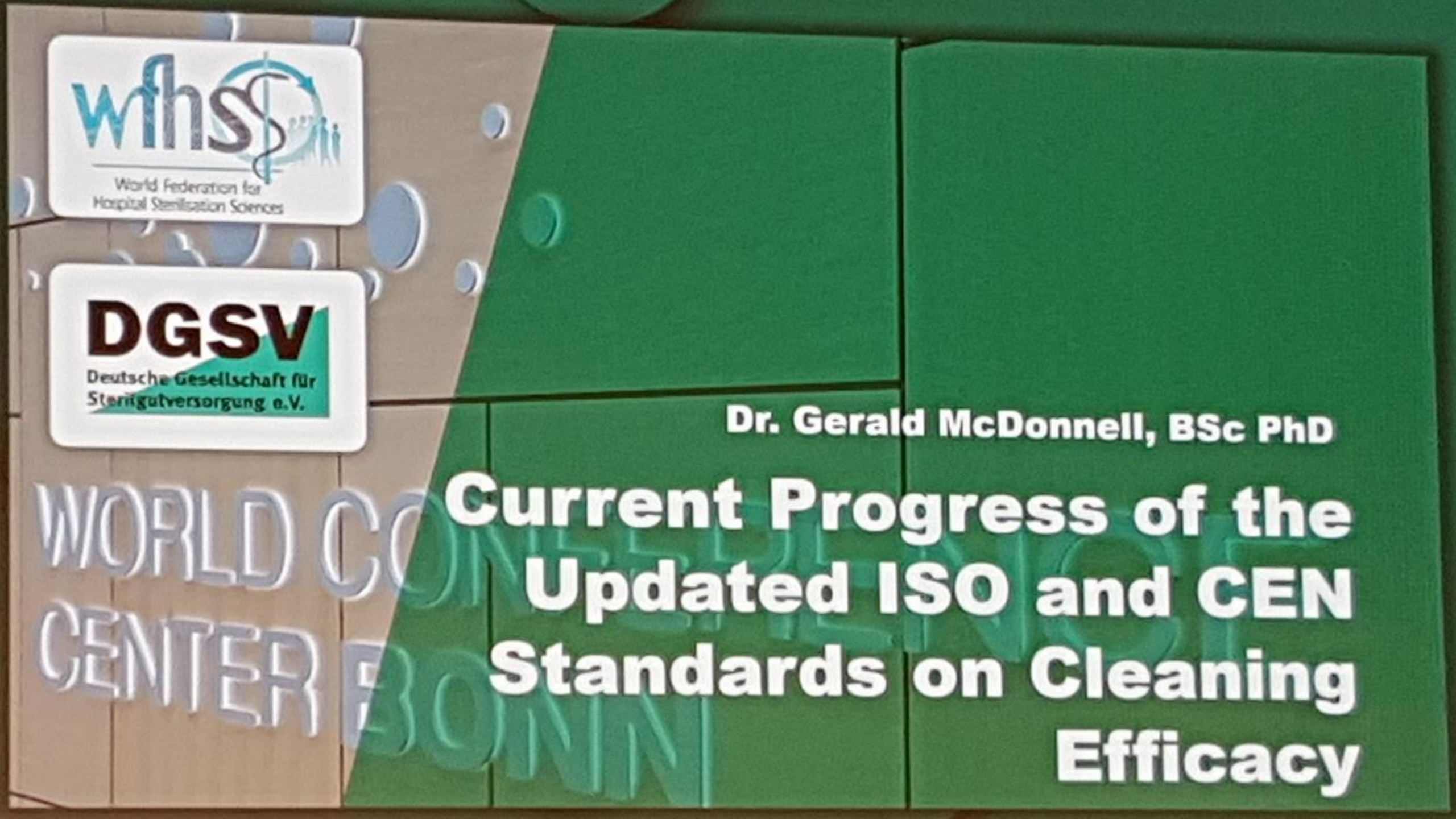


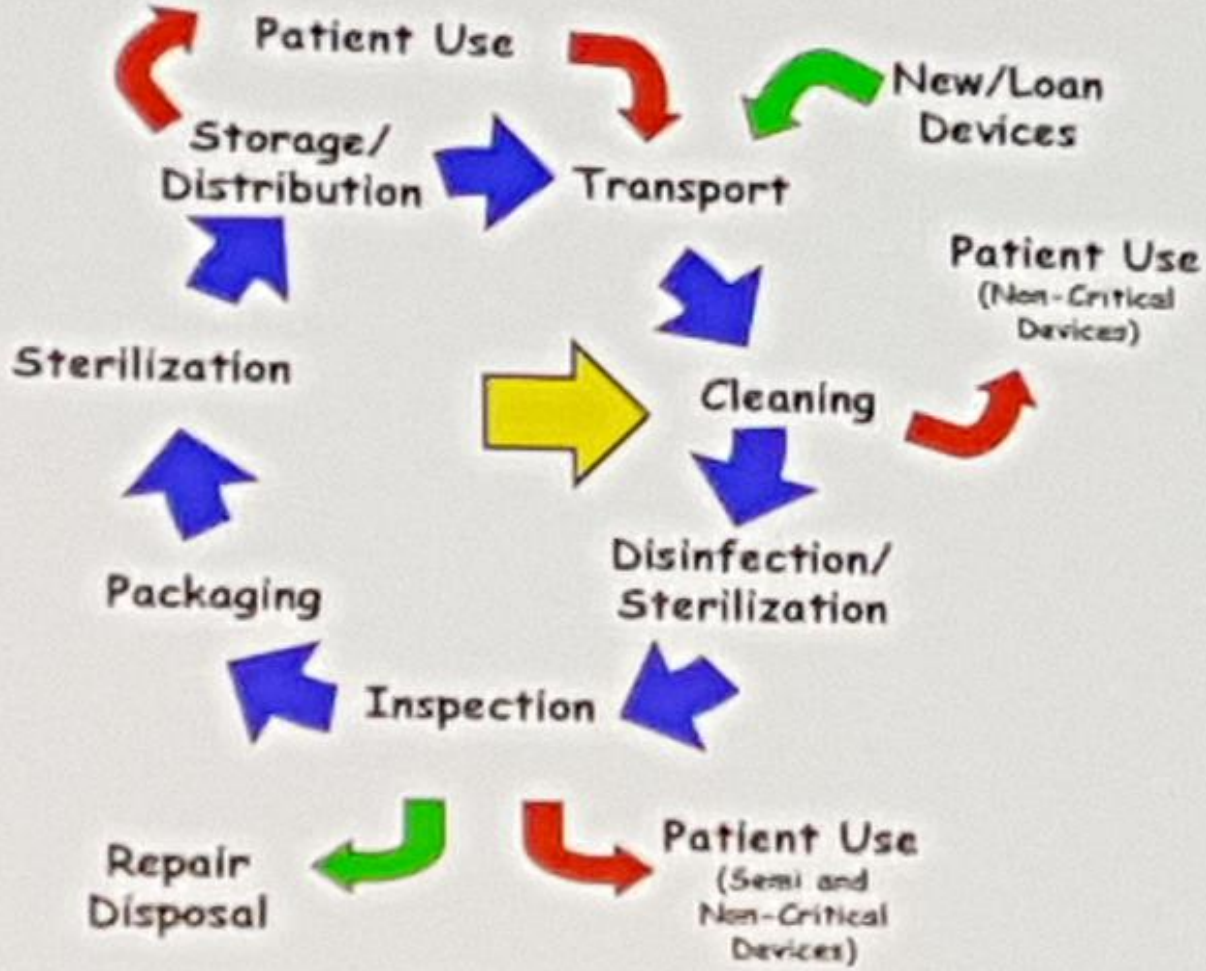
Dr. Gerald McDonnell, BSc PhD

Current Progress of the Updated ISO and CEN Standards on Cleaning Efficacy

Disclaimer

- Dr. McDonnell is an employee of DePuy Synthes, a Johnson & Johnson Company. The opinions expressed are those of the participant individually and are not the opinion or position of Johnson & Johnson or its affiliates

Reprocessing Cycle



McDonnell & Sheard, 2012

Objectives

- Review the current progress of the updated ISO and CEN standards on cleaning efficacy
- Discuss the scientific interpretations of cleaning efficacy requirements for their impact on disinfection/sterilization and toxicity

Definitions

- Cleaning: removal of contamination from an item to the extent necessary for its further processing and its intended subsequent use
- Clean: visually free of soil and quantified as below specified levels of analytes
  - Analytes are substances to be measured
    - Examples: protein and total organic carbon

What is important to achieve during cleaning?

- Process and any residuals
  - must not interfere with disinfection or sterilization
  - must not damage the device
  - must not leave toxic residues that may also be a patient risk

So how are we currently defining this?

- Manufactured (new) products
  - Defined by the manufacturer depending on their device classifications and regulatory approvals
  - For surgical devices, typically includes
    - Biocompatibility assessment (e.g., to ISO 10993 series)
    - Cleanliness requirements
      - No standardized requirements
      - Minimum visual cleanliness
    - Sterilization requirements (when applicable)
- Reused product expectations
  - Also defined by the manufacturer depending on their device classifications and regulatory approvals
    - Validated instructions for use
    - New version of ISO 17664
  - Cleaning, disinfection and sterilization validations (as applicable)
    - No standardized requirements
  - Verified during clinical use

New Cleaning Standards Under Development

- Manufactured (new) devices
  - ISO/DIS 19227 *Implants for surgery — Cleanliness of orthopedic implants — General requirements*
  - Currently limited to orthopedic implants, but may extend to other implantable devices
- Reused devices
  - No general standard under development
  - ISO/CEN activities
    - ISO WD 15883-5 *Washer-disinfectors — Part 5: Performance requirements and test method criteria for demonstrating cleaning efficacy*
  - Country-specific activities (examples)
    - Germany
    - UK
    - USA

New Cleaning Standards-Proposed Requirements

- ISO/DIS 19227 *Implants for surgery-Cleanliness of orthopedic implants-General requirements*
  - Visual Inspection
  - Organic contamination
  - Inorganic contamination
  - Particulates
  - Cytotoxicity
  - Bioburden (if applicable)
  - Endotoxin (if applicable)

- ISO WD 15883-5 *Washer-disinfectors-Part 5: Performance requirements and test method criteria for demonstrating cleaning efficacy*
  - Laboratory and Clinical testing
  - Visual Inspection
  - Choice of one or more analytes (e.g., protein, total organic carbon (TOC) etc.)
  - Cytotoxicity (if applicable)

Outline of a typical laboratory cleaning study

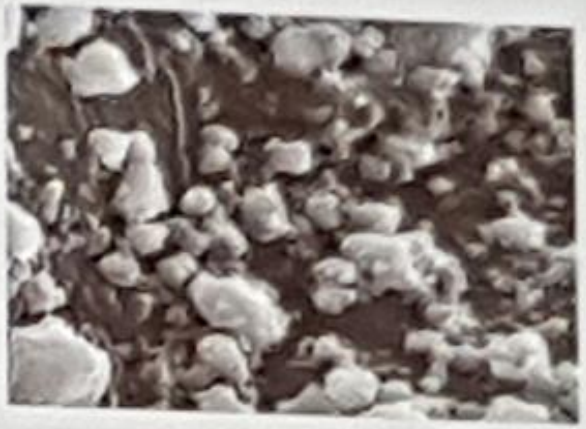
- Test method validation
- Choose and justify a test soil
  - e.g., coagulated blood
- Choose and justify test devices/load
- Contaminate the load, simulating clinical use
  - e.g., suctioning, articulation, cauterization
- Expose to a worst case cleaning processes
  - e.g., detergent concentration, temperature etc
- Evaluate visual cleanliness and levels of analyte
  - E.g., protein, TOC
- Pass or fail

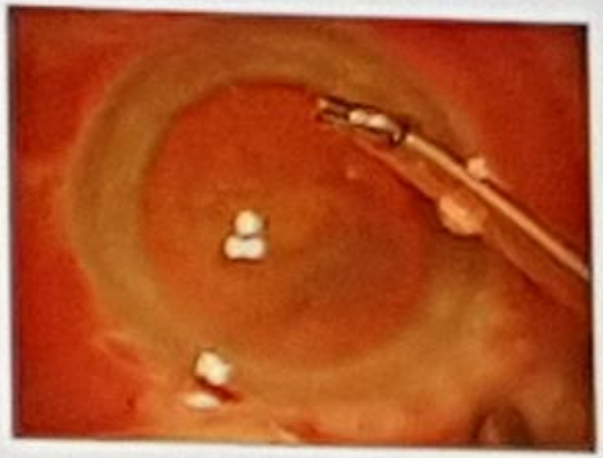
Why Visual?

Test Analyte	Result
Protein	Pass
Total Organic Carbon (TOC)	Pass

A Note on Particulates

- Examples
  - Dust, lint, debris, etc.
- Can lead to
  - Toxicity (without infection)
  - Immune reactions
  - Embolism or other blockage
  - etc…





Eye (Lond). 2014 Aug; 28(8): 958–961.

What do we find after surgery?

Device Type	Total Average Contamination/Device (Average Contamination/cm²)			
	Bacteria (log_{10})	TOC (µg)	Protein (µg)	Hemoglobin (µg)
Surgical Instruments	1.48 (-0.55)	3968 (52)	14482 (244)	1680 (18)
Flexible Colonoscopes	8.46 (4.93)	N/D	7110 (37)	1240 (6)

Cloutman-Green et al, 2015. AJIC 43(6):659-61.

ISO WD 15883-5 *Washer-disinfectors-Part 5 (Draft)*

- Recommended analytes and 'clean' levels include
  - Protein: ≤3 µg/cm²
  - TOC: ≤ 12 µg/cm²
  - Hemoglobin: ≤ 2.2 µg/cm²
  - Carbohydrate: ≤ 1.8 µg/cm²
  - ATP: ≤ 22 femtomoles/cm²
  - Endotoxin: ≤ 2.2 EU/cm²

- But also, lack of cytotoxicity (or chemical residue testing)

But Some Important Considerations

- One cleaning test may not be enough to test for build-up
- Cleaning per device or per side or per cm^2
  - e.g., requirements for ≤ 50-100µg protein/device
- Laboratory method validation
  - Extraction of device
  - Detection limits and dilution
  - Interference etc.
- Is one analyte enough?

Why these levels? Example: Protein

- We find high levels of protein on devices following clinical use…no surprise!
- Proteins can be sometimes easy and sometimes difficult to remove from surfaces…a good challenge
- When we do 'good' cleaning, these levels are achievable
- These levels are about 10X lower than what we can typically see as 'visual soil'
- Do these levels interfere with sterilization?
- Do these levels pose a toxicity risk?

Disinfection or Sterilization Interference

- Disinfection and sterilization processes should not be compromised, if used correctly in accordance with their label claims!
- Disinfectants and Sterilization processes are typically tested in the presence of soil
  - Examples: 5-10% serum or BSA (US-FDA), 3g/L BSA + red blood cells (EN)
  - Visual soil is ~50$\mu g/cm^2$

Are these levels of protein toxic to a patient?

- May depend on the protein and the level introduced
- Many factors, such as the patient's immune system
- What would be considered worst case proteins?
  - Example: human complement proteins (e.g., C3b)
    - Present in blood and tissues
    - Stable, not readily digested by the body
    - Part of the human body's immune system, activated early in an immune reaction (e.g., infection)
    - But if introduced from a foreign source, these same "helpful" proteins can become "toxic" to the host
  - What level would be considered 'toxic' to a patient?

Cytotoxicity Test Results

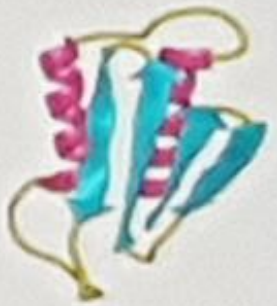
Protein	Why?	Test Condition	Protein Concentration (estimated) and Observed Cytotoxicity Score*				
			63µg/cm²	20µg/cm²	6.3µg/cm²	2.0µg/cm²	0.63µg/cm²
Cobra Venom Factor (CVF)	Represents C3b a foreign complement protein	CVF + 5% serum	0	0	0	0	0
		CVF + 20% serum	3	0	0	0	0
Horseradish peroxidase (HRP)	Present in blood and can cause tissue damage	HRP + 5% serum	4	1-2	0	0	0
Cathepsin G Human neutrophil protein (CHN)	Present in blood and involved in inflammation and cell damage	CHN + 5% serum	4	4	0	0	0
Albumin (A)	Present in blood but consider more benign	A + 5% serum	3	3	1	0-1	0-1

*Cytotoxicity score ranges from 0 (no reaction) to 4 (severe reaction); <2 is typically considered non-cytotoxic

T. Kramer et al, Nelson Laboratories, 2017

Prions: A Note of Caution

- Overall, these levels of proteins (and other analytes) seem 'safe' for patients based on our experience to date
- But one exception: transmissible proteins (or prions)
  - Composed of protein
  - Hydrophobic, likes surfaces
  - Can be resistant to cleaning, disinfection, and sterilization
  - Can cause severe, fatal diseases (e.g., CJD)
  - Can be transmitted by reusable devices



Prions: What the data tells us

- Very, very low levels can be transmissible (estimated 100 to 1000 times lower than levels proposed, if all the protein was prion)
- The detectable level of protein may not correlate with infectivity of proteins (e.g., no protein does not mean no risk)
- More effective cleaning may help…but only if those cleaning processes are shown to reduce the risk of prions
- Sterilization by steam and some hydrogen peroxide gas technologies can be effective (if verified as such)

Treatment	Infectivity Reduction (log$_{10}$)
Water washing	<1
Water washing + 134°C x 4 min	~3.0
Water washing + 134°C x 18 min	~5.0
Enzyme cleaner 1	~4.5
Enzyme cleaner 2	~1.0
Enzyme cleaner 1 + 134°C x 18 min	>6
Enzyme cleaner 2 + 134°C x 18 min	~3.0
Alkaline cleaning 1	~3
Alkaline cleaning 2	~4
Alkaline cleaning 1 + 134°C x 4 min	>6
Alkaline cleaning 2 + 134°C x 4 min	>6

McDonnell G. (2013). In, A. Fraise, P. A. Lambert, Jean Yves Maillard (Editors) Principles and Practice of Disinfection, Preservation and Sterilization, pp. 208 228.

Conclusion

- Cleaning is an essential part of the reprocessing cycle and the requirements for cleaning are being scientifically defined
- New standards are under development to better harmonize the requirements for reusable device cleaning efficacy studies
- The 'clean' requirements can be justified based on practical, microbiological, and toxicological considerations
- An exception to these requirements may be in consideration to prion contamination, which requires a coordinated approach to cleaning and sterilization to reduce risk

Danke!

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