

Contact dermatitis caused by iodopropynyl butylcarbamate in Denmark

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doi:10.1111/cod.12062

Summary

Background. Iodopropynyl butylcarbamate (IPBC) is a preservative that may cause contact allergy. The first cases were reported in 1997, and IPBC is currently included in our extended European baseline series in Denmark.

Objectives. To assess trends during the period 2000–2011 concerning IPBC allergy in Denmark, and to address the question of the significance of concomitant reactions to the thiuram mix.

Patients/materials/methods. Nine thousand seven hundred and fifty-five (6449 female; 3306 male) patients were patch tested with IPBC and the European baseline series at Gentofte Hospital during 2000–2011. The results were registered in an anonymized database, and analyzed with SPSS™.

Results. Fifty-four cases of IPBC contact allergy were detected. A significant rising trend during 2000–2011 was observed, with no significant changes during 2006–2011. MOAHLFA index analysis showed that IPBC contact allergy was, in our cohort, significantly more prevalent among male patients, occupational, related to hand eczema, and more frequent among patients over 40 years old. A significant relationship between IPBC and thiuram mix allergy was found.

Conclusions. IPBC continues to be among the less frequent allergens. A 0.2% concentration in patch testing has contributed to the diagnosis of more sensitizations to this substance. Further studies are needed to clarify the reason for the over-representation of thiuram allergy in patients sensitized to IPBC.

Key words: allergy; contact dermatitis; cosmetics; iodopropynyl butylcarbamate; occupational diseases; patch tests; preservatives; thiuram.

The preservative iodopropynyl butylcarbamate (3-iodo-2-propynyl-butylcarbamate; IPBC; CAS 55406-53-6) is a preservative that acts as a wide-spectrum fungicide, bactericide, and acaricide (Fig. 1).

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Conflicts of interest: The authors report no conflicts of interest. Funding: The underlying clinical work and data gathering process at the Gentofte University Hospital was funded by the Danish Healthcare System.

Accepted for publication 3 January 2013

Originally developed for industrial use in the 1970s, IPBC was first and is still used as a wood preservative. It has progressively been introduced into other products, such as paints, metalworking fluids, household products, and a variety of cosmetic products (1–4). According to the European Commission Cosmetics Directive and its current legislation (2007/22/EC), the maximum authorized concentrations in cosmetics marketed within the EU are 0.02% in rinse-off products, 0.01% in leave-on products, and 0.0075% in deodorants and antiperspirants. It should not be used in children under 3 years of age (except in bath products), in oral hygiene and lip care products, or in body lotions and creams intended to be applied on a

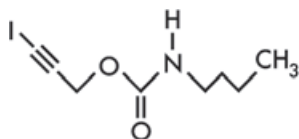


Fig. 1. Iodopropynyl butylcarbamate chemical structure.

large part of the body, given its iodine content and possible systemic absorption (5, 6).

IPBC is a small lipophilic molecule that may penetrate the skin and cause contact allergy. Although it has traditionally been considered to be of low allergenic potential (7), a recent study affirmed that it can pose a high risk of sensitization, particularly in leave-on formulations (8). Several forms of allergic contact dermatitis have been reported (1, 9–15). It is currently included in the cosmetics testing panels of patch test allergens in many clinics.

We reported the first cases of allergy in 1997, and have since included IPBC in our extended European baseline series. In this article, we assess the trends over a decade concerning IPBC contact allergy in Denmark, and address some of the questions that have been raised since IPBC contact allergy was initially identified, such as concomitant reactions to thiuram mix.

Patients and Methods

Study population

All dermatitis patients who underwent patch testing with the European baseline series at Gentofte Hospital between 1 January 2000 and 31 December 2011 were included in the present study.

Patch testing

Since 1996, the majority of the patients referred to the Department of Dermato-Allergy at Gentofte Hospital for patch testing have been tested with IPBC. Different commercial preparations and concentrations were used during the first period (9). Troysan® Polyphase® P100 (Troy Corporation, New Jersey, USA) was used in 2000–2005. The concentration of IPBC was initially 0.1% in petrolatum (pet.), and was raised to 0.2% pet. in 2004, following evidence uncovered by Brasch et al. to the effect that the 0.2% concentration yielded the most positive reactions and the least false-positive reactions (16). From 2006 on, patients were tested with 0.2% pet. IPBC supplied by Hermal/Trolab™ (Reinbek, Germany).

Patch testing was performed with Finn Chambers® (8 mm; Epitest Ltd, Oy, Finland) on Scanpor® tape (Norgesplaster A/S, Alfarma, Vennesla, Norway). The patch

test was placed on the upper back for 2 days, and read on D2, D3/4, and D7, according to the International Contact Dermatitis Research Group guidelines. Homogeneous redness and infiltration in the entire test area was considered to be the minimum positive reaction, scored as a 1+ reading. A 1+, 2+ or 3+ reading was interpreted as a positive response. Non-changing irritant, doubtful or negative readings were interpreted as negative responses (17).

Statistical analysis

Patients' demographic data, dermatitis site, final diagnosis, and occupation and probable source of sensitization, if relevant, were recorded in an anonymous codified database. Data were managed and analysed with the Statistical Package for the Social Sciences package (SPSS™ Inc., Chicago, IL, USA) for Windows™ (version 15.0). Comparisons were made mainly by the use of the Pearson chi-square (χ^2) test. Alternatively, Fisher's exact test was used when the expected numbers were small. The association between IPBC and thiuram contact allergy was tested and quantified by the use of odds ratios (ORs), accompanied by 95% confidence intervals (CIs), derived from logistic regression. This analysis also included explanatory variables that, in univariate analysis, had shown a significant or nearly significant association with IPBC contact allergy. A *p*-value of < 0.05 was considered to be significant throughout.

Results

From 2000 to 2011, a total of 9755 (6449 female; 3306 male) patients were tested with IPBC. A total of 54 cases of IPBC contact allergy were found through patch testing. No positive reactions were observed in 2003. A significant rising trend during the 2000–2011 period was observed (Mantel–Haenszel linear-by-linear association chi-squared test, *p* < 0.01), whereas the statistical analyses showed no significant changes in the last 6 years (2006–2011) (Fig. 2) (Mantel–Haenszel linear-by-linear association chi-squared test, *p* > 0.05).

The MOAHLFA index (18) analysis of the IPBC-tested patients (2000–2011) gave several noteworthy results:

- IPBC contact allergy was significantly more prevalent among male patients, in both univariate and multivariate analyses (OR 1.75; 95% CI 1.02–3.02).
- IPBC allergy was significantly over-represented among patients with occupational dermatitis. Nevertheless, this effect became insignificant in a multivariate analysis, as hand eczema was a stronger predictor (Table 1) of IPBC contact allergy.
- No statistically significant association was found when the relationship between atopic dermatitis

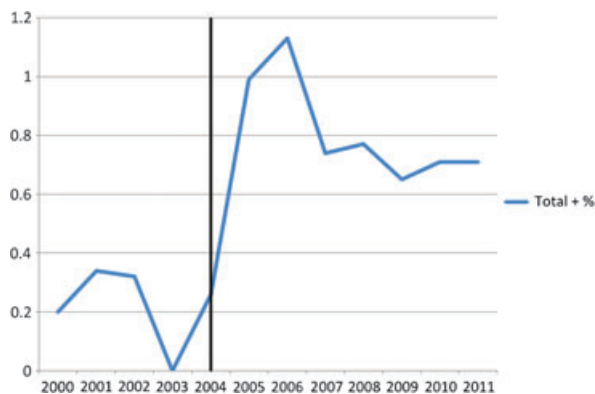


Fig. 2. Total positive reactions in the period 2000–2011. The black vertical line indicates the year in which the iodopropynyl butylcarbamate patch test concentration was changed to 0.2%.

and IPBC allergy was considered: 94.4% of the IPBC allergic patients did not have any history of atopic dermatitis.

- Regarding the sites of the dermatitis, hand eczema was found in 59.3% of the IPBC-positive patients (it was present in 35.3% of IPBC-negative patients), and this proved to be significant (OR 2.5; 95% CI 1.35–4.60) in multivariate analysis. No significant relationship between face or leg dermatitis was seen among IPBC-positive patients.
- Finally, being > 40 years of age was found to be a significant positive factor for IPBC sensitization ($p = 0.013$): 81.5% of the IPBC-positive patients were >40 years of age.

Co-reaction with thiuram mix was also evaluated in this study. Of the 191 thiuram mix-sensitized patients who were seen during the 12-year period, 8 had a

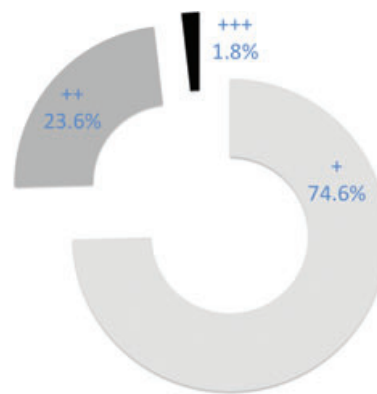


Fig. 3. Intensity of the positive reactions (2000–2011).

positive reaction to IPBC on patch testing. Concerning the most recent 6-year period, 106 patients tested positive to thiuram mix, 3 of whom were IPBC-allergic. In both periods (2000–2011 and 2006–2011), a significant relationship between IPBC and thiuram mix allergy was found both in univariate and multivariate analyses (OR 7.43; 95% CI 3.35–16.46), after adjustment for other risk factors (Table 1).

The intensity of the positive reactions is shown in Fig. 3.

The clinical features and the results of the routine evaluation, including other allergic reactions, of the 26 IPBC-positive patients found during the last 6 years (2006–2011) are shown in Table 2.

Discussion

Our group previously reported the details of patients from the 1996–1999 period (11). We have now reviewed and analysed the available data from the subsequent

Table 1. Patients patch tested with iodopropynyl butylcarbamate (IPBC) in 2000–2011: thiuram contact allergy and MOAHLFA index

	IPBC-positive (n = 54), no. (%)	IPBC-negative (n = 9518), no. (%)	p-value (chi-square)	Multifactorial logistic regression analysis ^a		
				OR	95% CI	p-value
Thiuram-positive	8 (14.8) ^b	183 (1.9) ^b	0.0001	7.43	3.35–16.46	<0.0001
Male sex	26 (48.1)	3280 (33.8)	0.014	1.75	1.02–3.02	<0.04
Occupational dermatitis	15 (27.8)	1514 (15.6)	0.014	1.20	0.61–2.38	0.6
Atopic dermatitis	3 (5.6)	1504 (15.5)	0.068 ^c	0.36	0.11–1.19	0.096
Hand eczema	32 (59.3)	3423 (35.3)	0.0001	2.50	1.35–4.60	0.003
Age > 40 years	44 (81.5)	6332 (65.3)	0.013	2.24	1.10–4.54	0.025
Facial eczema	10 (18.5)	1925 (19.8)	0.808		Not included	
Leg eczema	6 (11.1)	694 (7.2)	0.261		Not included	

CI, confidence interval; OR, odds ratio.

^aMultivariate analysis with IPBC contact allergy as response variable and thiuram allergy, sex, occupational dermatitis, atopic dermatitis, hand eczema and age > 40 years as explanatory variables.

^bPercentage among total IPBC-positive or IPBC-negative patients.

^cFisher's exact test.

Table 2. Iodopropynyl butylcarbamate (IPBC) patch test-positive patients during the period 2006–2011

No.	Sex and birth-year	Relevance of IPBC allergy	Source of IPBC allergy	M	O	A	H	L	F	A	Other allergies	Clinical complaint	Occupation (if considered to be a possibly relevant occupational exposure)
1	Female, 1965	Yes	Emollient cream				X			X	(None)	Hand eczema	Healthcare assistant (applying emollient on hands as a preventive measure)
2	Female, 1963	Yes	Emollient cream		X		X			X	MDGN, nickel, PPD	Hand eczema	–
3	Male, 1940	Unknown	–	X			X		X	X	Sesquiterpene lactate (R), multiple metals, mercapto mix, MCI/MI, MDGN, PPD, rubber	Hand and facial eczema; gardening as a hobby	–
4	Male, 1953	Unknown	–	X	X					X	FMI, mercapto mix, mercaptobenzothiazole, cinnamal, own latex glove	Hand eczema for 1 year; past history of psoriasis since age 13 years	–
5	Male, 1957	Yes	Hand cleaners; metalworking fluids?	X	X		X				None	Hand eczema	Metalworker
6	Male, 1954	Yes	Paints	X	X					X	Benzothiazolinone (R), octylisothiazolinone (R)	Hand eczema for 7 years	Building painter
7	Female, 1933	Unknown	–							X	None	Conjunctivitis	–
8	Male, 1956	Unknown	–	X	X		X			X	MDGN	Hand eczema for 5 years; past history of psoriasis since age 5 years	Machine operator
9	Female, 1931	Unknown	–				X			X	Thiuram mix (R), MDGN, 2-bromo-2-nitropropane-1,3-diol, formaldehyde, sorbitan sesquileate, <i>Evernia furfuracea</i> , MI	Recent aggravation of stasis dermatitis in a patient with chronic venous insufficiency; use of rubber gloves for treatment	–
10	Male, 1950	Yes	Paints	X	X		X			X	MCI/MI (R), octylisothiazolinone (R)	Hand eczema for 3 months	Building painter
11	Female, 1937	Unknown	–					X		X	Formaldehyde (past R), thiuram mix, sesquiterpene lactone mix, 2-bromo-2-nitropropane-1,3-diol (past), <i>Evernia furfuracea</i>	Facial eczema for months; previously, arm nummular eczema	–
12	Male, 1960	Yes	Shaving foam	X					X	X	Farnesol (probably R)	Facial and ear eczema for 2 months	–

Table 2. Continued

No.	Sex and birth-year	Relevance of IPBC allergy	Source of IPBC allergy	M	O	A	H	L	F	A	Other allergies	Clinical complaint	Occupation (if considered to be a possibly relevant occupational exposure)
13	Female, 1942	Unknown	–		X		X		X	X	Sesquiterpene lactate, primin	Hand and facial eczema	Cleaning lady
14	Female, 1948	Unknown	–							X	Disperse Orange, Disperse Blue – (R), PPD, MDGN, <i>Evernia furfuracea</i>	Genital eczema	–
15	Female, 1954	Unknown	–				X			X	Diethylthiourea, formaldehyde	Severe vesicular hand eczema since age 20 years; associated forearm eczema	–
16	Female, 1964	Yes	Lubricant and preserving oils		X		X			X	None	Hand and forearm eczema for 10 years	Packer in hearing aid and tooth implant (both covered in oils containing IPBC)
17	Female, 1986	Possible	Facial moisturizer						X		Paraben mix (R)	Acute facial eczema after applying Chinese facial moisturizer	–
18	Male, 1933	Unknown	–	X						X	<i>Myroxylon pereirae</i> , 2-bromo-2-nitropropane-1,3-diol, MDGN	Itchy follicular rash on trunk and extremities for 5 years; ceased after stopping antihypertensive drug	–
19	Female, 1949	Possible	Emollient cream				X		X	X	Mercapto mix, mercapto-benzothiazole, 2-bromo-2-nitropropane-1,3-diol, MDGN, sesquiterpene lactone mix, nickel	Severe vesicular hand eczema for 17 years; associated perioral dermatitis	–
20	Female, 1941	Unknown	–							X	Thiuram mix (R), FMI, MDGN	Hand and foot eczema for 4 months	–
21	Female, 1994	Yes	Different cosmetic products						X		None	Acute facial eczema	–
22	Male, 1985	Unknown	–	X					X		Colophonium and <i>Evernia furfuracea</i> (R), <i>Myroxylon pereirae</i> , MDGN, amyl-cinnamyl alcohol	Eczema on upper aspect of the arms, secondary to applying sports bandage	–

Table 2. Continued

No.	Sex and birth-year	Relevance of IPBC allergy	Source of IPBC allergy	M	O	A	H	L	F	A	Other allergies	Clinical complaint	Occupation (if considered to be a possibly relevant occupational exposure)
23	Female, 1965	Unknown	-		X	X	X			X	Formaldehyde, quaternium-15, DMDM hydantoin, chlorhexidine, MI	Aggravation of atopic dermatitis under treatment with local steroids; irritant hand eczema	Packer
24	Male, 1948	Unknown	-	X					X	X	Rubber chemicals	Acute redness and swelling during dentistry procedure	-
25	Male, 1958	Unknown	-	X						X	PPD, sesquiterpene lactone mix, FML, quaternium-15, DMDM hydantoin	Episodic forearm and back eczema for 10 years	-
26	Female, 1969	Unknown	-				X			X	None	Hand eczema for 10 years	-

FML, fragrance mix 1; MCI, methylchloroisothiazolinone; MDGN, methyl dibromo glutaronitrile; MI, methylisothiazolinone; PPD, *p*-phenylenediamine; (R), relevant.

12 years, and found that IPBC continues to be among the less frequent allergens. Our percentage of positive results (0–1.13%, average 0.55%) is similar to the rates for other infrequent preservatives (19). The intensity of the positive reactions is also concordant with a recently published series (2).

Regarding the global 2000–2011 period, we believe that the significant rising trend observed is coincident with the change, in 2005, of the patch test concentration from 0.1% to 0.2%. In a large study by Brasch et al. including 8106 patients tested with a range of concentrations from 0.1% to 0.5% IPBC, and based on an extensive analysis, it was suggested that 0.2% was the optimal patch test concentration, even though a marginal irritant effect was registered with all concentrations (16). In our study, we also saw an increase in doubtful, irritant and positive reactions when the IPBC concentration (Table 3) was increased. The choice of patch test concentrations is a balance, and we still believe that IPBC 0.2% testing provides better diagnosis of IPBC allergy.

In light of the results from the last 6 years, IPBC allergy remains stable, with a higher positivity rate than identified in previous years. Our opinion is that cosmetics-related sensitization will eventually decrease as a result of the recent European IPBC regulation and amended limits, which have affected all cosmetics produced since 10 October 2008 and marketed after 18 April 2009. This increased regulation was motivated by the concern that IPBC generates regarding the possible systemic absorption of iodine, which led to a reduction of its use in cosmetic products (5, 6).

According to the present data, IPBC sensitization continues to be proportionally more frequent among men. The evidence suggests that this may be related to hand eczema and occupational exposure, an important risk factor related to IPBC contact allergy that can, at times, go undetected (8). Furthermore, occupational exposure appears to be more relevant in Denmark than in North America, where most of the positive reactions (> 90%) have not been related to occupation, but to personal care products (2). EU regulations and other factors can explain this difference: the prevalence of preservative allergy in the European countries is different from that observed elsewhere (19).

The extent of IPBC usage in cosmetics on the Danish market has yet to be clarified. Of the 26 reviewed patients, 3 (with clinically relevant IPBC allergy) had been exposed to the same emollient cream, marketed before 2009 (which was reformulated to remove IPBC). In view of our findings, currently there are probably not many cosmetic products with IPBC available to the Danish consumer.

Table 3. Types of reaction to iodopropynyl butylcarbamate (IPBC) on patch testing: 2000–2011

Test period	Negative	Doubtful	Irritant	+	++	+++	Positive (%)	Comments
2000–2003	3480	69	7	7	1	0	0.22	IPBC 0.1%
2004–2005	1446	94	13	6	4	0	0.64	Concentrations of 0.1% and 0.2% were used simultaneously
2006–2011	4415	141	36	27	8	1	0.78	

The previous question of concomitant reactions of IPBC with thiurams (given their similar chemical structure) (11) has been also addressed. The results of this study show there is an over-representation of thiuram allergy in patients sensitized to IPBC, including when other risk factors are controlled for in a multivariate analysis. This means that the association cannot be explained by co-exposure at, for example, the workplace. What this association implies in practice for the patients remains uncertain.

The present study has certain limitations. First, this is a retrospective study, which implies certain inherent constraints. Likewise, the sample includes only our referral patch test patients, and therefore encompasses an important proportion of the dermatitis patients in Denmark, but, of course, not the general population. Finally, the noted relevance of the exposures has understandable limitations, as a long-term follow-up should be performed to correctly evaluate it.

Conclusions

IPBC continues to be among the less frequent allergens. A 0.2% concentration in patch testing has contributed to

the diagnosis of more patients with contact allergy to this substance.

In Denmark – and we believe that this conclusion may be extrapolated to the rest of the EU – IPBC allergy is related to male sex, age > 40 years, hand eczema, and occupational exposure. Physicians should be encouraged to investigate possible occupational exposure if IPBC sensitization is detected.

More studies are needed to assess the presence of IPBC in both occupational sources and cosmetics. As suggested by other authors, cooperation between physicians and cosmetics manufacturers is needed (20), and patch testing with both traditional and newly introduced preservatives is necessary to benefit patients and inform regulatory bodies (20).

Acknowledgements

The authors wish to thank Lone Holm Clausen, Ania Kayser and Hanne Knudsen (nurses in the Allergy Laboratory at Gentofte Hospital).

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