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Allergic contact dermatitis to synthetic rubber gloves in healthcare workers: sensitization to 1,3-diphenylguanidine is common

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Conflicts of interest: The authors declare no conflicts of interest.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cod.13269

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Abstract

Background. Allergic contact dermatitis has significantly increased in healthcare workers since the transition from latex to synthetic rubber gloves, with 1,3-diphenylguanidine identified as the most frequently implicated allergen.

Objectives. We aimed to highlight the role of 1,3 diphenylguanidine as culprit allergen in contact allergies to synthetic rubber gloves, to propose recommendations for patch testings, and to discuss alternatives for sensitized subjects.

Materials and methods. Patch-test data from healthcare workers who developed hand dermatitis after wearing rubber gloves and who tested positive to glove samples and rubber additives were collected from September 2010 to December 2017 in a Belgian hospital.

Results. A total of 44 caregivers were included in this study**.** Patch tests revealed that: (i) 84% of the study population tested positive to carba mix; (ii) 86% tested positive to 1,3-diphenylguanidine; (iii) 13 subjects (30%) reacted to thiuram mix. Half of the subjects tested positive to gloves containing 1,3-diphenylguanidine, whereas none reacted to accelerator-free gloves.

Conclusion. The most commonly identified allergen was 1,3-diphenylguanidine, far ahead of thiurams, previously described as the most sensitizing accelerators. Using 1,3-diphenylguanidine-free gloves is recommended. No subject reacted to gloves without accelerators, thus confirming their efficiency among accelerator-sensitized patients. We recommend that 1,3-diphenylguanidine be added into the European baseline series.

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Key words: allergic contact dermatitis, healthcare workers, rubber gloves, rubber accelerators, 1,3-diphenylguanidine, thiuram

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1. Introduction

Synthetic rubber gloves (e.g., polyisoprene, polychloroprene or nitrile) are increasingly used instead of latex gloves, in an effort to avoid IgE-mediated allergic reactions, with symptoms ranging from contact urticaria to anaphylactic shock (1). A growing number of hospitals have decided to completely phase out latex, thereby becoming "latex-free hospitals" (2). Nevertheless, many healthcare workers who have worked for years without any history of hand dermatitis have meanwhile developed contact dermatitis to these synthetic gloves.

Numerous potential allergens, such as antioxidants (3) and dyes (4) can be incriminated, but the most common group are the vulcanization accelerators (5). These chemicals are employed to enhance and speed up the vulcanization, that is, a glove manufacturing process chemically crosslinking the rubber macromolecules and thereby render the rubber more resistant. Since latex and synthetic rubber gloves are both similarly manufacted, including the use of vulcanization accelerators, the question as of why the occurrence of contact eczema has increased was raised. Several explanations have been put forth in the literature, such as

i. a greater concentration of vulcanization accelerators being applied for the production of synthetic rubber gloves (2). Indeed, in addition to *cis*-1,4-polyisoprene isomer (found in latex), artificial polyisoprene contains a small portion of *trans*-1,4-polyisoprene, negatively impacting vulcanization, with a higher concentration of vulcanization accelerators thus needed;

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ii. the sensitizing properties of the accelerators used in synthetic rubber gloves, such as 1,3-diphenylguanidine (DPG), are likely more relevant (6);

iii. Certain additives like cetylpiridinium chloride (CPC), an antimicrobial agent with irritating and sensitizing properties, may on top be applied in higher quantities (2).

The most common rubber accelerators include thiurams, carbamates, guanidines, benzothiazoles and thioureas (5). As reported by Crepy et al, accelerator-free gloves have recently been developed, enabling accelerator-sensitized workers to pursue their professional activity (7).

2. Patients and Methods

2.1 Patients

Based on the data collected at the Contact Allergy Unit of the Brussels Cliniques universitaires Saint-Luc from September 2010 to December 2017, all patients were included into the study who had (i) a history of contact eczema of the hands related to using rubber gloves; (ii) positive patch test reactions to at least one sterile synthetic rubber glove (Esteem Micro, Protexis Micro, Protexis Ortho; all produced by Medline International, Northfield, Illinois), or to a rubber vulcanization accelerator (DPG, carba mix, thiuram mix or benzothiazole). The study and data collection were conducted following the study protocol's approval by the Biomedical Ethics

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Committee of the Université Catholique de Louvain (Commission d'Ethique Biomédicale Hospitalo-Facultaire).

2.2 Patch tests

Patch tests were performed based on the European baseline series, rubber series, antiseptic and preservatives series (Chemotechnique Diagnostics, Vellinge, Sweden and Smartpractice, Reinbek, Germany), sample series from gloves used by patients, as well as on accelerator-free gloves. Tests were applied for 48 hours on the upper back using IQ Ultra test chambers from Chemotechnique Diagnostics. The patch tests were fixed with Fixomull stretch (BSN Medical, Hamburg, Germany), and then read on day (D)2 and D4 according to the criteria established by the International Contact Dermatitis Research Group and European Society of Contact Dermatitis (8).

The European baseline series contains thiuram mix 1% pet., mercapto mix 2% pet., and mercaptobenzothiazole (MBT) 2% pet. The rubber series used contains the four thiurams comprising the thiuram mix, namely, tetramethylthiuram monosulfide (TMTM) 1% pet., tetramethylthiuram disulfide (TMTD) 1% pet., tetraethylthiuram disulfide (TETD) 1% pet., and dipentamethylenethiuram disulfide (DPTD) 1% pet. In addition, the rubber series includes carba mix 3% pet. composed of two carbamates, *i.e.*, zinc diethyldithiocarbamate (ZDEC) 1% pet. and zinc dibutyldithiocarbamate (ZDBC) 1% pet., along with 1,3-diphenylguanidine 1% pet. 1,3-

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diphenylguanidine 1% pet. was also tested alone. Zinc dimethyldithiocarbamate (ZDMC) 1% pet., not part of the carba mix, was also tested, as well as 2-(4-Morpholinylmercapto)benzothiazole (MMBT) 1% pet., one of the benzothiazoles composing the mercapto mix.

Patch tests with personal gloves were performed by cutting the gloves into small pieces that were then applied "as is" on the upper back. Before application, the area was moistened with physiological saline solution. For each glove, both the inner and outer faces were applied, as the allergen concentrations may vary between inside and outside (6). The models commonly used at the Cliniques universitaires Saint-Luc are Esteem Micro and Ortho, and Sensicare Ice Nitrile Exam Gloves; all manufactured by Medline International (Northfield, Illinois). Sensicare Ice Nitrile Exam Gloves contain dithiocarbamates but no DPG while Esteem Micro and Ortho contain both dithiocarbamates and DPG (9).

Of note, Esteem Micro and Ortho were rebranded as Protexis Micro and Ortho, although the chemical formulation of these gloves remained the same. The accelerator-free gloves (as claimed by the manufacturer) tested were: (i) Gammex Dermaprene (Ansell, Richmond, Australia); (ii) Gammex Non-Latex Sensitive (Ansell); (iii) Sempermed Syntegra UV (Semperit, Vienna, Austria) and (iiii) Neoderm biogel (Gothenburg, Sweden).

3. Results

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Overall, 4068 patients with suspected allergic contact dermatitis underwent patch testing at the Contact Allergy Unit of the Department of Dermatology of the Cliniques universitaires Saint-Luc, Brussels. In total, 44 patients were included in the analysis. Online supplemental **Table 1** summarizes clinical and demographic data of all study subjects. The mean age was 38 years, the range from 19 to 60 years. The proportion of male subjects was 64%. The most common profession was physicians (27 subjects; 61% of the cohort), followed by nurses (11 subjects; 25%). Of the six remaining participants, there were two medical representatives, one operating room cleaner, one radiology technician, one assistant pharmacist, and one dentist. Among the 44 patients, 39 (89%) worked at the Cliniques universitaires Saint-Luc, Brussels. The remaining five were practicing in other Belgian hospitals. Half of the subjects (52%) had a history of atopy.

The patch test results are listed in **Tables 2** and **3.**

3.1 Vulcanization accelerators

The carba mix accounted for the largest number of positive reactions, with 37 positive subjects (84%). Subjects reacted strongly (++) in 51% of cases. Besides, 38 subjects were allergic to DPG, which is a guanidine contained in the carba mix (86% of the population tested). ZDEC, a carbamate which is also a component of the carba mix, was positive in seven patients. ZDBC was only positive in one subject with a low intensity (+) reaction. ZDMC, not included in the carba mix, turned out to be positive in four subjects.

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All the patients (44 subjects) had positive reactions to carba mix and/or DPG except one. Five subjects (11%) reacted to the carba mix only, but not to DPG. The reaction proved to be weak (+) in four subjects and strong in one. Lastly, six participants (14%) were DPG positive but carba mix negative. All these six reactions were weak (+).

A total of 13 subjects (30%) displayed a positive reaction to thiuram mix, which was strong in most cases. Of the 13 positive subjects, five reacted extreme (+++), six strong (++), and two weak (+). Among the four accelerators comprising thiuram mix, TMTM proved to be positive in six patients, with weak (+) reactions in the majority of cases (4/6). TMTD was positive in five patients, with nine subjects reacting to TETD; five cases were positive to DPTD.

Overall, 25 patients (57% of the subjects) reacted to carba mix without reacting to thiuram mix, whereas only one subject was positive to thiuram mix but not to carba mix, with 12 participants (27%) reacting positively to both. Of note, six subjects reacted to neither carba mix nor thiuram mix, all being only weak positive (+) to DPG.

Of the 14 subjects who reacted to one of the carbamates (ZDMC, ZDEC, and ZDBC) or thiuram mix (containing only thiurams), seven displayed a positive reaction to both, six reacted to thiuram mix but not to any carbamate, whereas only one was positive to a carbamate but not to thiuram mix. Only one subject reacted to the mercapto mix, who was also weak positive to

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MMBT and MBT. Another subject reacted weakly (+) to MBT.

3.2 Gloves

The results of the patch tests with different kinds of gloves are summarized in **online supplemental Table 4.** Among the gloves with accelerators, of the 34 subjects tested with Esteem Micro gloves (rebranded as Protexis Micro), 17 exhibited positive reactions, mostly weak (+). Strong (++) and extreme positive (+++) reactions were mainly observed to the inner face. Protexis Ortho gloves (Medline International), which were tested on 16 subjects, caused a positive reaction in nine. Concerning reaction intensity, the results were similar for the inner and outer faces. Most reactions were strong (++) reactions (5/9 cases). Nevertheless, three weak reactions (+) and one extreme reaction (+++) were also observed. Sensicare Ice Nitrile Exam Gloves (Medline International), which were tested on 30 subjects, resulted in positive patch tests in only four. In terms of reaction intensity, the results turned out to be similar for the inner and outer faces, with two weak reactions (+) and two strong (++).

Among the gloves without accelerators, (i) Gammex Dermaprene, (ii) Gammex Non-Latex Sensitive, (iii) Sempermed Syntegra UV, and (iiii) Neoderm biogel gloves were tested on (i) 24, (ii) 20, (iii) 14 and (iiii) 20 subjects, respectively, with all negative results.

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4. Discussion

DPG is found in sterile Protexis Micro and Ortho gloves (6) formerly named Esteem Micro and Ortho used at the Cliniques universitaires Saint-Luc, Brussels, Belgium. It is by far the accelerator that caused the largest number of reactions in our study, with 38 positives subjects out of total of 44, namely 86% of the cohort. In addition, more than half of the subjects (25/44; 57%) tested positive to DPG but did not react to any other accelerator. This very high proportion of sensitization to this guanidine is in line with our previous report (2), as well as with the Ponten et al study (6), published in 2013, where 12/16 subjects tested turned out to be positive to DPG. The authors concluded that DPG was a relevant contact allergen in sterile polyisoprene gloves, contrasting with an older study that suggested that most positive reactions to DPG were likely due to irritation and therefore, false positives (10). A recent study by Hamnerius et al (11) reported a large number of positive reactions to DPG, which were slightly more numerous than positive reactions to thiuram mix. Consequently, only DPG-free medical gloves are now used in the respective hospital.

Furthermore, Dahlin et al have recently demonstrated that another guanidine contained in medical gloves may induce allergic contact dermatitis, namely triphenylguanidine (TPG) (12). At the time of the study, it was still unclear whether TPG was added as vulcanizing agent to rubber, or was only formed during the vulcanization process. According to another hypothesis,

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TPG could be metabolized into DPG in the skin (12). In our study, the intensity of DPG reactions proved to be weak (+) in half (47%) of the positive subjects. This contrasts with the Ponten et al study, with all positive reactions being either strong (++) or extreme (+++) (6).

The number of positive reactions to thiuram remains relevant in our study (30% of the subjects), although far lower compared to DPG. This is consistent with several other studies that have reported a decrease in thiuram sensitization (13–16). One explanation for this is that manufacturers foster less allergenic accelerators like carbamates (6,10). Thiurams do cause severe allergic reactions, as supported by our study where reactions in 11/13 subjects positive to the thiuram mix were strong or extreme.

Most positive reactions to carbamates were found in subjects who were also allergic to thiurams. This relationship is, however, not reciprocal. Only one subject proved positive to carbamates but not to thiurams, whereas six reacted to thiurams but not to carbamates, as observed in several other studies (5). Thiuram mix, which is included in the European baselines series, remains a good marker for sensitivity to vulcanization accelerators (8). However, a large number of patients would have been missed if DPG is not tested separately. As proposed by Hamnerius et al (10), inclusion of DPG in the European baseline series or extended European baseline series is therefore suggested.

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Thiurams and carbamates with longer carbon chains (DPTD for thiurams and ZDBC for carbamates) caused fewer reactions than those with shorter carbon chains. In their study, Geier et al reported the same observation (17). As an explanation, the longer the carbon chains, the lower the compound's mobility in the rubber matrix could be. The allergen is thus less easily extractable by fluids like perspiration. Skin exposure to the allergen is therefore decreased and the sensitization power reduced (18).

The vast majority of synthetic rubber gloves are produced with accelerators like carbamates, among others. The fact that relatively few study subjects tested positive to carbamates further supports the choice of glove manufacturers who have stopped using thiurams in favor of less allergenic accelerators like carbamates. Given the low proportion of carbamate-positive subjects and very numerous carba mix-positive reactions induced by DPG contained in the mix, carbamates and DPG must be tested separately (5). Indeed, a large number of reactions to carba mix could suggest that carbamates are very allergenic, whereas most of the positive reactions are in fact due to DPG. Surprisingly, several subjects tested positive to DPG, though negative to carba mix (despite this containing DPG).

To control allergic contact dermatitis of their hands, the patients stopped using gloves containing accelerators in favor of neoprene "accelerator-free" gloves, namely, Gammex Dermaprene (Ansell) and Gammex Non-Latex Sensitive (Ansell). Thanks to this, no subject experienced a

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recurrence of allergic contact dermatitis. Accordingly, patch tests with four accelerator-free glove models did not result in any positive reactions. Our data thus corroborate the Crepy et al study published in 2018, in which a significant decrease in dermatitis severity was observed in all subjects wearing accelerator-free gloves. Of nine patients, seven achieved complete clearance of eczema (7). Accelerator-free gloves are therefore an effective alternative for subjects sensitive to vulcanization accelerators. However, accelerator-free gloves are currently expensive. The replacement of synthetic rubber gloves containing accelerators by the accelerator-free ones for all caregivers is thus also discussed from an economic perspective. However, if their cost decreases in the future, "accelerator-free" hospitals could emerge in a way similar to "latex-free" hospitals a decade ago.

As alternative, less allergenic accelerators can be used. Zinc diisononyl dithiocarbamate (ZDiNC), with long branched alkyl chains on the sides (nine carbons), seems to be a weak allergen (data provided by the manufacturer), contrary to the most frequently used carbamates in the industry: zinc diethyldithiocarbamate (ZDEC, 2 carbons) and zinc dibutyldithiocarbamate (ZDBC, 4 carbons). As discussed above, the long lateral chains make this compound less allergenic. Another alternative could also be the diisopropyl xanthogen polysulfide. This latter compound decomposes into gas when exposed to vulcanization temperatures. It thus disappears during the manufacturing process and is no longer found in the final product. Gloves containing these two accelerators should soon be available.

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5. Conclusion

A large number of caregivers who have worked for years without any history of hand dermatitis have presented with allergic contact dermatitis following the replacement of latex (natural rubber) gloves by synthetic ones. 1,3-Diphenylguanidine (DPG) was the allergen responsible of the largest number of reactions. In comparison, only few subjects were found to be sensitive to thiurams, although this was the number one allergen in older studies. One explanation is that most manufacturers stopped using thiurams, owing to their considerable allergenic potential, which was the case in our study. The gloves used by the subjects (Protexis Micro and Protexis Ortho) were free of thiurams but contained DPG or carbamates. Thiuram mix remains a good marker for sensitization to thiuram/dithiocarbamates. However, most allergic patients would have been missed without testing DPG separately. Therefore, inclusion of DPG in the European baseline series is suggested.

To reduce allergies to synthetic rubber gloves, several manufacturers now provide DPG-free gloves. It is recommended to preferably using less allergenic rubber accelerators, such as accelerators with long carbon chains or accelerators decomposing into gas at manufacturing temperatures. Moreover, gloves without accelerators have meanwhile been developed. According to our observations, these gloves do not cause any reaction. In addition, we encourage

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manufacturers towards a more detailed labeling on gloves packaging, clearly indicating the accelerators used during the manufacturing process in an effort to enable healthcare professionals to wisely select the most appropriate gloves more.

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Table 2. Rubber accelerator patch-test results

	Patient	Gender	Age	Occupation	Carba mix	DPG	ZDMC	ZDEC	ZDBC	Thiuram mix	TMTM	TMTD	TETD	DPTD	Mercapto mix	MMBT	MBT
201[illegible]	1	M	34	Surgeon	+	-	-	-	-	+	-	-	++	-	-	-	+
	2	M	50	Radiologist	+	-	++	+	+	+++	-	++	-	-	-	-	-
2011	3	M	25	Nurse	+	+	-	-	-	-	-	-	-	-	-	-	-
	4	M	34	Surgeon	++	+	-	++	-	++	-	-	++	-	-	-	-
	5	M	53	Surgeon	+	+	-	-	-	-	-	-	-	-	-	-	-
2012	6	M	30	Gynecologist	++	+++	-	-	-	-	-	-	-	-	+	+	+
	7	M	60	Surgeon	++	+	-	-	-	-	-	-	-	-	-	-	-
	8	F	42	Nurse	++	+	-	-	-	-	-	-	-	-	-	-	-
	9	M	59	Surface Technician	+++	+++	-	-	-	+++	+	-	+++	++	-	-	-
	10	F	55	Nurse	+	-	-	-	-	-	-	-	-	-	-	-	-
	11	M	31	Anesthesiologist	++	++	-	-	-	-	-	-	-	-	-	-	-
2013	12	M	54	Medical representative	++	+	-	-	-	+++	+	-	+	+	-	-	-
	13	M	31	Medical representative	++	-	++	++	-	+++	++	++	++	++	-	-	-
	14	M	56	Cardiologist	+++	+++	-	++	-	++	-	-	+++	-	-	-	-
	15	F	19	Assistant pharmacist	+	+	-	-	-	-	-	-	-	-	-	-	-
	16	M	29	Radiologist	++	++	-	-	-	-	-	-	-	-	-	-	-
	17	M	25	Surgeon	+++	+++	-	-	-	-	-	-	-	-	-	-	-
	18	M	37	Anesthesiologist	++	++	-	-	-	-	-	-	-	-	-	-	-
	19	F	54	Nurse	+++	+++	-	-	-	-	-	-	-	-	-	-	-

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	20	M	47	Nurse	+++	+++	-	-	-	-	+	-	+	-	-	-	-
	21	M	56	Cardiologist	++	++	-	-	-	-	-	-	-	-	-	-	-
	22	F	54	Nurse	+	-	-	-	-	-	-	-	-	-	-	-	-
2014	23	F	29	Gynecologist	++	++	-	-	-	-	-	-	-	-	-	-	-
	24	F	24	Nurse	+	+++	-	-	-	-	-	-	-	-	-	-	-
	25	F	27	Nurse	+	++	-	-	-	-	-	-	-	-	-	-	-
	26	M	31	Surgeon	-	+	-	-	-	-	-	-	-	-	-	-	-
	27	M	36	Surgeon	-	+	-	-	-	-	-	-	-	-	-	-	-
	28	M	46	Oto-rhino-laryngologist	-	+	-	-	-	-	-	-	-	-	-	-	-
2015	29	F	31	Gynecologist	++	++	-	-	-	-	-	-	-	-	-	-	-
	30	M	26	Surgeon	+++	+++	+	-	-	-	-	-	-	-	-	-	-
	31	M	25	Surgeon	++	++	-	+	-	++	-	+	-	-	-	-	-
	32	F	22	Nurse	+++	++	++	++	-	+++	+++	++	-	-	-	-	-
	33	M	33	Surgeon	-	-	-	-	-	++	-	-	-	-	-	-	-
2016	34	M	31	Surgeon	++	+++	-	-	-	-	-	-	-	-	-	-	-
	35	M	27	Surgeon	++	+	-	-	-	-	-	-	-	-	-	-	-
	36	M	58	Surgeon	+	+	-	-	-	++	+	+	-	+	-	-	-
	37	M	30	Urologist	++	+	-	-	-	-	-	-	-	-	-	-	-
	38	F	30	Surgeon	-	+	-	-	-	-	-	-	-	-	-	-	-
	39	M	28	Dentist	++	+	-	+	-	++	-	-	+	+	-	-	-
		F	23	Surgeon	-	+	-	-	-	-	-	-	-	-	-	+	+
2017	41	F	59	Nurse	++	++	-	-	-	-	-	-	-	-	-	-	-
	42	F	48	Nurse	++	+	-	-	-	+	-	-	++	-	-	-	-

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43	F	29	Surgeon	+++	+++	-	-	-	-	-	-	-	-	-	-	-	-	-
44	F	30	Surgeon	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-

DPG, 1,3-diphenylguanidine; ZDMC, zinc dimethyldithiocarbamate; ZDEC, zinc diethyldithiocarbamate; ZDBC, zinc dibutyldithiocarbamate; TMTM, tetramethylthiuram monosulfide; TMTD, tetramethylthiuram disulfide; TETD, tetraethylthiuram disulfide; DPTD, dipentamethylenethiuram disulfide; MMBT, 2-(4-morpholinylmercapto)benzothiazole; MBT, 2-mercaptobenzothiazole.

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Table 3. Rubber accelerator patch test results

	Carba mix	DPG	ZDMC	ZDEC	ZDBC	Thiuram mix	TMTM	TMTD	TETD	DPTD	Mercapto mix	MMBT	MBT
N positive	37	38	4	7	1	13	6	5	9	5	1	2	3
N +	10	18	1	3	1	2	4	2	3	3	1	2	3
N ++	19	10	3	4	0	6	1	3	4	2	0	0	0
N +++	8	10	0	0	0	5	1	0	2	0	0	0	0
N +/total +	27%	47%	25%	43%	100%	15%	67%	40%	33%	60%	100%	100%	100%
N ++/total +	51%	26%	75%	57%	0%	46%	17%	60%	44%	40%	0%	0%	0%
N +++/total +	22%	26%	0%	0%	0%	38%	17%	0%	22%	0%	0%	0%	0%

N, number of subjects; DPG, 1,3-diphenylguanidine; ZDMC, zinc dimethyldithiocarbamate; ZDEC, zinc diethyldithiocarbamate; ZDBC, zinc dibutyldithiocarbamate; TMTM, tetramethylthiuram monosulfide; TMTD, tetramethylthiuram disulfide; TETD, tetraethylthiuram disulfide; DPTD, dipentamethylenethiuram disulfide; MMBT, 2-(4-morpholinylmercapto) benzothiazole; MBT, 2-mercaptobenzothiazole.

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