

The Occupational Dermatology Research and Education Centre (ODREC), Skin Health Institute, VICTORIA, AUSTRALIA : (L to R) Associate Professor Rosemary Nixon AM, Dr Jenny Cahill and Dr Claire Felmingham are the authors of this edition of AnsellCares<sup>SM</sup> InTouch<sup>TM</sup>.

**The views of this article are the result of peer-reviewed research conducted by the authors as well as a current literature review on the subject of occupational contact dermatitis (to healthcare workers) resulting from rubber chemical accelerators used in the manufacture of medical gloves.**

## THE EVOLUTIONARY RESPONSE TO GLOVE ALLERGIES: A CURRENT DERMATOLOGY REVIEW

### Learner Objectives:

1. Review incidence, causes and impact of Type IV chemical allergies.
2. Examine manufacturing formulation development and improvements in synthetic gloves.
3. Understand differences and impact of chemical accelerators, including new biologically-safer options.

## INTRODUCTION TO HEALTHCARE WORKER CONTACT DERMATITIS

Occupational skin disease, and in particular contact dermatitis, is common among healthcare workers. There are two main types of contact dermatitis: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD).

ICD is usually confined to the hands and commonly occurs in healthcare workers, with the main cause being wet work. Frequent wetting and drying of the hands have a deleterious effect on the skin barrier. People with a history of eczema, even when it occurred in childhood and subsequently resolved, are at a greater risk of developing ICD.

ACD is a Type IV or delayed hypersensitivity reaction. It typically occurs hours after an allergen is in contact with the skin. There are certain chemicals with the ability to cause ACD. Some of the most common chemicals reported to cause ACD in healthcare workers include rubber chemical accelerators used in gloves, preservatives, and other ingredients of hand cleaners, including coconut diethanolamide, fragrance, and chlorhexidine.<sup>1</sup> It is important to understand that ACD might not occur until after many years of exposure to the same substance. Early referral for patch testing is important to diagnose ACD and identify the relevant allergen(s).

Patch testing is the gold standard for diagnosis of ACD and is typically performed by dermatologists. It involves reproducing exposure to standardized allergens on the patient's back, and because this reaction is delayed, testing is performed over 5 days. This is different to prick testing performed on the patient's forearm, which tests for Type I or immediate hypersensitivity reactions to substances such as pollens, grasses, house dust mite, natural rubber latex and foods and takes only 30 minutes. Prick tests are usually performed by allergists. Immediate

hypersensitivity reactions can also be diagnosed with blood tests, specific IgE tests (IgE), formerly called RAST tests. Patch testing and IgE tests are important investigations in elucidating the cause of hand dermatitis in healthcare workers: we often refer to this as a diagnostic journey, as there may be many factors playing a role.<sup>2</sup>

Simple measures can be undertaken by healthcare workers to care for and protect their skin. For those with suspected occupational contact dermatitis of the hands, helpful measures include avoidance of contact with irritants as much as possible; use of appropriate gloves especially at home, for example when washing the dishes; adoption of a good skin care routine, including the use of a soap substitute and a rich moisturizer; and treatment with a topical steroid ointment. For those who do not respond to these measures, referral to a dermatologist for patch testing and the establishment of a formal diagnosis is necessary. If a healthcare worker is diagnosed with occupational ACD, it is important to understand all the possible sources of exposure to the allergen, so that it can be adequately avoided and substituted where possible.<sup>2</sup>

Occupational skin disease can have a significant impact on an individual's personal life as well as on their working life. It results in impaired quality of life and may also be associated with time lost from work, contributing to economic burdens resulting from diminished earning capacity, loss of productivity, the cost of treatment and workers' compensation.<sup>1,3-5</sup>

## LATEX ALLERGY

An 'epidemic' of latex allergy emerged in the 1990s, when the use of disposable powdered latex gloves increased rapidly in the HIV epidemic. Natural rubber latex (NRL) can cause Type I or immediate hypersensitivity reactions leading to a range of presentations including urticaria, asthma, hay fever and sometimes anaphylaxis. Exposure to glove powder carrying latex proteins is now thought to have been a major route of sensitization, particularly from cheaper gloves with high amounts of NRL protein.<sup>6</sup>

Because of the latex allergy epidemic that has impacted both patients and staff, many healthcare workers now use non-

powdered latex gloves or synthetic rubber gloves. Subsequently the rate of allergy to latex among healthcare workers has declined significantly since the late 1990s and early 2000s.

However, latex allergy in healthcare workers is still occasionally seen,<sup>1</sup> and it should be considered in healthcare workers with contact dermatitis.

Information on the global burden of occupational contact dermatitis in healthcare workers is scant. The table below sheds some light on this issue.

**Table 1: Diagnoses in healthcare workers with occupational skin disease. Table modified from Higgins et al <sup>1</sup>**

Diagnosis	Healthcare workers with occupational skin disease (N = 555) n (%) <sup>*</sup>
<b>ICD</b>	439 (79.1)
<b>ACD</b>	276 (49.7)
<b>Natural rubber latex allergy</b>	72 (13.0)
<b>Contact urticaria</b> (excluding latex allergy)/protein contact dermatitis	21 (3.8)
<b>Dermographism/urticaria</b>	9 (1.6)
<b>Other</b> (e.g. endogenous eczema; psoriasis; other inflammatory skin disease; persistent post-occupational dermatitis; skin infections)	248 (44.7)
<b>Total diagnoses<sup>*</sup></b>	1,068

<sup>\*</sup>Note: patients could have multiple diagnoses

## RUBBER CHEMICAL ACCELERATOR ALLERGY

Rubber chemical accelerators are among the most common allergens causing occupational ACD in healthcare workers, and are found in both NRL and synthetic gloves, such as polyisoprene, neoprene and nitrile.<sup>1</sup> The accelerators' function is to catalyze the sulfur crosslinking reaction in both natural rubber latex and synthetic gloves to give strength and durability to the film.

However, at the end of the glove dipping process, there are residual accelerators remaining in the glove. As many of these

conventional accelerators are lower molecular size, they have low solubility in the film, meaning that over time, they will bloom to the surface of the glove creating a higher risk of delayed allergic reactions.

Common rubber chemical accelerators include thiurams, dithiocarbamates, mercapto compounds, diphenylguanidine and thioureas.

## THIURAMS

Thiurams (tetramethylthiuram monosulfide, tetramethylthiuram disulfide, dipentamethylenethiuramdisulfide, and tetraethylthiuram disulfide) have long been considered the most common rubber chemical allergens.<sup>14</sup> They are commonly responsible for occupational ACD, especially among healthcare workers.<sup>1, 15</sup> They provide faster and more effective curing rate and provides better strength to glove film.

In recent years, a downward trend in the frequency of thiuram sensitivity has been observed.<sup>1, 16-18</sup> This has been attributed to a reduction in thiuram use by glove manufacturing companies

and substitution with less allergenic accelerators such as dithiocarbamates, mercaptobenzothiazoles, or their derivatives.

Another reason why thiurams in gloves may be decreasing relates to the additional washing which occurs during the manufacture of non-powdered gloves, which are now much more commonly used.

Other studies have reported an unchanged prevalence in thiuram sensitivity despite its discontinued use in gloves.<sup>15, 19</sup> This may be explained by cross reactivity and/or co-reactivity with dithiocarbamates, where allergy to dithiocarbamates has led to thiuram sensitivity, as these chemicals have a close relationship.

## DITHIOCARBAMATES AND DIPHENYLGUANIDINE

Dithiocarbamates (zinc diethyldithiocarbamate, zinc dibutyldithiocarbamate, zinc dimethyldithiocarbamate, and zinc dibenzoyldithiocarbamate) are also frequent rubber allergens. Diphenylguanidine (DPG) is a rubber chemical accelerator and commonly used in polyisoprene gloves to improve the tensile strength of the final film.

Carba mix is a screening allergen included in many baseline patch test series to detect dithiocarbamate and DPG allergies. Carba mix comprises the following allergens: zinc dibutyldithiocarbamate, zinc diethyldithiocarbamate and DPG.

An increase in the frequency of occupational contact allergy to carba mix and its constituents has been reported.<sup>13</sup> It would appear that carbamates have replaced thiurams in the manufacturing of surgical gloves to some extent, explaining the increased reactivity to carba mix. Surveillance of rubber accelerators in medical and surgical gloves within the United States recorded the presence of carbamates in 90.5% (172/190) of glove lines.<sup>5</sup>

A very recent paper has reported a marked increase in ACD to DPG, which ranked far ahead of both thiurams and carbamates, indicative of changing glove compositions.<sup>14</sup>

## MERCAPTO COMPOUNDS

Mercapto compounds (MBT and mercapto mix) are widely used in the glove manufacturing industry, however the frequency of sensitization is relatively low and appears to be declining. When added with other accelerators it shortens the curing time and vulcanisation times and provides better glove strength.

The North American Contact Dermatitis Group (NADG) reported a statistically lower rate of contact allergy to MBT in the 2013-2014 (0.5%) period compared to that in the 2001-2012 period.<sup>17</sup>

## THIOUREAS

Thioureas (diethylthiourea, dibutylthiourea, diphenylthiourea, and thiourea) are predominantly used in the production of neoprene and foam rubber.<sup>5</sup> Shoes and medical devices containing neoprene are more frequent sensitizers than gloves.<sup>20</sup> Thioureas play a minor role in rubber glove allergy.

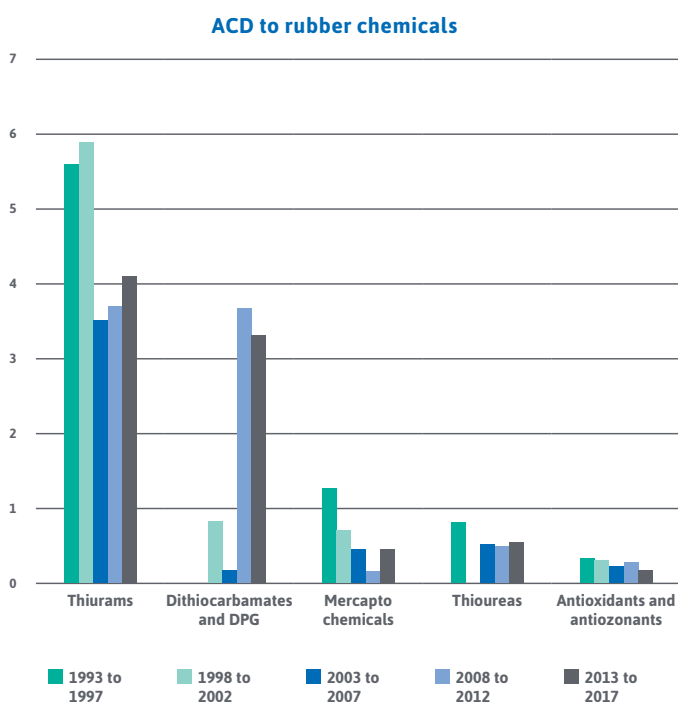
## OCCUPATIONAL DERMATOLOGY RESEARCH AND EDUCATION CENTRE (ODREC) DATA

A review of contact allergy to rubber chemical accelerators presented to ODREC has confirmed the overseas findings (refer to Fig. 1) with more reactions to carbamates in the period 2008-2017 compared to 1993-2007 and fewer reactions to thiurams in the period 2003-2017 compared to 1993-2002 (unpublished)

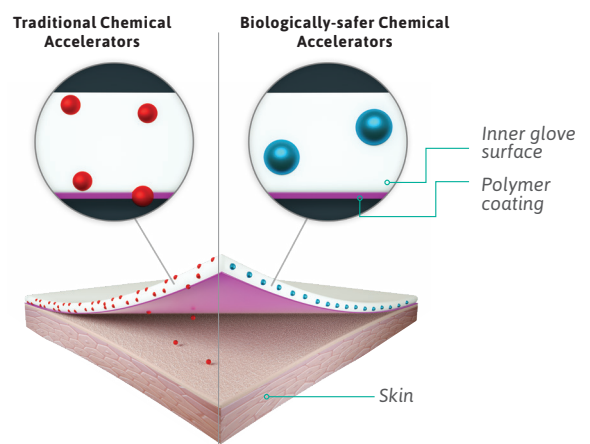
## NEW TECHNOLOGIES

Leading glove manufacturers are increasingly reformulating gloves in order to reduce the risk of allergy.

Zinc diisononyl dithiocarbamate (ZDNC) is a novel accelerator developed to eliminate Type IV (delayed hypersensitivity) allergic reactions associated with traditional dithiocarbamates. ZDNC has been introduced in the processing of polyisoprene latex and natural rubber latex for applications such as surgical gloves.<sup>21</sup> It is thought that the solubility of ZDNC in rubber and its large molecular size make it less likely to bloom to the glove surface, thus reducing its allergenic potential. Another accelerator is diisopropyl xanthogen polysulphide, where due to its low boiling point, it decomposes into gas during rubber vulcanization, therefore assisting in the cross-linking and durability of the glove but leaving no residue on the final glove and hence less potential for allergy. The use of these novel accelerators is a fresh approach, although awaits the emergence of more clinical evidence.



**Fig 1: Allergic contact dermatitis to rubber accelerators in the Occupational Dermatology Clinic, Melbourne 1993-2017**



**Unlike traditional chemical accelerators which may not remain in the glove, biologically-safer rubber accelerators are known to either be completely consumed during production or remain within the glove film.**

## CONCLUSION

While the phasing out of powdered latex gloves has seen a significant reduction in latex allergy, ACD from gloves still occurs.

Rubber chemical accelerator ACD has been a major cause of occupational ACD for many years, especially among healthcare workers.

There appears to have been a slight change in the epidemiology of rubber chemical accelerator ACD recently. While thiurams were previously the most common rubber accelerator to cause ACD, we are now seeing more reactions to dithiocarbamates and DPG. This corresponds to the increased use of both non-powdered latex

gloves and synthetic gloves. With leading glove manufacturers now developing accelerator-free disposable and surgical gloves and combined with the emergent technology of the novel accelerators, the rate of ACD to rubber chemical accelerators is expected to decrease further.

It is always important to have an accurate diagnosis of cases of suspected occupational hand dermatitis.

After thorough patch testing, culprit allergens can be avoided and appropriate treatment instituted. Cases of persistent dermatitis should be referred to dermatologists for investigation.

## REFERENCES

- Higgins C, Palmer A, Cahill J, Nixon R. Occupational skin disease among Australian healthcare workers: a retrospective analysis from an occupational dermatology clinic, 1993-2014. 2016;75(4):213-22.
- Nixon R, Frowen K, Moyle M. Occupational dermatoses. Aust Fam Physician. 2005;34(5):327-33.
- Cahill JL, Williams JD, Matheson MC, Palmer AM, Burgess JA, Dharmage SC, et al. Occupational skin disease in Victoria, Australia. Australas J Dermatol. 2016;57(2):108-14.
- Adisesh A, Meyer JD, Cherry NM. Prognosis and work absence due to occupational contact dermatitis. Contact Dermatitis. 2002;46(5):273-9.
- Goodier MC, Ronkainen SD, Hylwa SA. Rubber Accelerators in Medical Examination and Surgical Gloves. Dermatitis. 2018;29(2):66-76.
- Lundberg M, Wrangsjö K, Johansson SG. Latex allergy from glove powder--an unintended risk with the switch from talc to cornstarch? Allergy. 1997;52(12):1222-8.
- Politiek K, Oosterhaven JA, Vermeulen KM, Schuttelaar ML. Systematic review of cost-of-illness studies in hand eczema. Contact Dermatitis. 2016;75(2):67-76.
- Augustin M, Kuessner D, Purwins S, Hieke K, Posthumus J, Diepgen TL. Cost-of-illness of patients with chronic hand eczema in routine care: results from a multicentre study in Germany. Br J Dermatol. 2011;165(4):845-51.
- Cortesi PA, Scalone L, Belisari A, Bonamonte D, Cannavo SP, Cristaudo A, et al. Cost and quality of life in patients with severe chronic hand eczema refractory to standard therapy with topical potent corticosteroids. Contact Dermatitis. 2014;70(3):158-68.
- Diepgen TL, Purwins S, Posthumus J, Kuessner D, John SM, Augustin M. Cost-of-illness analysis of patients with chronic hand eczema in routine care in Germany: focus on the impact of occupational disease. Acta Derm Venereol. 2013;93(5):538-43.
- Diepgen TL, Scheidt R, Weisshaar E, John SM, Hieke K. Cost of illness from occupational hand eczema in Germany. Contact Dermatitis. 2013;69(2):99-106.
- Fowler JF, Ghosh A, Sung J, Emani S, Chang J, Den E, et al. Impact of chronic hand dermatitis on quality of life, work productivity, activity impairment, and medical costs. J Am Acad Dermatol. 2006;54(3):448-57.
- van Gils RF, Bosmans JE, Boot CR, Rustemeyer T, van Mechelen W, van der Valk PG, et al. Economic evaluation of an integrated care programme for patients with hand dermatitis. Contact Dermatitis. 2013;69(3):144-52.
- Kersh AE, Helms S, de la Feld S. Glove-Related Allergic Contact Dermatitis. Dermatitis. 2018;29(1):13-21.
- Geier J, Lessmann H, Mahler V, Pohrt U, Uter W, Schnuch A. Occupational contact allergy caused by rubber gloves--nothing has changed. Contact Dermatitis. 2012;67(3):149-56.
- Warburton KL, Bauer A, Chowdhury MM, Cooper S, Krecisz B, Chomiczewska-Skora D, et al. ESSCA results with the baseline series, 2009-2012: rubber allergens. Contact Dermatitis. 2015;73(5):305-12.
- Mortz CG, Jensen E, Madsen JT, Andersen KE. Should carba mix be reintroduced into the European baseline series? Contact Dermatitis. 2016;75(1):48-50.
- Fransway AF, Zug KA, Belsito DV, Deleo VA, Fowler JF, Jr., Maibach HI, et al. North American Contact Dermatitis Group patch test results for 2007-2008. Dermatitis. 2013;24(1):10-21.
- Schwensen JF, Menne T, Johansen JD, Thyssen JP. Contact allergy to rubber accelerators remains prevalent: retrospective results from a tertiary clinic suggesting an association with facial dermatitis. J Eur Acad Dermatol Venereol. 2016;30(10):1768-73.
- Liippo J, Ackermann L, Hasan T, Laukkanen A, Rantanen T, Lammintausta K. Sensitization to thiourea derivatives among Finnish patients with suspected contact dermatitis. Contact Dermatitis. 2010;63(1):37-41.
- Virdi RS, Grover BW, Stroyde D, editors. Novel Room Temperature Safe Accelerator Cure Compositions for use in Synthetic Polyisoprene Latex. 8th International Rubber Glove Conference & Exhibition 2016.

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## ISSUE 10: IN-SERVICE BRIEF THE EVOLUTIONARY RESPONSE TO GLOVE ALLERGIES

### NATURAL RUBBER LATEX ALLERGY - Type I Allergy: IgE Mediated

Immediate – reaction occurs minutes after exposure. Caused by contact with latex proteins. Typically diagnosed with skin prick testing (<30 Minutes) and/or specific IgE blood tests by an allergist.

### ALLERGIC CONTACT DERMATITIS (ACD) - Type IV Allergy: T-Cell Mediated

Delayed type hypersensitivity as the reaction does not occur immediately. Caused by exposure to specific chemical residues. Typically diagnosed with Patch Testing (over 5 days) by a dermatologist.

### IRRITANT CONTACT DERMATITIS (ICD) - Non-allergic

This is a condition affecting the skin, and is not an allergy. Common causes include exposure to wet work, hand hygiene and gloves.

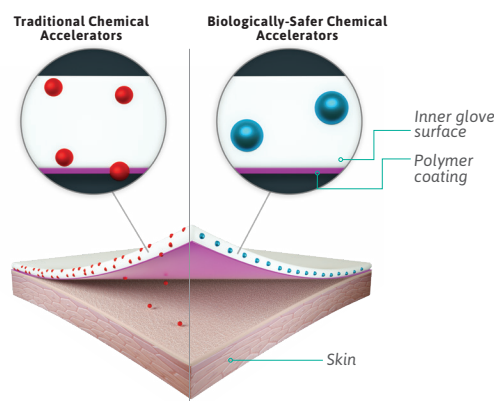
Diagnoses in healthcare workers with occupational skin disease.  
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Total diagnoses <sup>*</sup>	1,068

<sup>\*</sup>Note: patients could have multiple diagnoses

### NEW TECHNOLOGIES

As healthcare workers have transitioned from latex to more synthetic glove use, rubber chemical accelerators are among the most common allergens causing ACD today. As a result, leading glove manufacturers are reformulating gloves in order to reduce allergy risk. Biologically-safer accelerators that leave no residue or reduce residue from passing through the glove are being used to lower the risk.



Unlike traditional chemical accelerators which may not remain in the glove, biologically-safer rubber accelerators are known to either be completely consumed during production or remain within the glove film.



#### REFERENCES

- Higgins C, Palmer A, Cahill J, Nixon R. Occupational skin disease among Australian healthcare workers; a retrospective analysis from an occupational dermatology clinic, 1993-2014. 2016;75(4):213-22.

It is always important to refer to a dermatologist for persistent cases of dermatitis. After thorough history taking and patch testing, culprit allergens can be avoided and appropriate treatment and avoidance instituted.

Please read InTouch Clinical Update Issue 10 - THE EVOLUTIONARY RESPONSE TO GLOVE ALLERGIES: A CURRENT DERMATOLOGY REVIEW for more information on this topic.