

Allergic contact dermatitis to a photopolymerizable resin used in printing

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Organic photopolymerizable resins increasingly used in printing make it possible to produce flexible, lighter plates. A certain number of skin lesions and general symptoms appeared upon manipulation of plates made by the Letterflex® process. In the workshop where this study was carried out, 12 out of 15 people suffered various degrees of skin lesions. The epicutaneous tests and biopsies performed indicate an allergic type reaction to one of the resin's constituents, polythiol. Experiments with animals confirm the strong allergenicity of this compound.

Key words: Allergic contact sensitization – photopolymerizable resin – polythiol – printing.

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The printing of major daily newspapers has been evolving over the past few years, yielding changes in the methods of composition as well as in the printing processes. Thus, electronics has supplanted the manuscript, and modern chemical processes have replaced the five centuries' old lead method.

The use of synthetic resins with different chemical compositions, but having the common general property of polymerizing instantaneously under exposure to U.V. light, allows the production of flexible and light printing plates, usable on traditional rotary printing presses. One of its considerable advantages, among others, is that it does away with any manipulation of lead.

However, these new techniques are not free from drawbacks, and several cases of intolerance to different resins used in the

photo-composition of newspapers have already been noted in France. In this article, we describe a certain number of skin and general symptoms that appeared during manipulation of plates made according to a particular process known as the Letterflex® process. The clinical aspect of this problem is supported by a chemical study and animal experiments. We were able to determine precisely the chemical agent responsible for this occupational disease.

The Letterflex process

The newspaper is composed in two stages:

1. *photo-composition*: each page is laid out in its actual size by a computer coupled with a photo-composer and then photographed.
2. *use of the resin*: The negative is placed

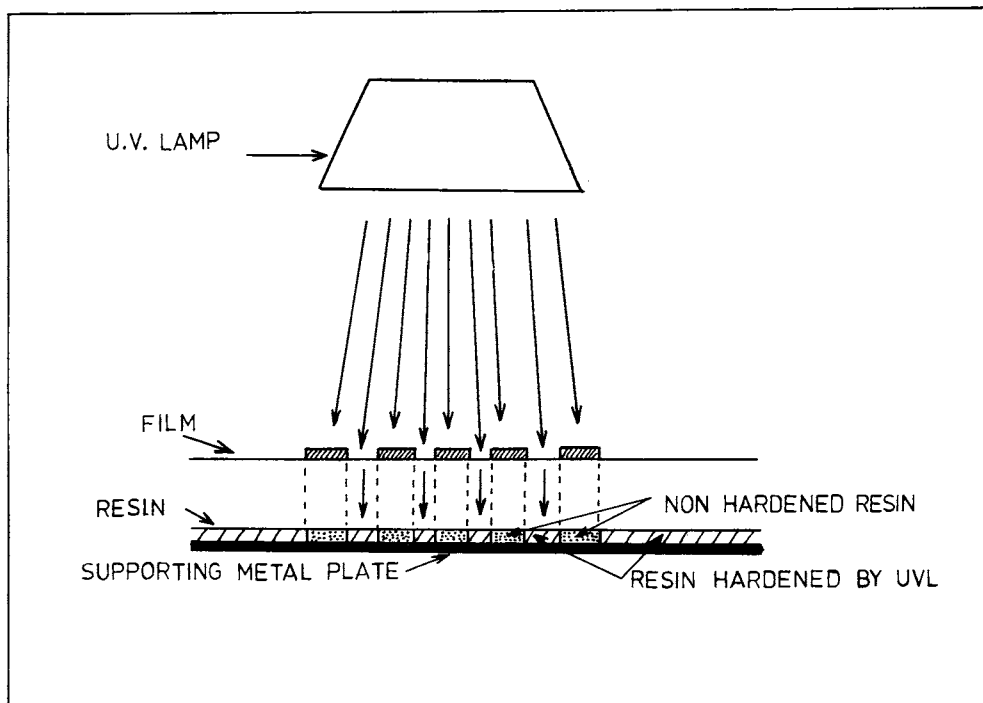


Fig. 1. Principle of the Letterflex process. First stage: exposure to ultra-violet light.

over a thin layer of Letterflex resin spread onto a flexible metal plate which will later be put directly on the rotary printing press (Fig. 1). The combined negative-plate is exposed to ultraviolet light for a few seconds, which triggers polymerization in the transparent spots, that is, in the letters and the lines of the photographs. The non-polymerized resin is blown off and recovered for further use. The text to be printed, optically inverted, thus appears in relief (Fig. 2).

Nature of the resin's components

The resin is not manufactured in France and its composition remains a professional secret. We therefore had to analyze it, if not to identify a substance already known for its allergenic properties, at least to ascertain its composition and perform laboratory tests on the different constituents.

Analysis. In the early stage, two essential additives were detected in the resin and identified after being separated out from the rest of the product. This was achieved through two different methods:

- vacuum distillation in a Büchi bulb tube oven (the resin's main constituents are not distilled)
- column chromatography separation (silica gel, benzene).

These two substances identified by means of infrared spectrophotometry are benzophenone (U.V. sensitizer) and ditertiarybutyl paracresol (anti-oxidant). They make up approximately 2 % of Letterflex resin. The principal constituents of the resin, about 98 %, were separated out by thin-layer chromatography, then by column chromatography (silica gel, methylene chloride). Traditional physico-chemical methods (infrared

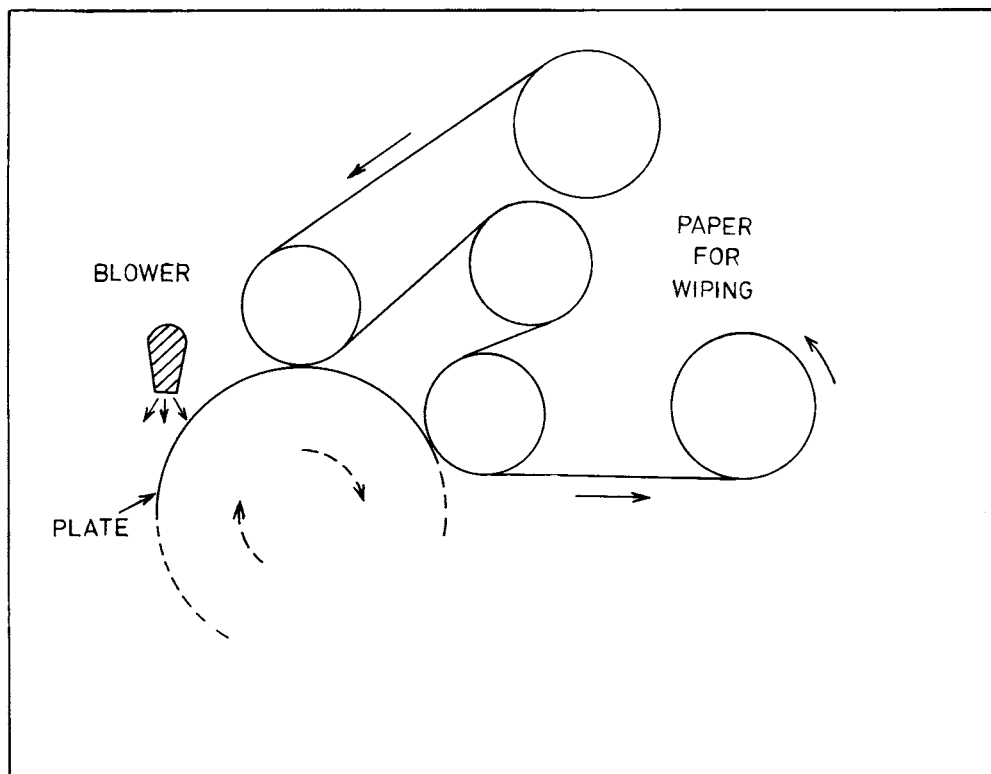
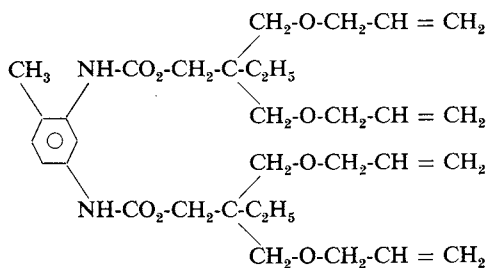


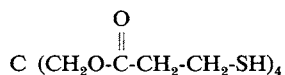
Fig. 2. Principle of the Letterflex process. Second stage: blow cleaning and wiping.

spectrophotometry, mass spectrometry) completed by chemical fractionation using lithium and aluminum hydride allowed us to identify these compounds as being:

1. a polyene derived from TDI (toluene diisocyanate)



2. a polythiol made up of pentaerythritol and mercaptopropionic acid



Preparation. Although polythiol can be obtained commercially, it is much cheaper to prepare it in the laboratory by direct esterification of mercaptopropionic acid by pentaerythritol in benzene. The polyene, not being available commercially, was also prepared in the laboratory from TDI and dimethylolpropane diallylether. (Aldrich Europe Beersse Belgique). The IR spectra of the products obtained in this way can be superimposed exactly upon those of the chromatographically separated constituents. An equal weight mixture of these products yields practically the same IR spectrum as the Letterflex resin sample we had at our dispo-

sal. The products thus prepared made the epicutaneous tests and animal experiments described here possible.

Clinical symptoms

We observed two types of symptoms:

1. skin lesions – some of an irritant pruriginous and erythematous nature appearing on uncovered parts of the body; others of a clearly eczematous nature, primarily affecting the hands.
2. general symptoms, including various degrees of conjunctivitis, and respiratory disturbances with sneezing and rhinorrhea, or conversely, nasal obstruction, coughing, dyspnea, and even, in one case, a true asthma attack requiring an injection of corticoids.

Investigation of allergies

Fifteen people worked in the printing shop in question:

- one supervisor who does no manual labor
- four mechanics appointed to maintain the machines, who had sporadic contact with the polymer when doing repairs
- ten operators.

Three of the workers (including the supervisor) exhibited no pathological symptoms at all and five, at certain times, displayed varying degrees of itchy erythema which disappeared when certain simple precautions were taken, especially when the handling of alcohol was concerned.

The last seven suffered from eczematous lesions on the hands, especially around the thenar and palmar sides of the fingers, where the hand grasps the plate, around the nails and in the subungual sulcus.

The first question that arose was whether these were irritant contact dermatitis or allergic-type true eczematous lesions. In an attempt to answer this question, we performed a biopsy of the thenar lesion in one of our patients and the result was "typical picture of vesicular eczema" (Pr. J. Sayag).

We then performed patch tests using Neodermotest® plasters (Servier et Cie) and our own series of standard routine allergens (Table 5). The allergens were applied on paper discs and the results read at 48 and 96 h. The following allergens were also tested:

Letterflex liquid resin in successive dilutions of 50 %, 10 %, 1 %, 0.1 % in acetone

Residue, resin collected in the washing machine at the same dilutions

Exposed dry and wet plates

New unused plate

Standard dilutions of low molecular weight epoxy resin and its hardener triethylene tetramine (for comparative reasons since, at the onset, we did not know the composition of the Letterflex resin).

Under these conditions:

- eight patients had negative tests (the supervisor, two mechanics and five operators)
- seven had positive tests, four to the resin, residue and the finished plate, one to the residue and hardened resin on the finished plate, one to the finished plate only, and one to the residue and resin.

All the epoxy resin and hardener tests were negative, as were tests with a new metal plate uncoated with resin.

We then had to make sure that these were in fact truly allergic reactions and not simply caustic effects brought on by the nature of the product tested. We therefore carried out two biopsies at the time of the 48-h reading

1. one corresponding to the resin test (1 %) in which slight eczematous lesions, rarely vesicular, were found
2. the other corresponding to the plate in which a typical vesicular eczema picture was found (Pr. J. Sayag).

Several months later, we were able to

Table 1. Irritant potential of Letterflex and its constituents in New Zealand rabbits

Products and concentrations	Macroscopic observations	3rd day microscopic examination	P.C.I.I.	Irritant potential
Undiluted Letterflex	moderate to medium erythema regressing within 3 days of test slight to moderate edema	moderate acanthosis with focal spongiosis and scattered clear cells; superficial focal necrosis with or without dyskeratosis slight infiltrate dermal	2.8	medium
Pure polyene	erythema and/or edema in half the animals, no reaction in the others	the same type of lesions but less marked co-existing with zones of normal histological structure; upper dermis intact	0.6	slight
Pure polythiol	slight to medium erythema and slight edema	moderate acanthosis with focal spongiosis and scattered clear cells;	1.8	slight
Benzophenone 20 g in 100 ml olive oil	slight to moderate erythema, edema most often slight, sometimes moderate (1/6) or intense (1/6)	focal necrosis with or without dyskeratosis	2.0	medium
Ditertiarybutyl p-cresol 10 g in 100 ml olive oil	medium erythema and edema	dermis normal	1.6	slight
Ditertiarybutyl p-cresol 25 g in 100 ml olive oil	medium erythema and edema	moderate acanthosis with spongiosis and scattered clear cells, focal necrosis with or without dyskeratosis slight dermal infiltrate	3.4	medium

avail ourselves of the resin's separate constituents, and were thus able to retest five of the seven subjects who had previously had positive test results. They reacted neither to the polyene, the benzophenone nor to the ditertiarybutyl 2-6 p. cresol, but they all had positive reactions to the polythiol diluted in acetone, at 1 % and .1 % concentrations.

In this case, we again performed a biopsy on one of the positive tests, and the histo-

logical picture was typical of vesicular eczema (Pr. J. J. Bonerandi).

Experimental pathology

Irritant potential. The possible irritant potential of Letterflex and its components was assessed by the Draize method (1944) on 42 New Zealand rabbits. Three products in the liquid state were used pure: Letterflex, polyene and polythiol. Benzophenone and ditertiarybutyl paracresol, which are pow-

Table 2. Sensitizing capacity of Letterflex photopolymer and its constituents in the guinea pig maximization test

Products	Induction concentrations (pet.)		Challenge concentration	% of sensitized animals	Degree of allergenicity
	Injection	Topical application			
Letterflex complete	1 %	20 %	0.5 %	60	III
			1 %	60	III
			5 %	75	III
Polythiol	1 %	20 %	0.5 %	94	V
			1 %	100	V
			5 %	100	V
			10 %	100	V
Polyene	1 %	20 %	5 %	0	
			10 %	0	
Benzophenone	1 %	10 %	1 %	0	
			5 %	0	
Ditertiary butyl p.cresol	1 %	10 %	1 %	0	
			5 %	0	

ders, were dispersed in olive oil (10, 20 or 25 % as shown in Table 1).

Undiluted products or oil dispersions (0.5 ml) were applied to the animals' scratched or unscratched skin. At 24 and 72 h the presence of erythema or edema was sought, their estimated intensity serving to calculate the primary cutaneous irritation index (PCII) whose interpretation, in turn, makes it possible to determine the irritant potential of the substances under study (Table 1).

The results were as follows. Undiluted polyene, polythiol and Letterflex are not strong primary irritants. We never observed necrotic lesions or gross erythema. Nevertheless these products cause slight (polyene) moderate (polythiol) or medium (Letterflex) erythematous and oedematous reactions on the rabbits' skin. The histo-pathological examination of the lesions on the third day confirmed these macroscopic observations. Any alterations of the skin were temporary:

those having spread the most disappeared naturally in less than 5 days. As for the benzophenone and ditertiarybutyl paracresol, we had to use much higher concentrations than those found in Letterflex composition in order to observe erythema or edema.

Sensitizing potential. The sensitizing potential of Letterflex and its components was determined according to the Magnusson & Kligman method (1970), using batches of 20 female guinea pigs of the Hartley strain weighing about 400 g each.

Sensitization was produced by two intradermal injections (2×0.05 ml) of one of the products in olive oil (1 %), by two injections of complete Freund's adjuvant (50 % in distilled water), and by two injections of the suspended product in Freund's adjuvant (1 %). After 1 week, following shearing and massaging with sodium lauryl

Table 3. Sensitizing capacity of polythiol without adjuvant in the guinea pig maximization test

Challenge concentration (pet.)	% of sensitized animals
1 %	95
0.5 %	90
0.25 %	76
0.1 %	52

sulfate, the products in petrolatum were applied to the animals' skin for 48 h at the same site.

There is a 2-week rest period before the reactions are triggered off by applying non-irritant concentrations of the products in petrolatum: the results were read at 24 and 48 h.

The results of the tests performed with Letterflex and its constituents are summarized in Table 2. Letterflex was shown to be a third degree allergen, according to Magnusson & Kligman's (1970) classification.

Among the components, polythiol proved to be a strong allergen (5th degree), whereas all the other products displayed no allergenic potential. These results concur with our clinical observations.

Polythiol, seems to be the chemical substance responsible for the allergenicity of Letterflex. The weaker sensitizing capacity of the complete Letterflex is due to the lower concentration of polythiol in the mixture.

It was verified that the animals sensitized to Letterflex could be challenged by application of 5 % polythiol in petrolatum: 95 % of the animals reacted. Polythiol being, according to our results, a strong allergen, we sensitized animals using the standard technique but without Freund's adjuvant. Polythiol still proves to be a strong allergen (Table 3). There seems, however, to be a dose-effect relationship, for the number of animals that react decreases if the concentration used for challenge is lowered.

Biopsies were performed 48 h after removal of the challenge application on sensitized, non-sensitized, and control animals. The skin of the non-sensitized guinea pigs displayed a slight epidermal acanthosis (absent in the control group); this results from the action of the petrolatum itself.

In the sensitized animals, according to the challenge substances, the following can be observed (Table 4):

- either a histological picture similar to that of the non-sensitized subjects (no epi-

Table 4. Guinea pig sensitization to Letterflex and its constituents: Biopsies performed 48 h after removal of challenge patch test

Product	Challenge concentration (pet.)	Histopathological reactions		
		positive	negative	uncertain
Letterflex	0.5 %	1/3		2/3
	1 %	1/3		2/3
Polythiol	5 %	3/3		
	10 %	3/3		
Polyene	5 %		3/3	
	10 %		3/3	
Benzophenone	1 %		2/2	
	5 %		2/2	

Table 5. Standard routine allergens

Lavender oil	10 % pet	Triethanolamine	2 % aq
Oil of bergamot	10 % pet	Laurel oil	1 % pet
Paraphenylenediamine	2 % pet	Balsam of Peru	25 % lanolin
Parabens	5 % lanolin	Turpentine	10 % olive oil
Injectable promethazine		Biocidan	0.10 %
Formaldehyde	5 % aq	Neomycin	50 % lanolin
Tincture of arnica		Streptomycin	50 % lanolin
Nickel sulfate	10 % aq	Chloramphenicol	50 % lanolin
Cobalt chloride	5 % aq	Lanolin	as is
Potassium dichromate	0.5 % aq	Aniline	10 % oil of sweet almond
Piperazine	5 % aq	Eugenol	10 % oil of sweet almond
Propylene glycol	10 % aq	Penicillin	100.000 µg in lanolin
Rubber allergens			
Mercaptobenzothiazole	2 % pet	Thiobetanaphthol	0.1 % pet
N-Phenylnaphthylamine	2 % pet	Hydroquinone	1 % pet
Diphenylguanidine	2 % pet	N-Phenyl-N'-isopropyl	2 % pet
		PPD (4010 NA)	

- dermal or dermal alteration or very slight focal infiltrate of the superficial dermis)
- or epidermo-dermal reactions as in allergic contact dermatitis, namely,
 - at the epidermal level: distinct acanthosis, with basal exoserosis with or without lymphocytic infiltration (“persillage lymphocytaire”), with or without epidermal pyknosis, with or without diffuse cellular necrosis, with or without dyskeratosis, with or without necrosis of superficial epidermal layers
 - at the dermal level: irregularly widespread papillary edema, a large increase in cell count which may or may not produce trails ascending toward the epidermis, with or without perivascular cuffs around vessels that are often hyperaemic
 - or finally, intermediate lesions which do not allow us to draw any conclusions.

Conclusion

Both irritant and allergic reactions caused by photopolymerizable resins are becoming more and more common. In the field of printing, the development of new techniques

using these resins has led to the appearance of skin lesions and sometimes even general symptoms, so that this technological evolution has produced new occupational hazards, modifying the traditional pathology of this particular industrial sector.

In France, several authors over the past 2 years have reported symptoms due to acrylic resins, of which almost all seem to be of the irritant type (Ducombs et al. 1974, Beurey et al. 1975). Conversely, in Sweden, Magnusson & Mobacken (1972) and Wahlberg (1974) published a number of cases showing allergic reactions to resins of this type.

Our observations of allergic reactions to a non-acrylic photopolymerizable resin used in printing seem to be the first to be published in France. It is the Letterflex urethane photopolymer mixture of which one component, a polythiol (penta erythritol-tetrakis-3 mercapto propionate) appeared to act as a skin sensitizer.

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