

1,2-benzisothiazolin-3-one (Proxel[®]): irritant or allergen?

A clinical study and literature review

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The isothiazolinone, 1,2-benzisothiazolin-3-one (Proxel[®]), is a popular preservative, as well as a skin sensitizer and irritant. Patch test studies have been performed with different concentrations and vehicles. The current suggested patch test concentration is 0.1% BIT in petrolatum (pet). This article evaluates the effects of patch testing at this concentration and reviews the current literature. An irritancy patch test was performed on 56 controls, using BIT in concentrations of 0.002% and 0.05% in aqueous dipropylene glycol (Proxel[®] GXL) and 0.1% in pet. 10 had positive readings at 4 days with 0.1% BIT in petrolatum, 9 of which were negative at retest. 0.1% BIT is, therefore, irritant and not a suitable concentration for patch testing. Literature review revealed 15 patch test studies, with varying testing techniques. Additional studies with adequate controls and experimental tests should be invaluable in furthering our insight into BIT sensitization and irritation.

Key words: 1,2-benzisothiazolin-3-one; BIT; Proxel[®]; (5-chloro)-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one; MCI/MI; Kathon[®]CG; isothiazolinone; biocide; preservative; patch test; irritant; allergic; occupational; contact dermatitis. © Munksgaard, 1997.

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Isothiazolinones, a chemically related group of preservatives used in household and industrial products, may cause allergic contact dermatitis (1). Kathon[®] CG (MCI/MI) (Rohm & Haas, Philadelphia), containing the active ingredients (5-chloro)-2-methyl-4-isothiazolin-3-one (Fig. 1) and 2-methyl-4-isothiazolin-3-one, may sensitize.

An alternative is another isothiazolinone: 1,2-benzisothiazolin-3-one (BIT) (ICI, Manchester, England) (Fig. 1) introduced as Proxel[®] (ICI) in the late 1960s (2). The BIT preservatives (Table 1) are used to prevent the growth of microorganisms in the aqueous phase of cleaning agents, polishes, paints, adhesives or glues, starches and metal-working fluids (1,2). However, reports of sensitization by BIT products were documented with Proxel[®] CRL (3), which contained ethylenediamine, a known allergen. ICI introduced Proxel[®] GXL (20% BIT in aqueous propylene glycol), which contained no ethylenediamine, to curb this problem, but reports of sensitization to either pure BIT or Proxel[®] persisted.

Patch test studies have been done on both BIT and Proxel[®], but the conditions and results vary

from study to study, and a confusing array of concentrations has been used (Tables 4, 5). The current suggested patch test concentration is BIT 0.1% in petrolatum (pet.) (4)(5), but this is not fully documented and it is sometimes difficult to differentiate between irritant and allergic reactions. The current questions which we face are:

Is BIT irritant or allergenic?

At what concentrations is BIT irritant/allergenic?

Are current patch test levels irritant, leading to false positives?

This article evaluates the current suggested patch test level of 0.1% BIT and reviews the literature on BIT and Proxel[®] reactions.

Materials and Methods

Test materials

The following materials were used:

1. 0.002% BIT in aqueous dipropylene glycol (0.01% aqueous Proxel[®] GXL)
2. 0.01% BIT in aqueous dipropylene glycol (0.05% aqueous Proxel[®] GXL)

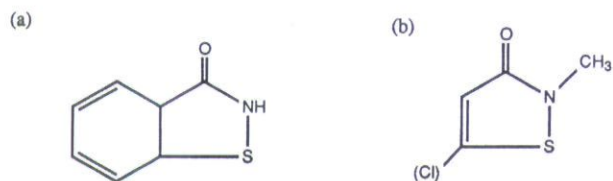


Fig. 1. (a) 1,2-benzisothiazolin-3-one. (b) (5-chloro)-2-methyl-4-isothiazolin-3-one.

3. 0.1% BIT in pet.

Proxel[®] was tested in aqueous dilutions, while pet. was used as the vehicle for BIT as it resists solubilization in water.

Volunteers

56 adult subjects (over 18 years of age) from a pool of healthy volunteers were examined and deemed to be free of any skin pathology. Medical histories and consent forms were obtained from all subjects.

Irritancy patch tests

Patch tests were performed as follows: Finn Chambers[®] (Epitest Ltd., Oy, Tuusula, Finland) were dosed with 17 μ l of solid or liquid, and Finn Chamber[®] pads (filter paper) were used for the liquids. Each of the test materials above was applied to the patches shortly before application to the panelists' skin (either upper arms or backs). Scanpor[®] (Norgesplaster A/S, Kristiansand, Norway) was used as the adhesive tape. Patches remained in place for 2 days and were read at 3 and 4 days. Follow-up testing was carried out for subjects who exhibited a positive reaction. On the retest, patches were left for 3 days, then read at 3 and 4 days. The scoring system employed was as follows:

- 0=negative
- $\pm$ =equivocal reaction
- 1=erythema
- 2=erythema and induration
- 3=erythema, induration and vesicles

Results

10 of the 56 subjects had positive readings at 4 days, with 0.1% benzisothiazolinone in pet (Table 2). These 10 were recalled for retest, at which 9 of the 10 were negative. The 10th showed macular erythema, suggestive of irritation.

With Proxel[®] 0.01% aq. and Proxel[®] 0.05% aq., there was no evidence of irritation or allergic reaction.

Discussion

Above we have shown that 0.1% BIT in pet. is irritant in some subjects and therefore not a suitable concentration for use in patch testing. Proxel[®] in aqueous solution at 0.01% and 0.05% (0.002% and 0.01% BIT respectively) was not irritant. Sensitization was not induced under the conditions of the assay, in that a repeat test in 9 of the 10 tested was negative.

In order to analyze our results in context with other investigators, literature research was performed using the Medline database from the years 1966-1996, using the following keywords: 1,2-benzisothiazolin-3-one, Proxel[®], isothiazolinone and benzisothiazolone. A total of 15 BIT patch test studies and case reports were obtained (Tables 4, 5).

BIT: irritant or allergenic?

The first report of sensitization to BIT was in 1976 by Pedersen (3), who described occupational allergy to undiluted Proxel[®] CRL in 2 Swedish in-

Table 1. BIT-containing biocides (9, 25)

Biocide name	Components
Proxel [®] AB	33% BIT in aqueous dispersion
Proxel [®] GXL	20% BIT in aqueous solution of dipropylene glycol
Proxel [®] CRL	33% BIT in aqueous solution of ethylenediamine
Proxel [®] XL2	9.5% BIT in aqueous solution of propylene glycol
Proxel [®] XL	20% BIT in aqueous solution of propylene glycol
Proxel [®] HL	30% BIT in morpholine di- & triethanolamine
Proxel [®] TN	BIT + triazine (60% active agent)

Table 2. Results of single application irritation assay and retest

Case no.	Age (years) /sex	Site no.			Retest
		#1	#2	#3	#3
4	46/F	0	0	1	0
9	29/M	0	0	1	0
10	25/M	0	0	2	0
12	74/F	0	0	$\pm$	0
27	68/F	0	0	$\pm$	0
39	58/F	0	0	1	0
41	62/F	0	0	1	1
42	62/F	0	0	1	0
44	74/F	0	0	1	0
46	56/F	0	0	1	0

Site numbers:

- #1 - 0.002% BIT in aqueous dipropylene glycol (0.01% aqueous Proxel[®] GXL).
- #2 - 0.01% BIT in aqueous dipropylene glycol (0.05% aqueous Proxel[®] GXL).
- #3 - 0.1% BIT in pet.

Table 3. Occupations associated with BIT-induced dermatitis

Occupation	Ref.
acrylic emulsion manufacturers	Pedersen 1976 (3)
metal workers	Brown 1979 (6) Alomar et al. 1985 (9) Damstra et al. 1992 (21)
paper makers	Cronin 1980 (10)
analytical laboratory technicians	Slovak 1980 (7)
pottery mouldmakers	Roberts et al. 1981 (18)
printers	Freeman 1984 (2) Damstra et al. 1992 (21)
paint manufacturers	Stejskal et al. 1990 (23) Greig 1991 (12)
air freshener manufacturers	Sanz-Gallen et al. 1992 (11)
decorators	Dias et al. 1992 (16) Damstra et al. 1992 (21)

dustrial workers employed in a polyacrylate emulsion factory. Both cases patchtested positive to BIT 0.1% in ethanol and Proxel® CRL 0.1% in water (0.033% BIT in aqueous ethylenediamine), and one tested positive to BIT at only 0.01% in ethanol. Tests with 1% BIT on 10 controls were negative.

In 1979, Brown (6) described contact allergy to a BIT-containing cutting fluid (not further defined) in a precision grinder, without stating clearly the concentration of BIT used.

Subsequently, reports featured a range of occupations implicated in dermatitis caused by BIT (Table 3). Noting the various industries and occupations affected by BIT sensitization, later articles would have been more useful had they defined the concentrations and conditions under which BIT sensitization or irritation was realized.

In 1980, Slovak (7) documents an outbreak of contact dermatitis due to BIT in a works analytical team. 7 men out of a 16-man workforce handling pure BIT were sensitized and gave positive patch

tests to BIT 1% in alcohol. 4 men were also tested with BIT 0.01% in alcohol and there were no positive responses; Slovak suggests this as a safe handling level, although Freeman (2) observed BIT sensitization to as low as 0.025% BIT (0.13% Proxel GXL) handled 10 times a day by a printer over a 3-month period.

Subsequent articles suggested that the 1% BIT level which Slovak employed could be irritant: Freeman (2) reported that 8 of 10 controls tested with 1% BIT had immediate irritant reactions necessitating removal of the patches within an hour. Slovak did not use controls; some of his 7 reported cases of 'sensitization' could well have been irritant. In 1984, Andersen & Hamann (8) confirmed that BIT 1% is indeed irritant when 30% of their 404 patch-tested patients exhibited irritation to 1% BIT in alcohol. Alomar et al. (9) further confirmed the toxicity of 1% BIT when this concentration had to be withdrawn from their study due to the intensity and frequency of the irritant responses.

At what concentrations is BIT irritant/allergic?

Thus, 1% BIT appears to be an irritant level, but what about lower concentrations? Andersen & Hamann (8) obtained 7 irritant reactions from 466 patients tested with Proxel XL 0.5% aq. Cronin (10) observed skin irritation in 1 of 30 controls with 0.1% BIT in methyl ethyl ketone. Ian Kimber (personal communication) found 0.1% BIT in ethanol to be irritant. No further documentation of irritation at lower concentrations has been obtained.

Is the current patch test level irritant?

Both Freeman (2) and Alomar et al. (9) recommend 0.1% BIT as a suitable patch test concen-

Table 4. BIT patch test studies

BIT concentration & vehicle	Choice of subjects tested	No. +ve reactions/subjects	% positive reaction	Interpretation according to author(s)	Ref.
BIT 1% alc.	occupational dermatitis	7/11	63.64%	? sensitization	(7)
BIT 0.1% aq.	occupational dermatitis	4/20	20%	contact dermatitis	(13)
Proxel XL 0.5% aq.	dermatitis patients	8/466	1.72%	1 unexplained 7 irritant	(8)
BIT 1% alc.		122/404	30.20%	1 unexplained 121 irritant	
BIT 0.1% aq.	occupational dermatitis	48/230	20.87%	sensitization	(9)
BIT 1% aq.		a)	a)	toxic	
BIT 0.1% pet.	eczema patients	14/1652	0.85%	unknown	(4)
BIT 0.04% aq.	occupational hand dermatitis	4/17	23.53%	contact allergy	(21)
	random dermatological patients	10/537	1.86%		

a) BIT 12 withdrawn due to irritation.

Table 5. Case reports of BIT-induced dermatitis

BIT concentration & vehicle	No. cases	No. of +ve controls /no. of controls	Interpretation according to author(s)	Ref.
Proxel CRL 0.1% in water BIT 0.1% ethanol	2	BIT 1%=0/10	contact allergy	(3)
BIT-containing cutting oil ^{a)} 10% & 5% dilutions	1	0/3	contact allergy	(6)
BIT 1% & 0.1% methyl ethyl ketone	5	BIT 1%=2/21 0.1%=1/30	sensitization 0.1%: irritation	(10)
Proxel XL2 1% & 5% water BIT 0.1% & 1% methanol	3	Proxel 5%=3/11 1%=0/11	contact allergy	(18)
Proxel GXL 0.1% aq. BIT 0.01% ethanol	1	Proxel 1%=0/10 BIT 1%=8/10 0.1%=1/10	1% BIT: irritant 0.1% suitable for patch testing	(2)
Proxel Press Paste ^{b)} 0.1% & 0.01% pet.	1	Proxel Press Paste 0.01% pet. =0/10	allergic contact dermatitis	(12)
Proxel CRL 1% aq. 0.3% alc.	4	Proxel 0.1% alc.=2/52	0.3% alc. suitable for patch testing	(16)
Mergal K-10 0.1% pet.	1	0	allergic contact dermatitis	(11)
BIT 0.1% pet.	2	0	contact allergy	(17)

^{a)} No name or concentration given. ^{b)} Proxel Press Paste is BIT in water. Author does not state concentration.

tration. This is in contradiction to our results, which clearly show that BIT at 0.1% concentration produces an irritant response in some putatively non-sensitized controls.

Evaluation of pre-existing data

One has to question the clinical validity of the data available. In 1992, Sanz-Gallen et al. (11) reported sensitization of a Spanish paint factory worker to Mergal[®] K-10 (a BIT-containing biocide) at 0.01% in petrolatum. The BIT concentration in Mergal[®] K-10 was not made clear and no controls were used. The diagnosis of allergic contact dermatitis cannot then be confirmed without ascertaining whether the patch test concentration was irritant. Similarly, Brown (6) did not define the concentration used for BIT patch testing. In 1991, Greig (12) used Proxel Press Paste[®] (BIT in water) in her patch testing of a paint manufacturer with sensitization to Proxel CRL, and did not state the dilution concentration of BIT in Proxel Press Paste[®].

Even when controls are used in the experiment, are the few controls used by the majority of case-report investigators sufficient to evaluate irritant responses? Brown (6) used 3 controls for her investigation while the majority use 10 to 20 controls. We recommend a larger number of controls for statistical validity and to account for biological variation.

The larger patch test studies exhibit similar

flaws. The subjects chosen for testing are usually either patients with suspected occupational dermatitis (7, 9, 13) or atopic eczema patients (4). Patch testing of atopic patients may cause a worsening of eczema in other skin sites (excited skin syndrome) or active sensitization to patch compounds, leading to misinterpretation of results (14).

Occlusion time and time of reading are 2 important variables in patch testing. The standard occlusion time is 2 days and all the patch test studies have matched this criteria. However, it is advisable to have 2 readings; one shortly after patch removal and another 1–2 days after, to distinguish between irritation and sensitization, as irritant reactions tend to fade during the 3rd and 4th days, while allergic reactions usually persist (15). Pedersen (3), Dias et al. (16) and Ezzelerab et al. (17) all removed the patches in their respective studies at 2 days and read once at 3 days. Roberts et al. (18) performed only 1 reading shortly after removal of the patches at 2 days.

We read the test results 2× on both the original patch test and the retest, and we chose to occlude the patches for 3 days on the retest to exaggerate any response there might have been. Despite this, 9 of the 10 panelists were negative on retest. The value of retesting seems to have been overlooked: of the 15 papers, none performed a retest to determine if the reaction was reproducible.

Additional studies such as retests, tests with

serial dilutions and provocative use tests are infrequently performed. Experimental studies are also scarce: guinea pig maximization studies (8) and a murine local lymph node assay (19) are among the few performed. In the guinea pig maximization test by Andersen and Hamann (8), Proxel XL and Proxel HL were used: 3 of 20 guinea pigs exhibited sensitization with 1% Proxel XL (0.2% BIT in aqueous propylene glycol) while 1 of 20 guinea pigs had a weak allergic reaction to 1% Proxel HL (0.3% BIT in morpholine di- and triethanolamine). Botham et al. (19), using the mouse local lymph node assay, discovered a significantly lower degree of allergenicity in BIT compared to MCI/MI. MCI/MI tested positive at concentrations of 0.01% whereas BIT was clearly active only within a 30-50% concentration range. These findings imply that BIT does not exhibit as much sensitizing potential under laboratory conditions as in the workplace (20). Experimental tests geared towards evaluating irritant potential were not found. Andersen and Rycroft reviewed this literature and recommended 0.1% pet. as a patch test concentration, noting that this concentration was not well documented.

MCI/MI and its relationship to BIT

MCI/MI is closely related to 1,2-BIT. Concomitant BIT and MCI/MI allergies have been reported and thought to represent the presence of 2 different allergies (17, 21). Although the isothiazolin-3-one structure is common to both molecules (Fig. 1), the conjugation with the aromatic ring in BIT gives it a different reactivity (22). Stejskal et al. (23) used a lymphocyte transformation test to evaluate in vitro lymphocyte responses in 2 workers exposed to high concentrations of BIT. Lymphocytes from these workers reacted to BIT and MCI, but the author believed specific sensitization to both products was more plausible than cross-reaction, as MCI-specific lymphocytes did not cross-react with BIT in vitro.

Conclusion

The history of BIT patch testing is plagued by inconsistencies such as discrepancies in doses, variations in patch test technique (including vehicle and test method), differing occlusion times, inadequate controls and inaccurate interpretations of results. The appropriate concentration for BIT patch testing is particularly controversial, as too high a concentration can easily produce a false-positive (maybe irritant) response, while too low a concentration results in false negatives. We have determined that BIT is irritant at a concentration

of 0.1% pet. In view of our results, we strongly support the value of larger series of controls in further patch test studies, as well as evaluating the patient utilization of the operational definition of occupational contact dermatitis (24). Additional studies such as retests, provocative use tests, serial dilutions and experimental studies should have value in furthering our knowledge of BIT reactions, as BIT allergenicity cannot be fully investigated until the irritant range is fully determined.

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