Polyamine hardeners, most frequently MDA, DETA and TETA, rarely IPDA, tris-DMP, EDA, TMD and XDA, were the second commonest causes of contact allergy induced by epoxy resin compounds, after DGEBA epoxy resins. Cycloaliphatic epoxy resins and other non-DGEBA epoxy resins, including heterocyclic dimethyl hydantoin, phenol novolak and brominated epoxy resins, were the third commonest causes, and reactive diluents the fourth commonest cause of allergic dermatitis due to epoxy resin compounds. Most patients sensitized to reactive diluents were allergic to PGE, *ortho*-CGE, HDDGE and BDDGE, whereas fewer patients were sensitized to AGE, NPGDGE and BGE. Cross-sensitization between reactive diluents was common. Cardura E 10 and Epoxide 8 provoked no reactions.

The present study also indicated that DGEBA epoxy resins with a high average MW ought to be regarded as potential sensitizers, and organic solvents probably promote sensitization to DGEBA, even if the amount of DGEBA is low in the causative products.

When contact dermatitis induced by epoxy compounds is suspected, an accurate diagnosis is made with the use of detailed data on the patient's exposure and extensive patch testing, including tests with the patient's own products. No chemical can be used alone to screen for sensitization to all different contact allergens of epoxy compounds. The patch test series should not only include the standard epoxy resin, but also separate

allergenic compounds (i.e., polyamine hardeners, reactive diluents and non-DGEBA epoxy resins) according to the contents of epoxy resin compounds used by the patient.

The recommended test concentrations are 0.25 % for reactive diluents, 0.5–1 % for non-DGEBA epoxy resins, 0.1–0.5 % for XDA and TMD, 1 % for tris-DMP, 0.5 % for IPDA, and 0.2 % for EPTMAC. The test concentration for two-component epoxy products and products containing epoxy acrylate is dependent on the main known allergenic compounds in the products (i.e., individual epoxy resins, polyamines and epoxy acrylates). A test concentration of about 1 % is the most suitable for polyamine type hardeners, and test concentrations of up to 10 % are recommendable for amine-epoxy adducts. In general, pet. is a practicable vehicle for epoxy compounds, but for solid materials acetone is preferred to soften the materials before application.

All compounds containing an epoxy group, epoxy acrylates or polyamine hardeners include a skin sensitization risk. The highest risk is connected with the handling of products in liquid form. Constant exposure, simultaneous use of organic solvents, alkaline milieu, elevated temperatures of epoxy compound liquids, and an unhealthy state of the skin may increase the risk of sensitization. Persons working with epoxy compounds should be aware of such risk factors. The skin and airways should be protected from exposure to the compounds. However, an automatic process as such does not guarantee protection against skin contact with the compounds. Proper personal protective measures, especially careful hand protection, minimizes the exposure. Impermeable disposable industrial gloves are preferable for the handling of epoxy compounds.

9. ACKNOWLEDGEMENTS

I wish to express my sincere gratitude and appreciation to:

Professor Jorma Rantanen, Director General of the Institute of Occupational Health, and Professor Vesa Vaaranen, Director of the Department of Occupational Medicine, who provided me with excellent working facilities, and Professor Sven Hernberg, Scientific Director, for his interest.

Professor Simo Laakso, Head of the Biochemistry and Microbiology Laboratory of the Faculty of Process Engineering and Material Science, Helsinki University of Technology, for his kindness, supervision, valuable advice, and support during the work.

Docent Lasse Kanerva, Chief of the Section of Occupational Dermatology, for introducing me to scientific work and for his valuable support and constructive criticism throughout this work.

Dr Tuula Estlander, for scientific collaboration, for her very expert knowledge in occupational dermatology, her constant encouragement and support throughout the entire work, her many constructive and stimulating discussions, and her excellent advice.

Docent Kirsti Kalimo, and docent Antti Zitting, for their critical review of the manuscript. I appreciate their constructive criticism and helpful advice.

Dr Marja-Liisa Sysilampi, my co-author and good friend, for introducing me to skin testing.

Maj-Len Henriks-Eckerman, L.Tech., and Pirkko Pfäffli, Ph.L., for their excellent knowledge and experience in epoxy chemistry and industrial hygiene, their valuable discussions and their chemical analyses of the epoxy compounds.

Outi Tupasela, M.Sc., and Liisa Halmepuro, M.Sc., my co-authors and friends, for their fruitful discussions and their establishment of test methods for immediate allergy caused by epoxy compounds.

Ulla Tiikkainen, M.Sc., for all her encouragement and support, and for her valuable help, giving me the opportunity to concentrate on this work as it neared completion.

Ms Kaarina Pylvinen, Ms Tuija Halonen, Ms Riitta Valio, Ms Marianne Pihlström, Ms Marjatta Partanen, my friends and co-workers, for their positive attitude towards my research work, their expert work in skin testing, and, last but not least, their excellent technical assistance.

Dr Helena Keskinen, my co-author, for her kind interest and valuable assistance with problems concerning respiratory diseases. The co-authorship of Dr Kyllikki Tarvainen is also gratefully acknowledged.

Professor Veikko Pirilä, for his interest and valuable advice, especially with regard to the history of patch testing with epoxy resins.

The staff of the library of the Institute of Occupational Health for their expert assistance in searching the literature, Juhani Jaakkola, L.Tech., for his good advice on the use of word processing programs and the layout of the manuscript, and Georgianna Oja, B.A., for her excellent revision of the language of the manuscript.

All the personnel at the Department of Occupational Medicine of the Institute of Occupational Health for their help and positive attitude in many stages of this study.

All the patients for participating in the study and the manufacturers and importers of epoxy compounds and the managements of workplaces for their positive attitudes and valuable knowledge concerning exposure to epoxy products.

My family, especially my mother Saima Jolanki, for her love, interest and support, and my friends for all the enjoyable moments we have shared throughout these years.

My love, Ilmo, for providing me with a care-free atmosphere and for all his encouragement and understanding while I was occupied with this study. I dedicate this thesis to him.

Financial support was provided by the Finnish Work Environment Fund and the Association of Finnish Industrial Hygienists, for which I am grateful.

Riitta Jolanki

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11. APPENDIX

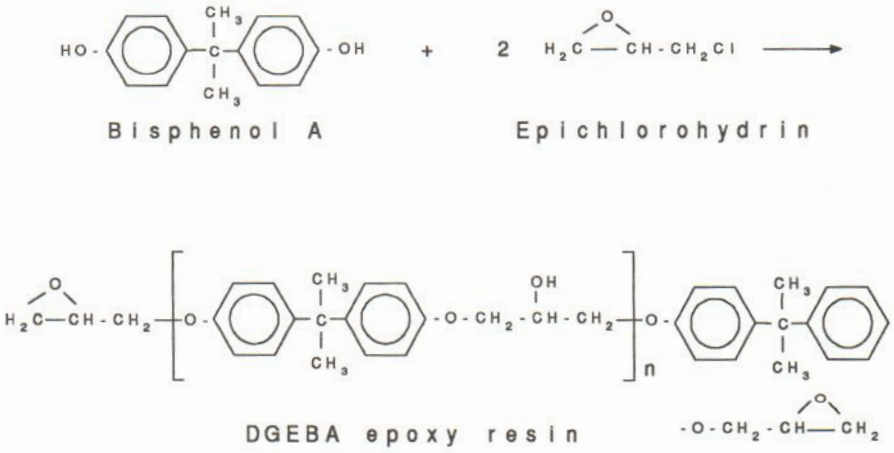
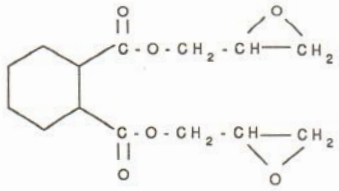
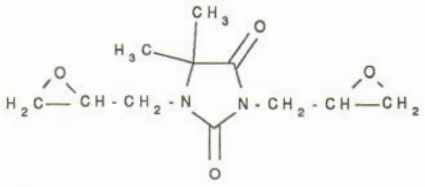


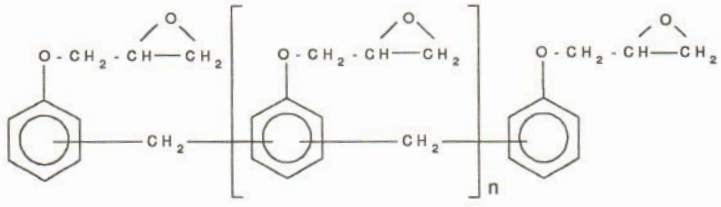
Figure 1. *Diglycidyl ether of bisphenol A (DGEBA) epoxy resin, and the main raw materials of the resin*



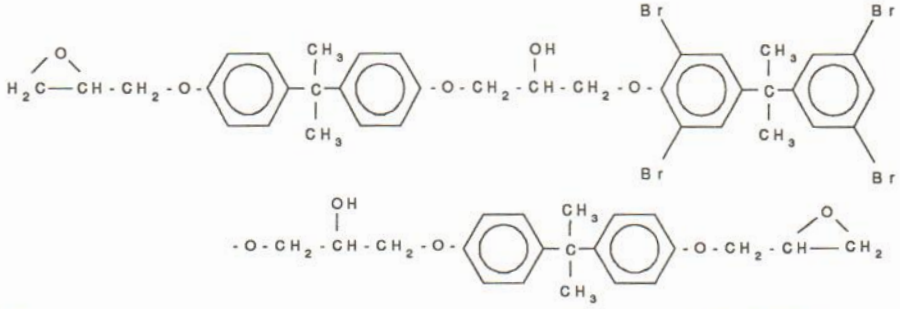
Diglycidyl ester of hexahydrophthalic acid (DGEHHPA) (cycloaliphatic epoxy resin)



Dimethyl hydantoin epoxy resin



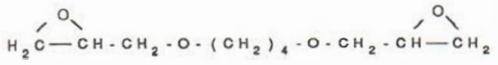
Phenol novolak epoxy resin



Diglycidyl ether of bisphenol A / tetrabromo-bisphenol A epoxy resin (brominated epoxy resin)

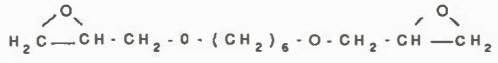
Figure 2. *Non-diglycidyl ether of bisphenol A (non-DGEBA) epoxy resins*

n-Butyl glycidyl ether (BGE)

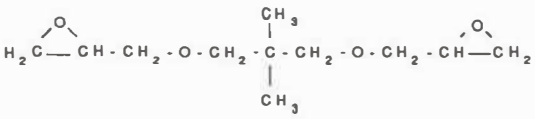


1,4-Butanediol diglycidyl ether (BDDGE)

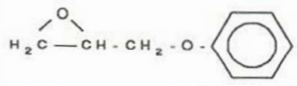
Allyl glycidyl ether (AGE)



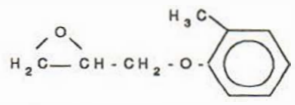
1,6-Hexanediol diglycidyl ether (HDDGE)



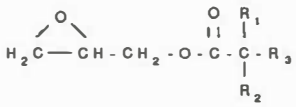
Neopentyl glycol diglycidyl ether (NPGDGE)



Phenyl glycidyl ether (PGE)



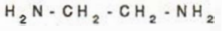
ortho-Cresyl glycidyl ether (ortho-CGE)



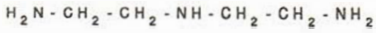
Cardura E 10 (glycidyl ester of synthetic fatty acids; R_1, R_2 and R_3 are alkanes)

Epoxide 8 (glycidyl ether of aliphatic alcohols; R is predominantly a C_{12} or C_{14} alkyl chain

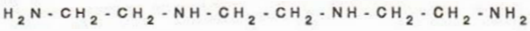
Figure 3. Reactive diluents



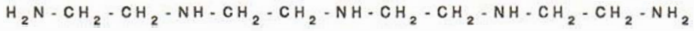
Ethylene diamine (EDA)



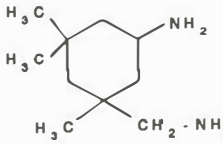
Diethylene triamine (DETA)



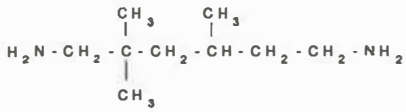
Triethylene tetramine (TETA)



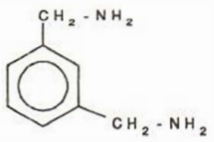
Tetraethylene pentamine (TEPA)



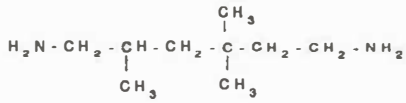
Isophorone diamine (IPDA)



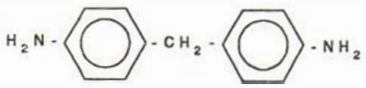
2,2,4-Trimethyl hexamethylene diamine (2,2,4-TMD)



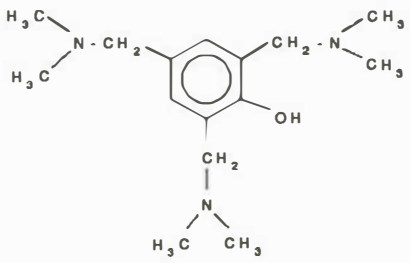
1,3-Xylylene diamine (1,3-XDA)



2,4,4-Trimethyl hexamethylene diamine (2,4,4-TMD)

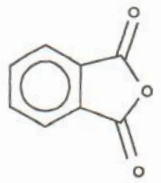


4,4'-Diaminodiphenyl methane (MDA)

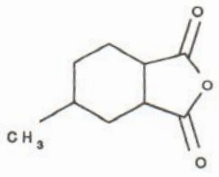


2,4,6-Tris-(dimethyl-aminomethyl)phenol (Tris-DMP)

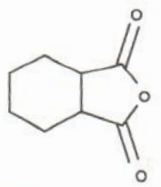
Figure 4. Polyamine hardeners



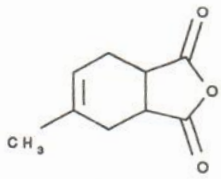
Phthalic anhydride (PA)



Methyl hexahydrophthalic anhydride (MHHPA)

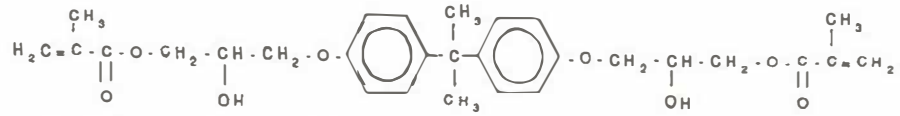


Hexahydrophthalic anhydride (HHPA)

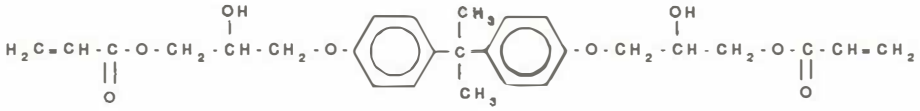


Methyl tetrahydrophthalic anhydride (MTHPA)

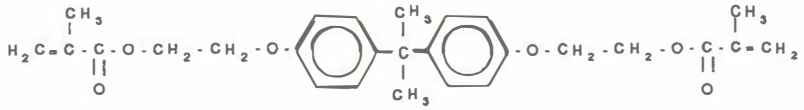
Figure 5. *Phthalic anhydride hardeners*



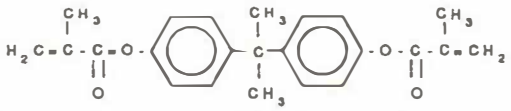
2,2-bis(4-(2-hydroxy-3-methacryloxypropoxy)-phenyl)propane (BIS-GMA)



2,2-bis(4-(2-hydroxy-3-acryloxypropoxy)phenyl-propane (BIS-GA)



2,2-bis(4-(2-methacryloxyethoxy)phenyl)-propane (BIS-EMA)



2,2-bis(4-(methacryloxy)phenyl)propane (BIS-MA)

Figure 6. *Epoxy acrylates*

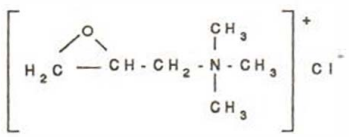


Figure 7. *2,3-Epoxypropyl trimethyl ammonium chloride (EPTMAC)*