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Instrument cleanliness and protein misfolding disorders

Sir,

The article 'Instrument cleanliness and protein misfolding disorders', referring to the earlier article by Smith *et al.*, poses questions regarding two statements [1]:

1. 'The 5 μg or less per instrument side represents a more exacting standard than the 6.4 μg/cm^2 currently being proposed by the International Organization for Standardization (ISO)' [2].

How can the limit of '5 μg or less per instrument side' be described as 'more exacting' than the limit of 6.4 μg/cm^2, given that the area variable in the first is undefined?

Figure 1 (from Simmons [3]) illustrates why 5 μg per side is inadequate. A side of this 'instrument' measures 5 cm × 1 cm. If contaminated at 5 μg per side, it would have a total on four sides of 20 μg. If solid, then there could be 1 μg on each end, i.e. 22 μg. Alternatively, if hollow, the total load would be 40 μg of protein.

The smaller the instrument, the bigger the risk associated with an undifferentiated standard. If, instead of our initial instrument, we now consider one as a solid or hollow cube with sides of 1 cm × 1 cm but still contaminated with 5 μg per side, then the total load for a solid instrument would be 30 μg and 40 μg if hollow or 5 μg/cm^2. This is only marginally better than the 6.4 μg/cm^2 proposed by ISO DIS15883:5 [4].

It is the amount of prion that is in contact with normal tissue that seems to matter.

Kirby *et al.* suggested that not only is the level of contamination important but also contact time [5]. They placed contaminated dental files in the gingival margin of mice for 5 min. The contamination was with ~20 μg/cm^2 of abnormal prion-infected brain homogenate, well in excess of ISO DIS 15883:5 (<6.4 μg/cm^2 of protein) [4]. Would 5 μg total load for 5 min produce the same effect as 2.5 μg for 10 min? As the development of a beta-pleated sheet is based on templating, a single abnormally folded prion protein adhered to an instrument may initiate a cascade.

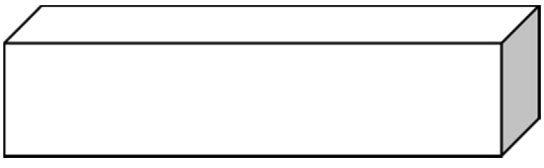

Figure 1. To illustrate a three-dimensional 'instrument' with four sides, each 5 cm × 1 cm.

2. 'in-situ measurement techniques are the safest option for instruments to be used on tissues at high risk of transmitting disease'.

As the currently available in-situ measurement technique does not give an accurate determination of protein left on the entire instrument surface, how can this be described as 'the safest option?'

There is no reference to support this opinion and we have been a part of the ongoing debate among services of the practicalities and issues this poses to service delivery.

Using in-situ methods for protein detection, departments have fine-tuned their cleaning processes. They have been able to take an instrument with, say, 15 μg of protein detected, re-wash, and see the level reduce to, say, 2 μg. However, if prion protein is firmly bound to the metal and cannot be removed, then what has been removed was not prion protein. A reduction from 15 μg to 2 μg offers clear evidence of cleaning efficacy, but this same improvement can be demonstrated by measuring protein in the effluent, i.e. through swabbing methods [6].

The current in-situ method only detects protein on one side of an instrument, which fails to address total load detection. The complexities of instrument design mean there are areas (box joints, lumens) where a shining light will fail to reveal protein, as discussed by Holmes *et al.*, and cannot be regarded as the safest method. A mixed economy of detection methods has value in demonstrating increased cleanliness [6].

The other issue not considered with the different shapes of instruments is that they do not make for a readily validated process.

The Welsh Health Technical Memorandum (HTM) includes advice around the use of challenge test soil devices, allowing cycle-to-cycle validation of the cleaning process [7].

The Scottish Health Technical Memorandum 01-01 focuses on improving the process both in theatres (e.g. keeping moist) and central decontamination units (e.g. validation and loading of washer-disinfectors) [8].

Conflict of interest statement
None declared.

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Instrument cleanliness and protein misfolding disorders

Sir,

My commentary seeks to reflect, for a more general audience, the debate on the desirable standards for protein decontamination of instruments and the best ways of measuring residual protein, whilst setting this debate in the wider context of the risks and burden of Creutzfeldt–Jakob Disease and other protein misfolding disorders [1].

Simmons and Holmes question two statements [2]. First, that 5 μg/side represents a more exacting standard than the 6.4 μg/cm^2 proposed by the International Organization for Standardisation (ISO). Of course, it is possible to conceive of instruments where this would not be the case, but since many instruments would have sides larger than 0.78 cm^2 (i.e. 5 μg/6.4 μg × 1 cm^2) which is equivalent to 8.8 mm by 8.8 mm) then 5 μg/side can reasonably be characterized as a more exacting standard. Furthermore, as a standard, 5 μg/side better reflects that transmissibility depends on the total amount of transmissible protein in contact with recipient tissue. Neither standard refers to contact time and Simmons and Holmes helpfully remind us of the importance of this [2].

Second, Simmons and Holmes ask how I can state that 'in-situ measurement techniques are the safest option for instruments to be used on tissues at high risk of transmitting disease', a statement that I do not reference [2]. However, they omit the earlier part of my sentence, 'most generally agree that'. This sentence is, therefore, a statement of my opinion as to the more commonly held view of the safest measurement technique. Simmons and Holmes, of course, are perfectly at liberty to challenge this view [2]. To repeat what I say in the commentary, 'ultimately, resolving this question would require a comparison of techniques using tissue containing PrPSc that would either show, or not, a consistent relationship between the protein measured on elution and that remaining on the instrument' [1].

Simmons and Holmes remind us that this debate remains live [2]. However, until further experimental evidence is obtained to resolve it, I believe decontamination services can best base their practices on the existing guidance [3]. Whilst allowing flexibility based on local risk assessment, this guidance was the product of a solid corpus of specifically funded scientific work and of a structured process of consultation.

Conflict of interest statement
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