

Occupational eczema from N-isopropyl-N'-phenylparaphenylenediamine (IPPD) and N-dimethyl-1,3 butyl-N'-phenylparaphenylenediamine (DMPPD) in tyres

B. HERVE-BAZIN¹, D. GRADISKI¹, P. DUPRAT¹, B. MARIGNAC¹, J. FOUSSEREAU²,
C. CAVELIER¹ AND P. BIEBER³

¹I.N.R.S., Nancy, France ²Clinique Dermatologique, Hospices Civils Strasbourg, France

³Hôpital Clinique Sarreguemines, France

Forty-two cases of contact sensitivity to N-isopropyl-N'-phenylparaphenylenediamine (IPPD), an amine antiozonant used in rubber manufacture, were collated from several firms and plants dealing with tyres. Ten motor car tyres manufactured by eight different firms all induce sensitivity reactions in seven subjects allergic to IPPD. Clinical cross-reaction tests show that 100 % of the subjects sensitive to IPPD are also sensitive to N-phenyl-N'-cyclohexy-paraphenylenediamine (CPPD), another amine antiozonant, and 37 % to paraphenylenediamine (PPD).

The various types of tyres were analyzed by gas chromatography and then by infra-red and thin-layer chromatography where necessary. None of the 12 tyres examined was found to be free from aromatic amines.

Test reactions carried out with various automobile accessories on subjects allergic to IPPD in tyres gave positive results precisely in those cases where the articles contained IPPD.

The authors then studied occupational sensitivity to N-dimethyl-1,3 butyl-N'-phenylparaphenylenediamine (DMPPD), a rubber antiozonant purported to be non-sensitizing and marketed in the United States. The DMPPD tests were positive for all the IPPD-allergic patients tested; there is no doubt as to the allergenic nature of DMPPD.

The irritant and sensitizing potentials of the four amines in question were tested in laboratory animals: PPD proved to be the most allergenic product, IPPD the least allergenic, and DMPPD and CPPD seem to give identical results. All these products produce positive cross-reactions in varying degrees of severity.

Key words: Allergic occupational eczemas – antiozonant amines – tyre rubber.

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The first cases of contact allergy to N-isopropyl-N'-phenylparaphenylenediamine or IPPD (an antiozonant used in rubber manufacture) were reported by Crow (1967) (two non-occupational cases) and by Bieber (1967) (nine cases, including four from oc-

cupational causes, Bieber & Fousereau 1968).

Since then, very few reports of occupational allergies to IPPD have appeared in the literature. Two cases have been reported in Britain: one by Wilkinson (1968)

in a rubber factory worker, and another by Calnan (1971) in a driver. The only case of IPPD sensitivity reported in the United States was not really occupational, since the patient involved was not a driver by profession.

In France, tyre rubber sensitivities are not infrequent. Geraut (1974) from Nantes noted two cases at a tyre factory, three at a synthetic rubber factory producing automobile accessories, and two in car service workers (the allergen was not specified).

We have collated 42 cases of occupational IPPD sensitivity: 17 in the tyre manufacturing industry, five among tyre dealers (three storage workers and two tyre mounters), and 20 in the automobile transport and servicing sectors (nine drivers, nine mechanics, one petrol station attendant and one carriage work painter).

Occupational sensitivity to IPPD in tyres is very similar to that caused by N-phenyl-N'-cyclohexylparaphenylenediamine (CPPD), also used as an antiozonant, which was studied by Schultheiss in 1959. Cross-reactions between these two substances are very common. The following study deals with IPPD since, as will be seen, chemical analysis of tyres has shown that IPPD was present in nine tyres out of 12, whereas no CPPD was present in 12 tyres out of 12. It is also proposed to study occupational sensitivity to N-dimethyl-1,3 butyl-N'-phenylparaphenylenediamine (DMPPD), an antiozonant similar to IPPD used in a purportedly non-allergenic rubber which is marketed in the United States, but which is in fact equally allergenic.

The present paper appears under the following headings:

1. Job distribution of occupational IPPD sensitivities
2. The clinical appearance of these reactions
3. Test reactions with various tyres on persons already sensitized to IPPD

Table 1. Job distribution of occupational IPPD sensitivities

Job definition	Number of cases
Tyre production workers	17
Tyre dealers, storage workers	3
Tyre mounters	2
Drivers	9
Garage mechanics	9
Petrol station attendants	1
Carriage-work painters	1
Total	42

4. Cross-sensitivity tests between IPPD and two other chemically related products: CPPD and PPD
5. Analytical-chemical investigation of the antiozonants of the aromatic amine type used in tyres and other automobile accessories
6. The allergological implications of these chemical investigations
7. Chemical and allergological investigations into DMPPD
8. Safeguards to be observed when interpreting test reactions with IPPD and its derivatives

Table 2. Distribution of occupational IPPD sensitivities within a given tyre factory

Job definition	Number of cases
Compounding room workers	2
Vulcanizers	1
Assemblers	5
Atomizers	1
Maintenance staff and cleaners responsible for collecting production room waste scraps	3
Retreading department	1
Tyre balance staff	1
Production end staff	1
Total	15

Table 3. Tyre sensitivity tests on persons already sensitized to IPPD (readings mostly taken at 48 hours)

Test product	S... Antoine		Z... Albert		L... Yves		F... Dino		F... Léon		M... Victor		B... J. Claude	
	48 hours		Day 4		48 hours		Day 4		Day 4		Day 4		Day 4	
IPPD	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Firestone	+	+	0		+		+		+		(+)		+	
Michelin XAS	+	+	doubtful		N.T.		N.T.		+		+		+	
Michelin X	+	+	0		+		+		(+)		+		(+)	
Kléber Colombes V10	+	+	0		N.T.		+		+		(+)		+	
Kléber V10S	+	+	doubtful		N.T.		+		(+)		+		+	
Esso E420	+	+	0		0		+		+		+		+	
Pirelli Cinturati	+	+	0		0		+		+		+		+	
Good Year 125	(+)	+	doubtful		N.T.		N.T.		doubtful		(+)		+	
Dunlop SP Sport	+	+	0		N.T.		N.T.		(+)		(+)		+	
Uniroyal Rallye 180	+	+	0		N.T.		N.T.		(+)		+		+	

N.T.: not tested.

9. Irritant and sensitizing potential of these amines (PPD, DMPPD, CPPD and IPPD) in laboratory animals.

1. *Job distribution of occupational IPPD sensitivities*

The results are summarized in Tables 1 and 2.

2. *The clinical appearance of these sensitive reactions*

Allergic eczema can be characterized by distinctly vesicular lesions; these affect the back of the hands and sometimes the forearms. Atypical lesions can also occur, these being purely fissured and keratotic in appearance and situated on the palms. The latter form is frequent, as is the mixed form in which both types of lesion appear.

We have not noted any purpura-like symptoms such as those reported by Bat-scharov & Minkov (1968) in sensitivities caused by IPPD in clothing.

Another atypical form is the lichenified dermatitis observed by Calnan (1971) in a lorry driver: this lesion of a mauvish colour was histologically proved to be in fact a lichenified dermatitis.

In certain cases, the lesions spread to other parts of the body. Their development depends on the extent to which contact with the allergen is continued.

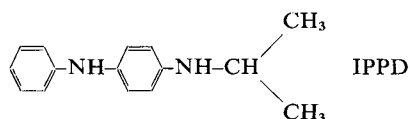
3. *Test reactions with various tyres on persons already sensitized to IPPD*

Seven persons sensitive to IPPD were tested with ten different types of motor car tyres manufactured by eight different firms.

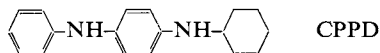
The results of these investigations, which are shown in Table 3, indicate that all ten types of tyres tested produce sensitivity reactions in these persons. The following tyres were used in the tests: Firestone, Michelin XAS, Michelin X, Kléber-Colombes V10, Kléber V10S, Esso E420, Pirelli Cinturati, Good Year 125, Dunlop SP Sport, and Uniroyal Rallye 180.

4. *Cross-sensitivity tests between IPPD and two other chemically related products: CPPD and PPD*

Cross-sensitivity between IPPD and CPPD. According to Schonning & Hjorth (1968) cross-sensitivity between IPPD and CPPD is a common occurrence. These authors studied a series of 12 persons sensitive to IPPD, seven of which were also sensitive to CPPD, and a second series of 15 persons sensitive to IPPD, 13 of which were also sensitive to CPPD. By extension it can be stated that 60 to 85 % of all persons sensitive to IPPD are also sensitive to CPPD.



N-Isopropyl-N'-phenylparaphenylenediamine



N-Phenyl-N'-cyclohexylparaphenylenediamine

Nater (1975), however, reports cross-sensitivity to CPPD in each of six IPPD-sensitive patients tested. We tested eight IPPD-sensitive patients with CPPD. As can be seen from Table 4, all these patients developed cross-reactions.

Table 4. Cross-sensitivity between IPPD and CPPD

Patient	IPPD tested in 2 % concentra- tion in lanolin	CPPD tested in 2 % concentra- tion in lanolin
B... J.		
Claude	+++	+
F... Léon	+++	++
M... Victor	+++	+++
F... Joseph	++++	+++
L... Ar- mand	++	++
S... Gilbert	++	++++
V...		
Georges	+++	++
K... H.	++++	+++

Some of the names under which IPPD and CPPD are marketed are listed below:

IPPD	CPPD
4010 NA, Bayer	4010, Bayer
Nonox ZA, ICI (U.K.)	
Eastozone, Eastmann (U.S.A.)	
Flexzone 3c, Nauga-tuck	Flexzone 6H, Nauga-tuck
Permanax 115, Rhône Poulenc	
Santoflex 36, Monsanto	
Cyzone I.P., American Cyanamid	

Cross-sensitivity between IPPD and PPD.
The question of cross-sensitivity between IPPD and PPD presented itself because of certain formula similarities:

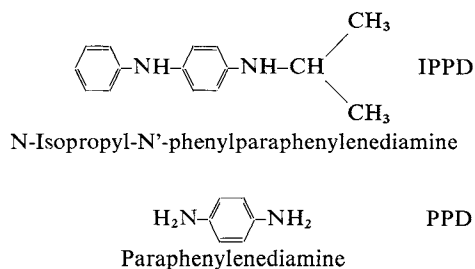


Table 5. Cross-sensitivity between IPPD and PPD

Case no.	IPPD tested in 2 % concentra- tion in lanolin	PPD tested in 2 % concentra- tion in lanolin
1	+++	0
2	+	+
3	++++	+
4	++	+
5	++	(+)
6	++++	++
7	+++	0
8	+++	0

Bieber & Foussereau published the data in Table 5 in 1968, and reported that IPPD- sensitive patients are often also sensitive to PPD.

Table 6 gives the comparative results of recent PPD tests carried out on 40 patients already sensitized (occupationally or otherwise) to IPPD.

Cross-sensitivity to PPD seems to be fairly frequent. In such cases, reactions to the PPD test however, are distinctly less pronounced, apart from possible exceptions, than those observed with the IPPD test.

5. Analytical-chemical investigation of the antiozonants of the aromatic amine type used in tyres and other automobile accessories

Determination of aromatic amines in vulcanized rubbers: Extraction.

Various solvents and procedures (methanol, methanol and dilute hydrochloric acid, acetone, acetonitrile, hot and cold processes) have been suggested by Burns et al. (1975) and Protitova et al. (1974). We chose the 24-hour Soxhlet extraction method, taking 10–15 g of finely grated rubber (prepared with a wood rasp) to approximately 250 ml of acetone. This solvent seems to have the requisite efficiency, easy purification and evaporation qualities. The colour of the extract varies from dark yellow to near black; a precipitate is often observed in the boiler flask.

Table 6. Comparative results of tests with IPPD and PPD

IPPD tested in 2 % concentration in lanolin	PPD tested in 2 % concentration in lanolin
On 40 allergic patients:	15 patients show allergic reactions:
32 +++ or >	2 +++ or >
8 ++	7 ++
	6 +

Concentration. The composition of the extract, which depends on that of the rubber, is highly complex; it requires maximum simplification for the purpose of analysis.

After careful drying at a moderate temperature, the extract is dissolved in acetone at normal temperature and centrifuged. A large proportion of impurities, usually composed of zinc stearate, is thus eliminated. The acetone solution is dried again and dissolved in n-hexane, then centrifuged again; this poor solvent eliminates the small amount of polymers extracted. This hexanic solution is extracted twice with nitromethane, and the nitromethanic fraction is washed three times with hexane. The nitromethanic and hexanic phases are dried. It is noted that the aromatic amines are mainly concentrated in the nitromethanic phase, apart from a few exceptions (particularly when there is a high percentage of phthalates).

Analysis. Colorimetry tests were ruled out (interference, extract discoloration) and gas chromatography (GC) chosen rather than thin-layer chromatography (TLC) (see Ivan & Ciutacu 1974, Uchytíl 1974, Kreiner & Warner 1969 for the following reasons:

- a) GC makes for easier separation of the eluted compounds, especially when oils and phthalates are involved;
- b) because of its relatively high detection limit (using a catharometer), it is possible to make a thin-layer chromatography of selected parts of the chromatogram (after trapping);
- c) it is easier to combine selective infra-red spectrophotometry; the trapped quantity is also sufficient to obtain an ultra-violet spectrum.

The procedure is as follows: the nitromethanic extract, after being dried at 50–60°C, is dissolved in acetone and injected into a 2 m × 0.6 cm chromatograph column filled with Chromosorb® with 7.5 % Apiezon L, set at 150 rising to 300°C (temperature increase 6°C/min), and then maintained at 300°C. The compounds corresponding to peaks are trapped at the catharometer exit in $\frac{1}{8}$ in. stainless steel tubes and examined with infra-red (Blinn 1971) and, where necessary, with ultra-violet and TLC (Table 7) (Dacher 1975). It should be mentioned that these conditions do not give satisfactory phenyl-beta-naphthylamine (PBN) and DMPPD separation (especially if there is a large amount of PBN).

Table 7. Approximate retention indexes of some products contained in tyres

Product	Approximate Retention Index*
1 – Diphenylamine	1750
2 – Dibutyl phthalate	1950
3 – p-Isopropylidiphenylamine	2030
4 – Dimethyl-10,10 acridane	2100
5 – N-Phenyl-N'-isopropyl-paraphenylenediamine (IPPD)	2150
6 – Phenyl-beta-naphthylamine (PBN)	2350
7 – N-Dimethyl-1,3 butyl-N'-phenylparaphenylenediamine (DMPPD)	2380
8 – Di (ethyl-2 hexyl) phthalate (DOP)	2500
9 – Dehydroabietic acid	2580
10 – N-Phenyl-N'-cyclohexylparaphenylenediamine (CPPD)	2680
11 – N,N'-Diphenylparaphenylenediamine (DPPD)	2750

* Poor repeatability

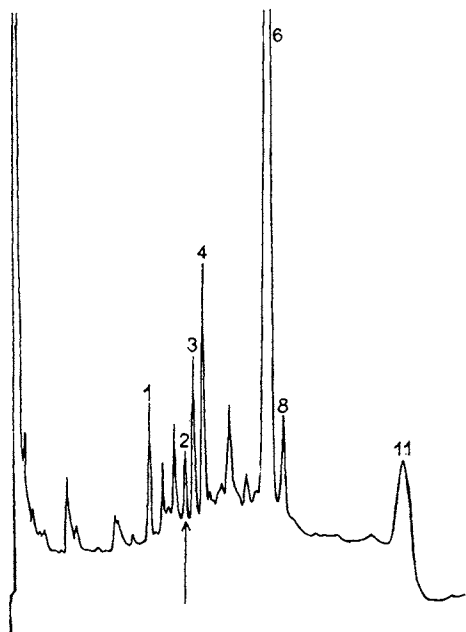


Fig. 1. Chromatogram of the nitromethanic fraction of the extract obtained from a Kléber Colombes V10GT tyre. Column filled with 7.5 % Apiezon L on Chromosorb 60-100 mesh, temperature set at 150° C rising to 300° C at a rate of 6° C/min. The numbers correspond to the identified components listed in Table 7.

Thin-layer chromatography provides complementary information because of:

- its lower detection limit, whereby amines not revealed by GC can be detected;
- the unlimited molecular mass of the products, which is useful with heavy products such as N, N'-dinaphthyl-paraphenylenediamine;
- the data provided (although it is not in fact very usable) by the R_f values and the spot colour (with several eluents and revealing agents, if need be) (see Ivan & Ciutacu 1974, Kreiner & Warner 1969, Millingen 1974). The total nitromethanic extract can also be examined by two-dimensional chromatography on a silica gel plate

approximately 0.25 mm thick, using benzene/acetone/20 % ammonia water (volume 100:5:0.5) for elution, which is carried out twice to a distance of 15 cm, and benzoyl peroxide as a revealing agent. The number of spots thus obtained is often larger than the number of amines detected by means of GC (Figs. 1 and 2).

Results of analysis. The results are listed in Table 8. The comments are divided into four groups:

- None of the 12 tyres is free of aromatic amines
- No CPPD was found in any of the tyres
- IPPD, on the contrary, was found in nine tyres out of 12. It is present in eight of the nine brands (Michelin, Dunlop, Esso, Good Year, Klé-

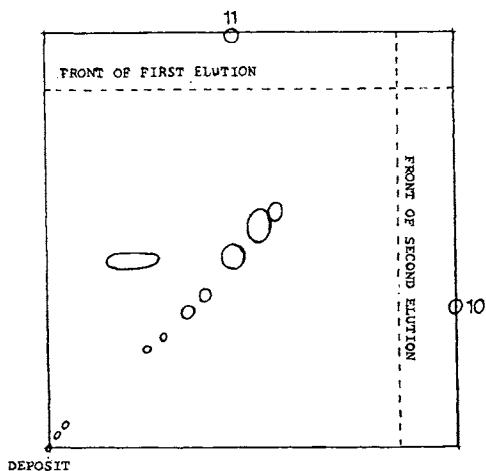


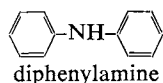
Fig. 2. Thin-layer chromatography on GF 254 (Merck) silica gel of the nitromethanic fraction of the extract obtained from a Kléber Colombes V10GT tyre. Eluent benzene/acetone/20 % ammonia water, volume 100:5:0.5 on 2 x 13 cm. Revealing agent 4 % benzoyl peroxide in benzene. The numbers correspond to the identified components listed in Table 7; systematic identification was not carried out.

Table 8. Chemical analysis of tyres

Type of tyre	IPPD	CPPD	PBN	DMPPD	N-N'- Diphe- nyl PPD	Diphe- nyla- mine	Dehy- droabi- etic acid	Di (N- butyl) phtha- late
Kléber Co- lombes V12	+		+		+		+	+
Kléber Co- bes V10			+				+	+
Kléber V10S	+		+			+	+	
Firestone Ca- vallino				+			+	+
Michelin ZX Radial	+		+					
Xas Michelin			+					
Dunlop SP Sport	+		+		+	+		+
Esso E 420 Radial	+		+			+	+	+
Good Year 125	+		+			+		+
Uniroyal Rallye 180	+		+				+	+
Pirelli	+		+		+		+	+
Continental	+		+				+	+

ber, Uniroyal, Pirelli, Continental). DMPPD, which is a close derivative of IPPD (in which one of the IPPD hydrogen atoms is replaced by an isopropyl group), was detected in the Firestone brand. All these tyre manufacturers (nine out of nine) therefore use IPPD or its derivatives in some of their products.

- d) Diphenylamine is present in four tyres out of 12 and in four brands out of nine.



Results of chemical analysis for the purpose of detecting IPPD in other automobile accessories. Patients who are allergic to IPPD and whose work brings them into contact with automobiles should naturally be warned about rubber articles other than tyres likely to cause fresh outbreaks of sen-

sitivity. Jordan (1971) reported that one of his patients, who was sensitive to the IPPD in his car tyres, also reacted to tests carried out with the rubber from the bumper bracket. In this connection, allergy investigations can help the chemist in his task of identifying IPPD in various articles and automobile accessories, as is shown by the following case.

Gilbert S., age 38, an automobile mechanic, was sensitive to the IPPD in tyres. Further allergy tests gave the following results:

Rubber Citroën overrider	0
Pirelli belt	0
Kléber Colombes belt	0
Hutchinson cooling system hose	0
Kléber Colombes cooling system hose	0
Carburaigle fuel hose	+++
Citroën S fuel hose	+++

Chemical investigations confirmed that

there was IPPD in Carburagile and Citroën S fuel hoses.

6. The allergological implications of these chemical investigations

In the light of the chemical tyre analysis results, it would seem logical to include the following substances among the rubber allergens commonly used in patch test series:

- a) colophony, or better still, colophony and dehydroabietic acid, since this resin acid has been detected by chemical analysis in eight tyres out of 12. Dehydroabietic acid is not at all widely known as an allergen. By testing subjects sensitive to the colophony in adhesive tape, we found dehydroabietic acid to be allergenic in four out of nine colophony-sensitive patients. Generally speaking, col-

ophony is considered to be one of the usual rubber allergens, but no cases of sensitivity to this substance in rubber workers or utilizers seem to have been mentioned to date in the literature. Schultheiss (1959), for instance, does not mention any such cases in the rubber industry.

- b) A phthalate (for example butyl phthalate) and diphenylamine, which is not widely used in industry, but exists as a tracer in fuel oil as well as being a tyre component.

7. Chemical and allergological investigations into DMPPD

The positive results obtained on testing IPPD-sensitive patients with DMPPD show this product to be allergenic (Table 9).

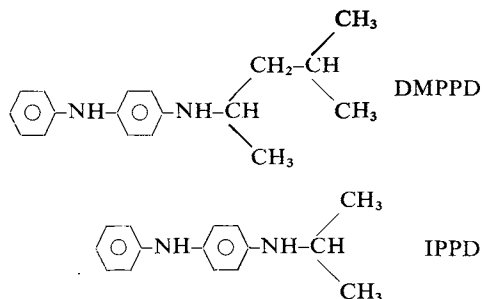
In Case no. 5 (Antoine S.) a biopsy was made of the DMPPD test, and histological examination (biopsy CN 132) showed that it was "clearly an allergic reaction producing an acute, vesiculo-bullous response identical to the elementary histological lesions characteristic of eczema" (Dr. Strobel).

There can be no doubt that DMPPD is allergenic. This product was marketed in the U.S.A. by Monsanto under the name of Santoflex 13. "It has been found that p-phenylenediamines with small alkyl groups, e.g. N-isopropyl-N'-phenyl-p-phenylenediamines, are very active antiozonants but can cause problems due to their sensitizing effect on the human skin when used at higher concentrations such as 2 phr. and above, and when used under hot conditions... By careful selection of the alkyl substituent, it was found possible to eliminate the skin sensitizing effect whilst still retaining the excellent antiozonant properties of the N-isopropyl N'-phenyl - p-phenylenediamine. This led to the introduction of Santoflex 13... which is not a skin sensitizer and can be used safely in factories

Table 9. DMPPD tests on IPPD-sensitive patients (readings taken during the 48th hour)

Patient	IPPD tested in 2 % con- centration in lanolin	DMPPD tested in 2 % con- centration lanolin
1. B... J. Claude	+++	+++
2. T... Pierre	++++	++++
3. C... J. Marie	++++	+++
4. K... M. L.	+++	+
5. S... Antoine	++++	++++
6. H... Lucie	+++	+++
7. L... Yves	++	+++
8. Z... Albert	+++	+
		0 after
9. F... Dino	++	24 hours,
		++ on
		day 4
10. F... Léon	+++	+++
11. M... Victor	+++	+++
12. M... Roger	+++	+++
13. M... Robert	+++	+++
14. R... Arsène	++	++
15. C... Guy	++	++

where other alkyl aryl p-phenylenediamines have caused problems due to skin irritancy" (Monsanto data sheet).



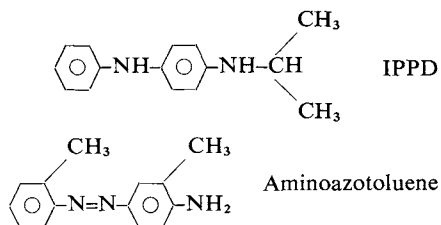
Incidentally, in France DMPPD was detected in Firestone (Cavallino type) tyres; on the other hand, Santoflex 13 was found on chemical screening analysis to contain no IPPD. Santoflex 13 seems to be a very pure product.

8. Safeguards to be observed when interpreting test reactions with IPPD and its derivatives

The significance of positive test reactions to IPPD can vary according to the circumstances. Three possibilities should be considered (apart from accidental sensitization by the actual test, resulting in a positive reaction after more than seven days):

- a) sensitivity with clinical symptoms due to occupational (tyres, etc.) or non-occupational (boots, etc.) sensitization to IPPD
- b) a similar sensitivity, but without clinical manifestations. This is a latent form of sensitivity, which we observed, for instance, in a hospital patient under treatment for scabies who underwent systematic testing
- c) or cross-sensitivity caused by sensitization to another chemically related substance: according to Hjorth & Røthenborg (1967), 20 % of all persons sensitive to the azoic dyes used in nylon are also sensitive to IPPD. Foussereau et al. (1973) showed that

patients sensitive to orthoaminoazotoluene were sensitive or not to IPPD to greatly varying degrees, according to the circumstances. None of the patients sensitive to aminoazotoluene were sensitive to IPPD (zero patients out of six). Conversely, out of 12 patients already sensitized to aminoazotoluene (probably by cross-reaction due to previous sensitization to related substances), seven were also sensitive to IPPD.



9. Irritant and sensitizing potential of rubber amines (PPD, DMPPD, CPPD and IPPD) in laboratory animals

Irritant potential. The irritant potential of these rubber amines was established according to the method of Draize (1944) using 12 sets of six female New Zealand albino rabbits weighing between 2.4 and 2.7 kg. The amines were dispersed in vehicles which were known to be non-irritating to

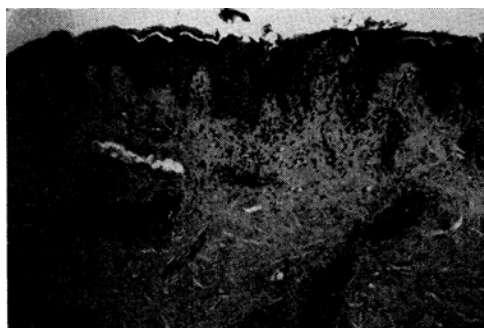


Fig. 3. "Reaction test to DMPPD with acute vesicular bullous reaction identical to the elementary histological lesions characteristic of eczema" Dr. Strobel - $6.3 \times 1.25 \times 3.2$.

Table 10. Irritant potential of rubber amines

Products	Vehicles	Concentration	PCII	Irritant potential
DMPPD	Vaseline	2.5 %	0.6	L
	Vaseline	25 %	1.0	L
	Olive oil	1 g/20 ml	3.3	M
CPPD	Vaseline	2.5 %	1.8	L
	Vaseline	25 %	2.0	L
	Olive oil	1 g/20 ml	2.7	M
PPD	Water	6 g/12 ml	3.2	M
	Vaseline	2.5 %	1.4	L
	Vaseline	25 %	2.3	M
	Olive oil	1 g/20 ml	3.4	M
IPPD	Vaseline	2.5 %	1.8	L
	Vaseline	25 %	2.7	M
	Olive oil	1 g/20 ml	3.2	M

M = Medium L = Low

rabbit skin. The two vehicles selected in which the products were dispersed in identical concentrations, were:

- Codex olive oil: 1 g per 20 ml
- Codex vaseline which is used as an excipient in ointment manufacture: 2.5 and 25 %.

The oil dispersion (0.5 ml) or 0.5 g of the ointment is applied to the scarified and unscarified skin of the rabbits. These are examined after 24 and 72 hours for erythema (or necrosis) and oedema and the

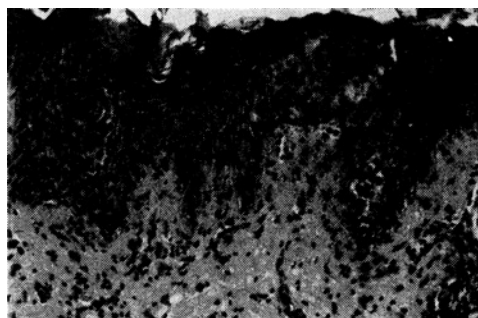


Fig. 4. "Reaction test to DMPPD with acute vesicular bullous reaction identical to the elementary histological lesions characteristic of eczema" Dr. Strobel - $16 \times 1.25 \times 3.2$.

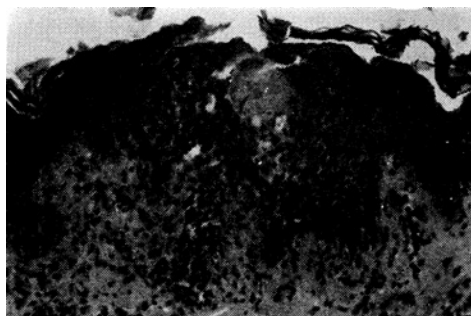


Fig. 5. "Reaction test to DMPPD with acute vesicular bullous reaction identical to the elementary histological lesions characteristic of eczema" Dr. Strobel - $16 \times 1.25 \times 3.2$.

results are used to calculate the primary cutaneous irritation index (PCII) for a given concentration. Interpretation of these values gives the irritant potential (see Table 10 for indexes and interpretation). Skin samples taken after 72 hours are subjected to histological examination.

Under the described experimental conditions, we found that:

- the DMPPD, unlike the other substances (PPD, IPPD and CPPD), does not discolour the skin and dermoskeleton. The strongest and most long-lasting discoloration is produced by PPD
- the test concentrations cause erythematous reactions (which are difficult to read because of discoloration caused by the products) and oedematous reactions which differ according to the concentrations and products employed, but no skin necrosis. These effects diminish spontaneously within 5 to 15 days
- the histopathological examinations carried out on certain subjects confirm the macroscopic results; they show moderate to medium reaction patterns:
 - at epidermis level, degenerative le-

Table 11. Percentage of sensitized animals after application of 0.05 and 0.5 % concentrations of the products in vaseline

Product	Set	Reaction test concentration	% of sensitized animals
Paraphenylenediamine or PPD	Control	0.05 %	0
		0.5 %	20
	Treated	0.05 %	80 IV
		0.5 %	100 V
N-Phenyl-N'-dimethyl 1,3-butyl PPD Santoflex 13 or S13 or DMPPD	Control	0.05 %	0
		0.5 %	0
	Treated	0.05 %	50 III
		0.5 %	90 V
N-Phenyl-N'-cyclohexyl PPD 4010 or CPPD	Control	0.05 %	0
		0.5 %	0
	Treated	0.05 %	50 III
		0.5 %	90 V
N-Phenyl-N'-isopropyl PPD 4010 NA or IPPD	Control	0.05 %	0
		0.5 %	0
	Treated	0.05 %	10 II
		0.5 %	70 IV

sions (superficial or total necrosis, atrophy, dyskeratosis and cavitory modifications) and regenerative lesions (acanthosis) alternate and sometimes coexist with zones of normal histological structure;

- ii. at dermis level, an inflammatory exocytosis of varied composition is observed to be either diffuse or concentrated in small clusters around the superficial congested vessels.

Sensitizing potential. The contact sensitizing potential was examined according to the Magnusson & Kligman (1969) technique on sets of 20 female Hartley albino guinea pigs weighing approximately 400 g. Sensitization is produced by intra-dermal injections of the products (0.5 % concentration in olive oil) and of complete Freund's additive, followed 1 week later by cutaneous application of the products (1 % vaseline).

Reaction is tested 1 week later by epicutaneous application of the products in

Table 12. Sensitizing potential according to Magnusson & Kligman (1969)

% sensitization	Degree	Description
0- 8	I	very low
9- 28	II	low
29- 64	III	medium
65- 80	IV	high
81-100	V	very high

various concentrations in vaseline (see Table 11 for results). The sensitizing potential is evaluated according to Magnusson & Kligmann's (1969) definition based on the number of animals sensitized with respect to the total number of animals tested, that is, the percentage sensitization (see Table 12).

A set of control animals were given the reaction test without the prior sensitizing treatment: it was thus possible to check whether the reaction test produced any irritation (as in the case of 0.5 % PPD). Cutaneous biopsies were carried out on the sensitized animals 48 h after the reaction or cross-reaction test and comparative readings were made with the control group.

In all cases, the histopathological examinations showed:

- a) at epidermis level:
 - widespread acanthosis with basal exoserosis, with or without epidermal exocytosis (mononucleated cells) and with or without degenerative lesions (cavity modifications, acidophilic necrosis)
- b) at dermis level:
 - congestion of the dermal vessels and distention of the lymphatic sacs
 - focal and discrete or widespread papillary edema
 - variable increase in mononuclear infiltration of the dermis, without any perivascular cuff formation.

On the basis of these observations, allergic contact dermatitis was diagnosed.

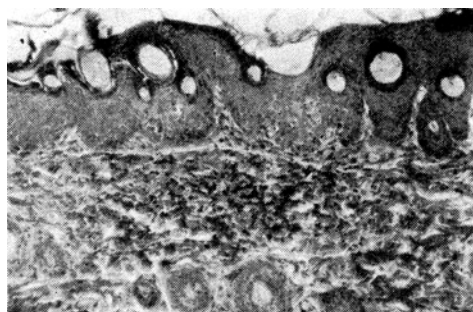


Fig. 6. Allergic dermatitis on flank skin of albino guinea pig after DMPPD:

- epidermal changes: marked acanthosis (thickened stratum corneum and stratum granulosum) with obviously basal spongiosis and mononuclear infiltrate;
- corium changes: hyperaemia and large round-cell infiltration.

With identical reaction test concentrations administered to albino guinea pigs under the given experimental conditions, PPD proved to be the most sensitizing product and IPPD the least sensitizing. DMPPD and CPPD seem to give identical results. In all cases, the sensitizing potential depends on the reaction test products concentrations. At 0.5 % all four products are highly or very highly sensitizing according to Magnusson & Kligman's classification.

Table 13 gives the various cross-sensitization possibilities: all the products give cross-reactions of varying severity. All four products produce a high degree of sensitivity after sensitization of the animals to PPD.

Conclusion

Occupational contact sensitivity to IPPD still remains a current problem in France. Forty-two cases of occupational sensitivity to IPPD were investigated. Chemical analysis shows that this product is used as an antiozonant in the manufacture of eight

Table 13. Cross-reactions. Reaction test concentration: 0.05 % in vaseline

Sensitizing product \ Reaction test product	CPPD	DMPPD	PPD	IPPD
CPPD	50	5	15	
DMPPD	30	50		
PPD	100	95	80	95
IPPD	90	85	100	10

tyre brands marketed in France. Analysis also shows that these tyres often contain dehydroabietic acid, phthalates, etc. DMPPD was found in one brand of tyre only. Allergy tests prove that this product, which is advertised as being non-allergenic, is in fact just as allergenic as IPPD.

Cross-sensitization between IPPD and PPD is fairly frequent, but PPD produces a considerably lower test reaction than IPPD.

The direct and cross-sensitizing properties of these rubber antiozonant products were tested on laboratory animals. Under the conditions described above, there is

general agreement between the clinical allergy investigations and the experimental results. The various degrees of sensitivity response in human beings and animals do not coincide exactly, but the differences are slight and there are no major discrepancies to be reported as far as this experiment is concerned. Predictive tests of this type are thus shown to be extremely interesting: it only remains for them to be further perfected and increased in number in order to become a useful means of prevention in this particular dermatological branch of industrial toxicology.

Table 14. Full tyre references

Tyre type	Full trade name
Kléber Colombes V12	Radial-ply tyre 155 SR 12 DOT EWC 8 121 504 3 340 7056
Kléber Colombes V10	135 × 380 M 795-24 M 64843 D
Kléber V10S	145 SR 14 DOT EX JP 14 412 radial-ply tube type DOT 1 86
Firestone Cavallino	SR 1 radial-ply tyre 155 SR 14 02 EW AD-29188-1 T. W. I. C 22 4000 10
Michelin ZX Radial	165 SR 15 DOT FHTB A ₁ CX 481 DOT 133 V ₁ 3 C FFG 64731 V
Xas Michelin	165 HR 380/165 HR 15 radial-ply tyre DOT 133 V ₁ 217 VAM 326 07417 A VFW 41789
Dunlop SP Sport	145 HR 10 (145-255)SP radial-ply tyre 41N 41660 061 CB A n° 41659
Esso E420 Radial	155 SR 14 OE 85 L 6
Good Year 125	SR 15 Polyester G 800 F 00648-26 KZX
Uniroyal Rallye 180	(wet service) 135 SR 13 radial-ply tyre SE 83 B ₁ TW ₁
Pirelli Cinturato	CF 67 135 SR 13 radial-ply tyre 367 F (1647-00/2) 1
Continental	full name unknown: manufactured in Sarreguemines

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Address:

Dr. C. Cavalier

I.N.R.S.

Avenue de Bourgogne

54500 Vandoeuvre-les-Nancy

France