Chemical Residues in Surgical Gloves

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Introduction

The wearing of surgical gloves for avoidance of cross infection between surgical staff and patient remains an essential practice of operating theatre routine. Over the years the quality, ease of donning and comfort of gloves has improved and with it the safety to both wearer and patient. From the first reusable, industrial quality, natural rubber gloves which were donned over wet hands, to the thinner, single-use powdered gloves, to the current-day powder free versions, the hazards associated with glove use have been progressively reduced if not totally eliminated. These hazards relate to patients and glove wearers and encompass reduction in wearer dexterity/sensitivity of touch, breakdown of barrier protection, patient tissue contamination, wearer skin irritation, and patient and wearer allergic responses.

Before the emergence of latex protein allergy as a concern for healthcare workers in the late 1980s/early 1990s, the dominant adverse issues with the wearing of natural rubber latex (NRL) surgical gloves were the incidence of allergic contact dermatitis and the effects of glove powder contamination of surgical sites leading to the formation of adhesions/starch granuloma. The cause of the dermatitis was largely the presence of residual chemicals used in the curing process and remaining in the gloves post manufacture. Steps taken to minimise residual protein levels in NRL gloves, (additional washing and/or chemical treatments), had the benefit of also reducing residual levels of harmful chemicals in the gloves. At the same time manufacturers were encouraged to produce gloves made from alternative materials to natural rubber latex and in consequence introduced new curing systems with a range of new chemical additives. These have given rise to further incidence of contact allergy amongst glove users. Indeed, according to a 2008 latex allergy report by the Royal College of Physicians, changing to latex alternatives may only substitute one set of problems for another[1].

In order to understand the background to these developments and the steps taken by manufacturers to minimise or avoid the potential hazards to glove wearers, we need to explore the mechanics of glove manufacture and the technologies available to optimise user safety.

The role of chemicals in glove manufacture

Generally, glove materials are polymers which are long chain molecules made up of repeating smaller (monomer) units (Figure 1).

Figure 1. Monomer and polymer chains

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To turn the raw polymer into a material having the required strength and elasticity for a glove, requires chemical bonds to be formed between polymer chains, often referred to as cross linking (Figure 2).

Figure 2. Drawing of crosslinked polymer chains

For most common glove materials this need the addition of chemicals to both take part in the reactions and/or to speed up the reactions, (accelerators), and/or to stabilise the product against chemical breakdown, (antioxidants). Other additives such as surfactants, pigments and fillers may also be used to provide the desired product properties.

Role of chemicals

Accelerators - to speed up reaction
Antioxidants (and accelerators) - to improve shelf-life
Soap/surfactant - to help mix ingredients and stabilise the system
Pigments - to improve appearance

Residual levels of many of these chemical agents have the potential to cause contact irritation or allergic response (Picture 1) in the skin of the glove user.

Picture 1. Allergic contact dermatitis or type IV allergy

The manufacturer has a few options for minimising the likelihood of such effects by either choosing ingredients with low irritant/allergenic potential, minimising residual levels of the chemicals by removing excess in a washing process or making the residual chemicals difficult to extract by binding them to the polymer to reduce bioavailability. Reducing residual levels has the disadvantage that resistance to degradation (breakdown) may be reduced and hence shelf life diminished.

Historically allergic contact dermatitis to chemicals amongst surgical glove users was a known but limited problem. The emergence of the AIDS pandemic in the 1980s leading to Universal Precautions and the widespread wearing of examination gloves amongst all healthcare workers increased the population exposure to these allergens. The rapid increase in availability of examination and surgical gloves made from man-made materials to avoid NRL protein allergy reactions, led to use of new formulations having higher levels of potentially allergenic ingredients and this spread the problem to the Surgical arena.

Complete avoidance of use of chemical crosslinking agents by use of polymers that do not require them is possible but has disadvantages. The possible options and their drawbacks are discussed in detail later in this paper.

Natural Rubber

Considering first the composition of the most common type of surgical glove, natural rubber, (NR) manufactured by dipping natural rubber latex (NRL). NRL is produced as a milky aqueous dispersion, of rubber particles by the Hevea brasiliensis tree (Figure 3).

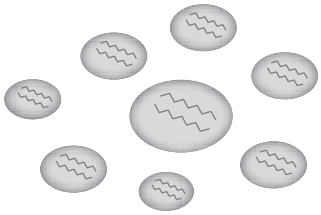
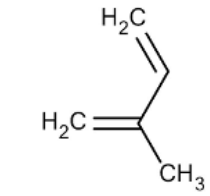
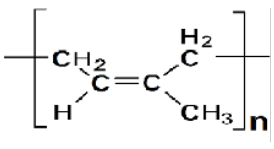


Figure 3. Natural rubber dispersion with polymer chains within the particles

Natural rubber is a polymer of cis-polyisoprene. Each rubber particle contains tangled chains (polymers) of isoprene rubber molecules (Figure 4).



Isopropene monomer



Polyisoprene (PI) or Natural Rubber

Figure 4. Chemical structures of isoprene and polyisoprene/ natural rubber

The raw latex extracted from the tree is processed in the field to produce the stabilised NRL which is supplied to the glove manufacturing plant. Figure 5 shows the steps necessary to make the quality standardised product that the manufacturer relies upon to produce a consistent product.

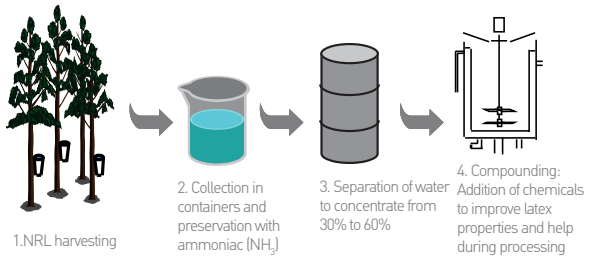


Figure 5. Natural rubber latex production

If this raw material was used to make a glove it would not have the physical properties required and would not be fit for purpose. In order to provide the requisite strength and elasticity it is necessary to introduce links between the polymer chains. This is achieved in a process known as vulcanisation in which sulphur bonds are introduced. In this process zinc, sulphur and accelerator, link with one polymer chain via a double bond. The sulphur then links to a second polymer chain and releases the accelerator which is constantly recycled and does not become part of the polymer structure (see Figure 6).

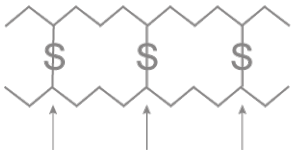


Figure 6. Sulphur bridges inserted between polyisoprene chains

Vulcanisation can be controlled to give:

- High strength
- High elasticity (stretchiness)
- Greater comfort (lower modulus/greater softness)

Historically the most common accelerator groups used have included:

- thiurams,
- dithiocarbamates (DTCs)
- and mercaptobenzothiazoles (MBTs).

Of these, dithiocarbamates are currently the most commonly used.

Synthetic Rubber

There are several synthetic rubbers available which have been used in commercial manufacture of medical gloves. These are elastomeric materials which have varying degrees of elasticity and hardness in relation to natural rubber. A list of commonly used materials and their properties/usage is shown in Table 1. Based on consideration of user comfort, and durability, synthetic surgical gloves based on PI and CR are the most commonly commercially available. While rarely used in surgical glove manufacture, nitrile and polyurethane are also sometimes used as coatings for natural rubber surgical gloves.

Common accelerators used in addition to the above for curing synthetic polymer gloves include:

- Thioureas (DPTU)
- Guanidine's (DPG).

Table 1. Glove materials and common usage

		Common glove use	
Material	Summary	Surgical	Examination
Natural rubber, (NR)	Gold standard for fit feel comfort and barrier properties Residual protein and accelerators may cause allergic response	Yes	Yes
Synthetic rubber, (PI, IR)	Very close to NR in properties Residual accelerators may cause allergic response	Yes	No
Nitrile	Soft and commonly used as exam glove Tendency to stress relax in use leading to distortion (finger flop) and catastrophic tearing Residual accelerators may cause allergic response Accelerator-free formulations are available	Rarely alone, but more often as a coating	Yes
Polychloroprene, Neoprene, (CR)	Homopolymer relatively stiff. Copolymer very close to NR Residual accelerators may cause allergic response Accelerator-free formulations are available	Yes	Yes
Block copolymers, (SIS,SBS etc)	Less comfortable than NR. Poor resistance to temperature, bone cement and sometimes alcohols	Yes	Yes
PVC	Relatively stiff and inelastic. More used as exam gloves Puncture resistance relatively poor Residual phthalate plasticisers are of concern	No	Yes

Adverse effects of rubber chemicals

Dermal reaction to residual chemicals present in medical gloves have been reported over many years in variable rates of prevalence. The effects are summarised in Table 2.

Table 2. Reactions to glove chemicals

Type of reaction	Sensitisation stage required	Delayed reaction	Localised reaction	Symptoms
Dermal Irritation	no	no	yes	Red itchy skin
Type IV delayed allergic contact dermatitis	yes	yes	yes	Dry red, itchy, swollen and blistered, skin

Such reactions are possible with gloves made of any material whose manufacture involves use of chemical additives at any stage of the manufacturing process. Factors which contribute to the risk of reaction include:

- the concentration and ease of extraction of the chemicals
- the duration and frequency of skin contact with gloves
- the confined moist conditions of extended glove use

Contact dermatitis amongst repeated glove wearers has several contributing factors including:

- frequent hand washing and disinfection
- exposure to harsh chemicals and poor hand hygiene

The UK Royal College of Nursing[2] listed the possible contributors to skin problems as being:

'Glutaraldehyde, acrylates and methacrylates, biocides, anti-bacterials, preservatives or disinfectants, formaldehyde and its resins, soaps and detergents, antibiotics and other pharmaceuticals and therapeutic agents. There is also a general category of any other known irritant or sensitising agent including, in particular, any chemical bearing the warning 'may cause sensitisation by skin contact' or 'irritating to the skin'.'

More recently they updated this list to specifically include chemical accelerator exposure through glove use[2].

Diagnosis of skin allergy to particular classes of chemicals is usually by skin patch test against groups of allergens. These for glove wearers are usually some or all of the following groups of chemicals classified by dermatologists:

- Thiuram mix
- Carbamix
- Mercaptomix
- Black rubber mix

Table 3 lists the range of chemicals that have been published as relevant to glove manufacture[4]. Of these thiurams have been used as stabilizers for field latex and as vulcanising agents for many years but due to allergy concerns their use in surgical gloves has largely been discontinued. They may still be used in the field in small quantities and may possibly be formed in processing using the still favoured dithiocarbamate (DTC) accelerators. The latter along with mercaptobenzothiazoles (MBTs), are still widely used. The first commercialised formulations of synthetic polyisoprene and nitrile rubber used combinations including guanidines and thioureas, as conventional dithiocarbamate mixtures proved to be less effective. Widespread use of Diphenylguanidine (DPG), led to reported increases in incidence of allergic responses[3] and brought renewed focus on the issue both in Europe and the USA.

Table3. Relevant contact allergens in medical gloves[4]

Chemical name	Reference
Mercaptobenzothiazole and derivates	
2 Mercapthobenzothiazole (MBT)	Gisbau[5]
Zinc 2-mercaptobenzothiazole (ZMBT)	Rose[6]
2,2morpholinothio)benzothiazole; (MOR, MBS)	Gisbau
2,2'Dithiobis(benzothiazole) (MBTS)	Gisbau
N-cyclohexyl-2-benzothiazolesulfenamide (CBS)	Gisbau
Dicyclohexylbenzothiazolesufenamid (DCBS)	Gisbau, Rose
	Gisbau
Dithiocarbamates	
Zinc diethyldithicarbamate (ZDEC)	Gisbau, Rose
Zinc dibutyldithiocarbamate (ZDBC)	Gisbau, Rose
Ziram, Zinc dimethyldithiocarbamate (ZDMC)	Gisbau, Rose
Zinc bis (N-ethyl-N-phenyldithiocarbamate) (ZEPC)	Gisbau
Zinc Pentamethylenedithiocarbamate (ZPD)	Gisbau
Zinc dibenzyldithiocarbamate (ZBEC)	Gisbau
Sodium Dibutyldithiocarbamate (SDBC)	Gisbau
Cyclohexyl ethyldithiocarbamate (SHEC	Gisbau
Thiurams	
Tetramethylthiuram Monosulfide (TMTM)	Gisbau, Rose
Disulfiram; Tetraethylthiurame Disulphide (TETD)	Gisbau, Rose
Tetramethylthiurams Disulfide (TMTD)	Gisbau, Rose
Dicyclopentamethylenethiuram Disulfide (DPTD)	Gisbau, Rose
Thiourea combinations	
N,N'-Dibutylthiourea (DBTU)	Gisbau, Rose
N,N'-Diethylthiourea (DETU)	Gisbau, Rose
N,N'-Diphenylthiourea (DPTU	Gisbau, Rose
Other additives	
1,3-Diphenylguanidine (DPG)	Gisbau, Rose
1,2 Benzisothiazolinone (BIT)	Rose
2-Mercaptobenzimidazole (MBI)	Gisbau
4,4'-thiobis (6-tert-butyl-meta-cresol)	Rose
Butylated hydroxyanisole (BHA)	Rose
Cyclohexylthiophthalimide (CTP)	Gisbau

Market approach to improving glove safety

The relevant Product Standard, ENISO 10993[7] recognised by the European Union and the United States Food and Drug Administration (USFDA) prescribes safety testing to determine sensitisation and irritancy potential to eliminate poor quality, unsafe products.

However, there is a potential risk that residual chemicals can move to the surface of the glove in storage and result in a product which is less safe to the wearer.

Manufacturers have therefore sought to minimise exposure of users to chemicals in their products by removing excess chemical at the end of the manufacturing process or making residual chemical harder to extract. Complete removal of residual accelerator chemical has the disadvantage that storage stability of the glove is reduced, leading to reduced shelf-life.

At one time it was possible to demonstrate the safety of a product by undertaking human patch testing of a panel of 200 volunteers, (the modified Draize or Shelanski test). Because such tests cannot screen for potential latex protein allergy, they are not used for NR gloves.

More recently the FDA have defined alternative 25-person, patch tests that are conducted on sensitised individuals to support claims of 'low chemical allergy potential'. Due to the difficulty in recruitment of such sensitised panels and the low threshold for provocation of reaction these tests are rarely used, however.

The universal move to powder free surgical gloves has meant that powder free processes have generally reduced residual levels of extractable chemicals. However, the rapid increase in synthetic glove use to avoid NRL protein allergy has led to use of new formulations incorporating higher levels of chemicals with potential to cause allergy. In turn manufacturers have sought to modify their processes and ingredients to minimise bioavailability of residual chemicals. We can consider how these improvements have been achieved under the headings of

A. 'Modified/improved processing',
B. 'Novel processes', and
C. 'Accelerator-free formulation'.

A. Modified/Improved Processing

The glove wearer can only have an allergic response on contact with the glove if the allergenic chemical can be released from the polymer and interact with the skin, i.e. become 'bioavailable'.

Conventional natural rubber vulcanisation is often carried out in two stages known as pre-vulcanisation and post-vulcanisation the terms differentiating between the stages of the manufacturing process that the crosslinking process is carried out.

Pre-vulcanisation occurs within particles of rubber while it is still in the form of a water dispersion (i.e. as latex).

Figure 7. Crosslinked chains in particles

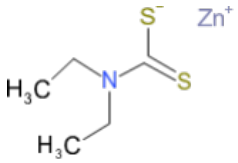
If further vulcanising chemicals are then added to the latex and a glove is formed by dipping and then heated in an oven, post-vulcanisation occurs,

If some degree of pre-vulcanisation is used therefore the residual chemicals can become bound up in the rubber particles and therefore not bioavailable to the glove wearer. They are more resistant to aqueous extraction but can be extracted by organic solvents such as ethanol, acetone acetonitrile etc. Some manufacturers claim to have proprietary washing processes which minimise levels of bioavailable accelerator and are then able to support these claims with data on extractable residues. Care should be taken in evaluating such data however to ensure that the extraction and assay methods used are appropriate and valid.

B. Novel processes

The idea that the accelerator can be locked into the rubber matrix has been taken up by accelerator manufacturers who have developed dithiocarbamates based on much longer alkyl chains so that they are bound into the rubber matrix regardless of the stage of vulcanisation. See Figure 8 for comparison of chain length between dithiocarbamates (ZDEC and ZDNC).

Zinc diethyldithiocarbamate (ZDEC)
$\{(CH_3CH_2)_2NC(S)\ S\}\ Zn$



Zinc diisononyldithiocarbamate (ZDNC):
$\{(CH_3CH_2\ CH_2\ CH_2\ CH_2\ CH_2\ CH_2\ CH_2)_2NC(S)\ S\}Zn$

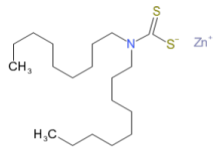


Figure 8. Comparison of chain length between ZDEC and ZDNC

The extended chain length of the ZDNC offering a far greater opportunity for entanglement with the polymer chain, and its high solubility in rubber prevents migration from the bulk of the rubber. Used in combination with the co-accelerator diisopropylxanthogen polysulphide, (DIXP) which is totally consumed in the vulcanisation process, the system is claimed to be able to provide gloves based on natural rubber latex, deproteinised softer NRL, and synthetic polyisoprene rubber which have extremely low levels of bioavailable accelerator.

The first synthetic polyisoprene gloves which came to market were formulated with diphenyl guanidine DPG which led to reports[8] of increased allergy amongst users. This was probably related to widespread use of DPG in nitrile examination glove formulations, use of which increased rapidly in the 1990s and lead to sensitisation amongst many healthcare workers. Because of this DPG is now much less commonly used.

C. Accelerator-free formulation

Currently the only surgical glove which is vulcanised without the use of accelerators is that based on polychloroprene. Most synthetic rubbers were first vulcanised using conventional curing systems as used for natural rubber. The AIDS crisis of the 1980s led to a huge increase in demand for NRL examination gloves. The subsequent development of latex allergy meant that alternative synthetic gloves were needed, and their widespread use led to chemical allergy problems. This resulted in the increased demand for accelerator-free gloves. This meant that neglected methods were soon rediscovered and adapted to produce accelerator-free versions of examination gloves. Thus 'nitrile' examination gloves are widely produced using a metal oxide cure and accelerator-free neoprene surgical gloves are produced using a similar process. While this process cannot be directly used for natural rubber latex, manufacturers are working on blends of polymers which might provide an accelerator-free product that compares favourably with the properties of NR. Natural rubber products having nitrile, neoprene or polyurethane internal coatings have also been developed as potentially more skin friendly offerings, without being able to claim accelerator-free.

The quest for an accelerator-free process for natural and synthetic polyisoprene remains a priority as no synthetic alternative has yet been developed with the unique blend of fit, feel, comfort and barrier properties that these materials provide. Many processes have been investigated and there are many Patent filings of ideas which have as yet failed to achieve commercialisation. The reasons for lack of progress is undoubtedly financial in that the increased complexity of novel processes and the high cost of development and production cannot be matched by the market need at the higher price point that would be required. While it can be demonstrated that low levels of extractable chemicals do not lead to sensitisation, most glove wearers will be perfectly happy with current offerings. Those who are already sensitised can choose from a number of existing products on the market until they find one which they can tolerate.

Meeting Customer expectations

Glove users have found it difficult to obtain definitive information on the chemical composition of gloves and have not been able to fall back on International Standards to obtain reassurance on residual levels of potential allergens. While some manufacturers of surgical gloves have sought to support their products with technical information this has not been universally the case. The European Glove standard EN455[9] defines requirements for freedom from holes, physical properties, extractable protein, and product shelf life. It does not yet cover residual chemical allergen content. This has meant that manufacturers are free to make claims about residual chemical levels based on non-standardised tests that have not been validated as being appropriate or meaningful.

For example, examination glove manufacturers rely on a method which requires extraction for an extended period with boiling water. Results of this test are meaningless as they invariably record no residual chemical. However there is no evidence that the method extracts the chemicals or that they are stable to such extreme conditions!

This situation is being addressed however by the European Standards working group. The upcoming revision of part 3 of the standard introduces the need for labelling to indicate the presence of Type IV chemical allergens to comply with the EU Medical Device Regulations. Moreover, a new part 5 of the standard on 'Extractable chemical residues' is under development. While this is still a work in progress it is intended that it will specify the information manufacturers are required to provide on the chemical composition of their gloves, and the extraction and assay procedures to be followed in providing information on residual extractable chemical content. Thus, glove buyers and users carrying out their risk analysis on glove use, will have access to meaningful data on the bioavailable chemical content of products allowing informed choice of which are the most appropriate to the safety of users.

While products may be emerging which demonstrably have no residual extractable chemicals, they may potentially have disadvantages in their physical properties and cost, which limit their wider use. It is likely to be some time before universally acceptable products become readily available to the wider market.

References:

1. Royal College of Physicians Latex Allergy: Occupational aspects of management 2008. https://www.rcplondon.ac.uk/file/25/download
2. Royal College of Nursing, "Tools of the Trade". Guidance for health care staff on glove use and the prevention of work-related contact dermatitis. https://www.rcn.org.uk/-/media/royal-college-of-nursing/documents/publications/2020/may/009-109.pdf?la=en
3. Ponten, Hamnerius, Bruze, Hanssen, Persson, Svedman, Andersson and Bergendorff, Contact Dermatitis, 2012, 68,103-110.
4. Bergendorff O, Communication via TC 205 WG3
5. Gisbau: BG BAU Allergen, https://www.bgbau.de/themen/sicherheit-undgesundheit/gefahrstoffe/gisbau/allergene-in-schutzhandschuhen/allergenliste/
6. Rose R F, Lyons P, Horne H, Wilkinson S M. A review of the materials and allergens in protective gloves. Contact Dermatitis 2009, 61, 129-137
7. EN ISO 10993-1:2020 Biological evaluation of medical devices
8. Ponten, Hamnerius, Bruze, Hanssen, Persson, Svedman, Andersson and Bergendorff, Contact Dermatitis, 2012, 68,103-110
9. EN 455 - Medical gloves for single use.

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