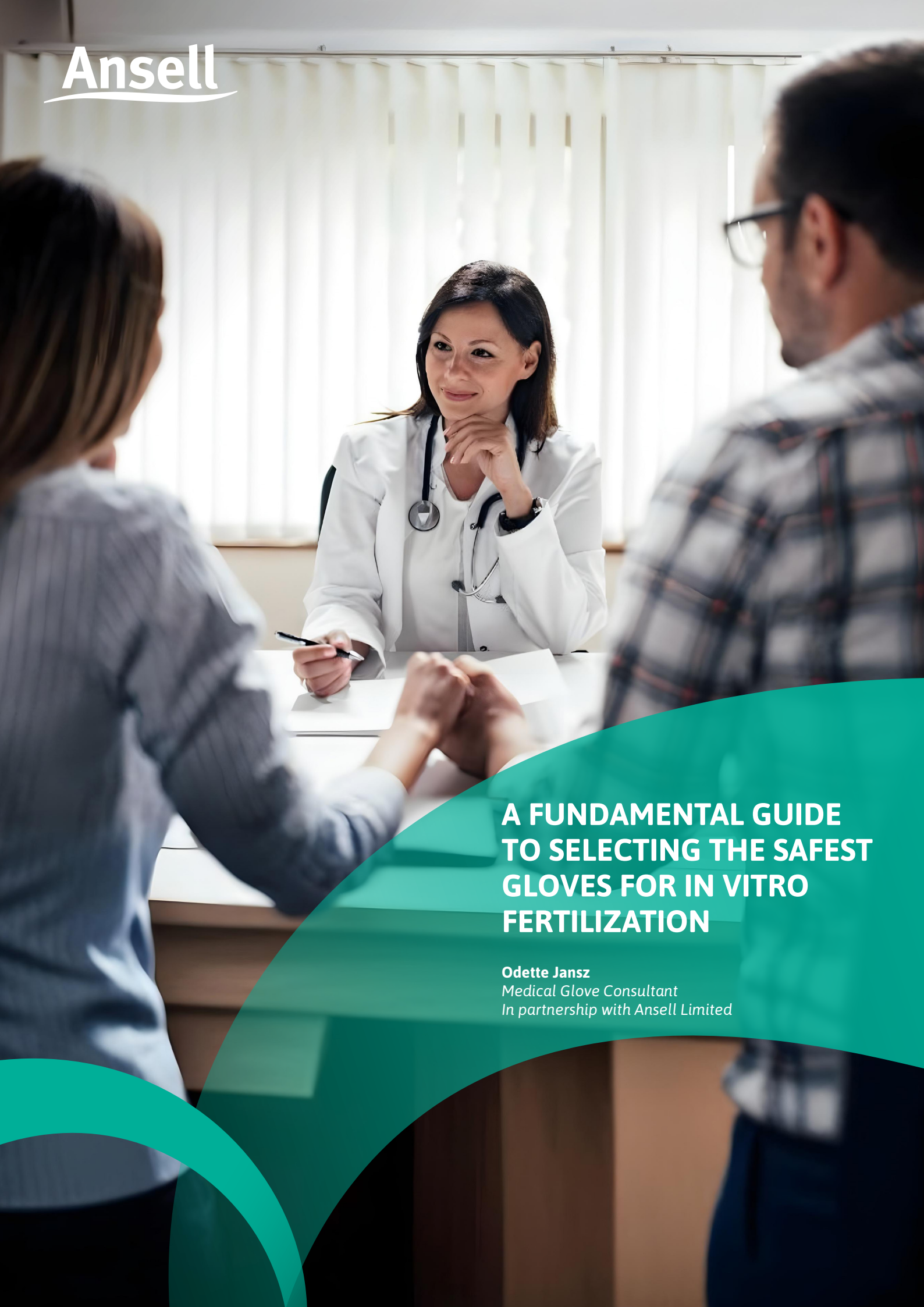

A FUNDAMENTAL GUIDE TO SELECTING THE SAFEST GLOVES FOR IN VITRO FERTILIZATION

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WHAT YOU SHOULD KNOW WHEN SELECTING MEDICAL GLOVES TO SAFEGUARD STAFF WITHOUT JEOPARDIZING IVF OUTCOMES

INTRODUCTION

Glove use is ubiquitous in the medical industry and is an essential personal protective equipment (PPE) requirement to protect both staff and patients. The use of gloves in fertility clinics and embryology labs is fundamental to protecting staff from exposure to pathogens and harmful chemicals or reagents while also preventing contamination to eggs, sperm and embryo cultures throughout the in vitro fertilization (IVF) journey *(Figure 1 on page 6)*.

There is evidence some medical gloves, sterile and non-sterile, may contain reprotoxic substances that could leach during use, proving detrimental to gametes (sperm or eggs) and embryos. Reprotoxic substances are defined as agents that may adversely affect human reproductive function or damage the reproductive process. The raw materials used in the production of gloves range from natural rubber latex (NRL) or synthetic rubbers such as nitrile butadiene rubber (or simply, nitrile), polyisoprene (PI), and polychloroprene (neoprene). Chemicals such as vulcanising accelerators are typically included to speed up the manufacturing process. Some of the accelerators added include thiurams, dithiocarbamates (DTCs), mercaptobenzothiazoles (MBTs) and diphenylguanidine (DPG). Known to leach through gloves, these standard chemical accelerators may be one of the possible reprotoxic substances.[1,2]

Limiting exposure to reprotoxic agents may help reduce risks to IVF outcomes. It is critical for medical facilities, particularly those involved in reproductive medicine, to carefully select gloves not containing potential reprotoxic substances such as harmful chemical accelerators, or to investigate alternate glove materials to optimize IVF success rates and staff/patient safety.

It is important to remember that the use of gloves is just one aspect of the equipment used in IVF labs or clinics. Other equipment such as pipettes, petri dishes, catheters plus the broader protocols and practices put in place to maintain a conducive and sterile environment, are also factors that contribute to the overall success of fertility treatments.

ARE ALL CHEMICAL ACCELERATORS IN GLOVES REPROTOXIC?

Chemical accelerators are used by many manufacturers of synthetic and NRL gloves to provide elasticity and allow for cross-linking to enable film strength – two key performance attributes sought by glove wearers for comfort and protection.

Dependent on the residual amount remaining on the finished product, the leaching of some chemical accelerators through the glove film could lead to negative outcomes on gametes and embryos resulting in poorer fertilization, embryo development and embryo implantation rates.[1,2] Reprotoxic substances are known to be readily transferred by touch and during brief contact with equipment[2,3,4] such as the embryo transfer catheter. This is particularly relevant as gloves are the required PPE worn at oocyte collection, sperm preparation and embryo transfer.

Standard chemical accelerators and additives including thiurams, phthalates, DPG, MBTs, DTCs such as Zinc Diethyldithiocarbamate (ZDEC) and Zinc Dibutyldithiocarbamate (ZDBC) are known to leach through the glove film during use and may be reprotoxic.

Not all chemical accelerators leach through gloves. Some advanced chemical accelerators such as Xanthates will completely vaporize during the vulcanisation process while others like Zinc Dialkyldithiocarbamate (ZDiNC), with long side chain structures, remain within the glove film during use to result in biologically-safer gloves with minimal contact possibilities. ZDiNC has been approved by the German BfR (Bundesinstitut fur Riskikobewertung: Federal Institute for Risk Assessment) and recommended for the manufacture of baby teats and toys.[5]

While MBT accelerators are known as contact allergens, standard DTC accelerators have been reported to show strong cytotoxicity, again, dependent on their residual amount.[2] Understanding the profile of the chemical accelerators used in gloves helps avoid contact with reprotoxic substances to minimize any associated risks to IVF outcomes.

The selection of 100% chemical accelerator-free gloves or gloves made only with advanced, non-reprotoxic chemical accelerators are safer options for consideration by IVF clinics and labs. In addition, as standard chemical accelerators account for up to 45% of (the top 25) allergens tested for delayed-type skin allergies,[5] these options help optimize staff protection against glove-related Type IV chemical allergies that, at its worst, may be career-ending for some.

OTHER RISKS TO IVF OUTCOMES ASSOCIATED WITH GLOVES

Evidence shows that some gloves are more reprotoxic than others *(Table 1)*[2] and this could be due to several possibilities. Reprotoxic substances could originate from any one or a combination of parameters ranging from the glove formulation including the use of standard chemical accelerators, the glove material itself, the production process, as well as how a product is sterilized.[1]

A literature review reveals the diversity of factors that may influence the presence of reprotoxic substances in gloves other than chemical accelerators. Below are some key findings.

- **NRL gloves demonstrate high incidence of toxic responses** based on bioassays conducted with sterile and non-sterile powder-free surgical, cleanroom and examination gloves *(Table 1)*.[1, 2, 4]
  - Sperm exposed to NRL gloves showed no survival even after 1 minute[1, 3]; while toxic substances on NRL material were readily transferred by touch.[1, 2]
  - Another study attributed the stretching of NRL gloves (which happens upon donning) to the release of contaminants and odors that may be toxic to gametes and embryos.[7]
  - Radiation vulcanized NRL materials are considerably less toxic than sulphur-vulcanized materials.[2]

Table 1: Biological response of cell viability (using mouse fibroblasts) to extracts of glove material expressed in relative values of toxicity[2]

	NRL Gloves				Synthetic Gloves					
Level of Toxicity	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**
Strong	✓	✓	✓	✓	✓	✓				
Moderate										
Slight									✓	
None							✓	✓		✓

NOTE: *Toxicity of 4 NRL and 6 synthetic gloves were rated based on cell viability relative to controls as severe, moderate, slight or not cytotoxic, where activity relative to controls were <30%, between 30 and 60%, between 60 and 90% and >90% respectively. Results use the Lysis index to indicate the degree of toxicity to cell membranes.*

- **Synthetic gloves show diverse toxicity results** attributed to their different composition of materials or formulations.
  - Nitrile gloves are manufactured from three monomers; acrylonitrile, butadiene and any one of many carboxyl acids. The differences in toxicity could be due to the different stabilizers or chemical accelerators needed for the different material compositions.[1]
  - Some PI gloves have also shown to be reprotoxic and may be attributed to their formulations and production processes.[1]
  - There are however, nitrile, polychloroprene and PI gloves, proven via bioassays such as Mouse Embryo Assays (MEA) and Human Sperm Motility Assay (HuSMA), to be safe for IVF use. This may due to their chemical accelerator-free formulations or the inclusion of advanced chemical accelerators such as Xanthates and ZDiNC.

- **Powdered NRL gloves are more toxic than non-powdered gloves.** The use of talcum powder and corn starch in powdered gloves are proven to be toxic to embryo development. In one study, where talcum-powdered gloves were tested, only 6.6% of embryos reached the blastocyst stage. When the same gloves were rinsed with sterile distilled water and air-dried, 56.1% embryos reached the blastocyst stage.[3]
  - Additionally, when powdered gloves are donned or removed, the released particles may heighten contamination risks to culture specimens.[6]

- **Sterilizing with Ethylene Oxide (EtO) gas leaves behind ethylene glycol, a residue known to be highly toxic to cells[8]**
  - EtO is found on the binding values limit list of 41 carcinogenic, mutagenic, and reprotoxic agents provided by the European Agency for Safety and Health at Work (OSHA Europe) pursuant to Directive 2004/37/EC.[9]
  - Gloves sterilized by gamma irradiation are not known to leave behind toxic residues.

ALWAYS VALIDATE A GLOVE FOR SAFE IVF USE WITH A BIOASSAY SCREENING TO ASSESS FOR POTENTIAL REPROTOXICITY

Given the diversity of influences impacting on the reprotoxic profile of a glove, all gloves used in IVF clinics and labs should undergo a bioassay screening to ensure it is safe for use. Bioassays help reveal the toxicity of items such as gloves, pipettes, culture dishes and catheters that come into contact, directly or indirectly, with gametes and embryos.

Not all consumables undergo reprotoxic screening with bioassays. IVF labs and clinics who insist on a 'first pass' screening (from their device manufacturers) for reprotoxic substances using bioassays will provide staff with quality assurance and a higher degree of user and usage confidence.

What are the relevant bioassays available?

Of the many different in vitro and in vivo bioassays available to labs and glove manufacturers for reprotoxicity testing, the in vitro Mouse Embryo Assay (MEA) and Human Sperm Motility Assay (HuSMA) are most referenced by researchers as they offer sensitive detection of possible embryotoxicity and serve as a reliable and objective quality control (QC) measure independent of clinical factors.[1, 4]

- MEA and HuSMA can either be used on their own or in combination to provide double quality control as these assays are both complementary and confirmative of each other.[1, 4]

Some quality requirements and guidelines upholding importance of bioassays

- **US FDA require the MEA test** to be carried out in culture, media and consumables used for IVF (FDA, 1998).
- **EN ISO 10993-Part 5:** Biological evaluation of medical devices require testing for in vitro cytotoxicity.
- **The European Society of Human Reproduction and Embryology (ESHRE)** require confirmation that all media/reagents/disposables are tested for quality using appropriate bioassays whenever possible.

GLOVES MUST FULFIL THEIR PRIMARY ROLE TO PROTECT

The fundamental role of gloves in a healthcare environment is to provide protection to both staff and patients. This role goes deeper than human skin when used in fertility labs and clinics where importance is also placed on the successful pregnancy outcomes for couples seeking IVF treatment *(Figure 1)*.

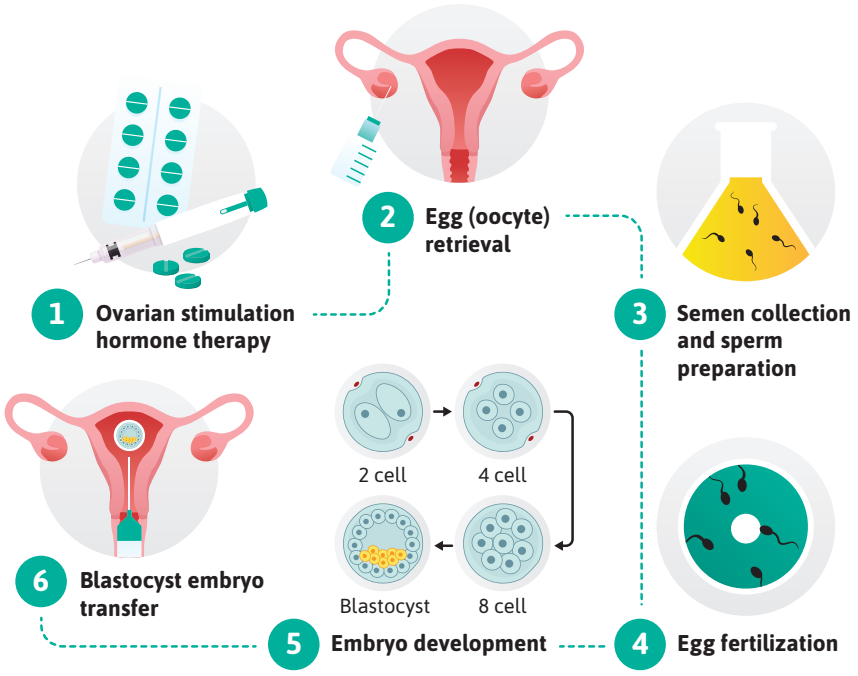
While there should be no risk of reprotoxic substance exposure to gametes and embryos, good barrier protection helps prevent cross-contamination, reducing the risk of infections from exposure to blood and bodily fluids, while ensuring reproductive materials are handled under controlled and sterile conditions to prevent contamination of sperm, eggs and embryo culture.

Figure 1: The role of gloves during IVF treatments

IN VITRO FERTILIZATION

Protecting Staff

- Prevents exposure to potentially contaminated semen and follicular fluids
- Provides barrier protection to prevent exposure risk from harmful substances such as chemicals and reagents used for sperm preparation, egg retrieval and embryo culture



Protecting IVF Outcomes

- Prevents exposure to reprotoxic substances known to negatively affect sperm, eggs and development of embryos
- Maintains sterility to prevent contamination of sperm, eggs and embryo culture

In fertility labs and clinics, sources of infection are most commonly patients and/or staff, and less frequently the immediate environment and instruments used. Staff are exposed to semen and follicular fluid which can be potentially infected with Hepatitis B (HBV), Hepatitis C (HCV) and Human Immunodeficiency Virus (HIV).[10]

HBV infection is the most common lab-acquired infection. The risk of lab workers being infected with HBV is approximately 10-fold that of the general public; and almost 3-fold that of other hospital employees.[11]

Additionally, gloves used by lab staff must also provide excellent chemical protection to protect them from exposure to various chemicals and reagents used for procedures such as sperm preparation, egg retrieval, and embryo culture.

Fundamental principals for glove quality must be considered to fulfil its primary role to protect. **Medical gloves should not lead to the development of Type I latex or Type IV chemical allergies; should not tear, puncture or rupture easily upon donning or during use; while providing optimal protection of freedom from pinholes or micro perforations by ensuring Acceptable Quality Levels (AQL) set for sterile and non-sterile gloves are met *(Table 2)*.**

Table 2: International Surgical and Examination Glove Standards for AQL

Surgical Glove Standards	AQL	Examination Glove Standards	AQL
ASTM D3577	1.5	ASTM D3578 ASTM D6319 ASTM D6977	2.5
EN 455-1	0.65	EN 455-1	1.5
ISO 10282	1.5	ISO 11193	2.5
Ansell surgical gloves are manufactured to an AQL of 0.4 - 0.65 (Meeting or exceeding recommendations set by ASTM, EN & ISO)		**Ansell examination gloves are manufactured to an AQL of 1.5 (Meeting or exceeding world standards of 1.5 - 2.5)**	

CONCLUSION

Professionals involved in IVF, more than any other medical care providers, must be aware of potential risks associated with gloves. The presence of reprotoxic substances known to harm gametes and embryos may destroy the hopes and dreams of couples pursuing parenthood.

Chemical accelerators that leach through gloves are just one of the reprotoxic substances possibly found in gloves. All possible origins of reprotoxic substances as well as cross contamination should be considered, and avoided, when reviewing the selection of a glove for safe use in IVF fertility labs or clinics.

- **Avoid gloves made with standard chemical accelerators** including MBTs, ZDEC and ZDBC, known to leach through the glove film that may be considered harmful to gametes and embryos. These same chemical accelerators may also be allergens leading to a Type IV chemical allergy.
  - **For peace of mind:** Consider gloves using only advanced chemical accelerators such as Xanthates and ZDiNC known to minimize contact possibilities.
  - **For complete peace-of-mind:** Avoid chemical accelerators entirely by using 100% chemical accelerator-free gloves.
- **Avoid NRL gloves** given this material's high toxicity risk to sperm and embryos.
- **Avoid powdered gloves** using ingredients such as corn starch or talcum powder.
- **Avoid gloves sterilized with EtO** as it leaves behind a highly toxic residue. Consider gloves sterilized by gamma irradiation instead.
- **Avoid poor quality gloves** that tear or puncture easily or that do not meet the minimum AQL to minimize the risk of staff and patient infections from cross-contamination; or, contamination of gametes and embryos.

While these basic tenets of avoidance should be considered, bioassay screenings such as MEA and HuSMA are an effective quality control measure acting as a first line of assurance against potentially harmful reprotoxic substances.

Always talk to your glove manufacturer to better understand their glove formulations, use of chemical accelerators and the production processes to make safer glove choices for IVF use.

For more information about our skin-friendly gloves, please contact your Ansell representative.

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