

**SSI's response to the hearing on COUNCIL REGULATION (EC) No 1167/2008
of 24 October 2008
Community regime for the control of exports of dual-use items and technology**

p. 69

IC351 Human pathogens, zoonoses and "toxins", as follows:

...

c. bacteria

...

15. enterohaemorrhagic Escherichia coli, serotype O157 and other verocytotoxin producing serotypes;

Note: IC353 does not apply to nucleic acid sequences associated with the pathogenicity of enterohaemorrhagic Escherichia coli, serotype O157 and other verocytotoxin producing strains, other than those coding for the verocytotoxin, or for its sub-units.

Response prepared by Flemming Scheutz;
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Comments

General:

The designation "enterohaemorrhagic *Escherichia coli*" is not appropriate because this group is not clearly defined. VTEC isolated from animals are usually not related to disease in these animals – see below (1).

The designation "other verocytotoxin producing serotypes;" is misleading because it can be misinterpreted as all serotypes isolated as verocytotoxin-producing *E. coli*. Many serotypes are found both as verocytotoxin- producing and as **NON**-verocytotoxin-producing – including O157.

Access to VTEC outside SSI is likely to be very easy as up to 75% of ruminants have been found positive for VTEC. Not all these types are associated with disease in humans.

Specific:

ad 1; 15.

Our control should in principle only include isolates from diseased humans. Many isolates from animals, eg verocytotoxin-producing *E. coli* (*vtx2e*) from swine with oedema disease are not considered to be pathogenic to humans - see (2), p. 5.: "*Presence of the vtx2e subtype has not been significantly associated with human disease and vtx2e positive strains are probably not human pathogens.*"

In humans, the clinical spectrum of disease is very wide: from asymptomatic carriers to life threatening acute kidney failure (haemolytic uremic syndrome: HUS). The control should therefore be limited to types of VTEC associated with severe disease in humans. An EU forum of VTEC experts have defined this in 2006 (1):

A new paradigm was proposed that depends on the detection and subtyping of virulence genes regardless of serotype. Consensus was reached that 1) the term enterohemorrhagic E. coli based on serogroups can be misleading, 2) an alternative nomenclature based on patterns of virulence genes associated with severe disease is needed, and 3) the combination of virulence genes that make a strain pathogenic needs to be determined.

The combination of *eae* and *vtx2* genes is – regardless of serotype – foremost associated with severe disease in humans. We would like to see this supplemented with isolates (or sero-virulence types? see comment*), which are positively known to have been isolated from human disease with bloody diarrhoea and/or HUS.

We consider it very unlikely that other VTEC sero-virulence types than those mentioned above could be used in relation to biological terror against humans, and hence these types represent no danger to public security.

SSI's specification of bullet 15. "enterohaemorrhagic *Escherichia coli*, serotype O157 and other verocytotoxin producing serotypes" will therefore include:

- **VTEC isolates – regardless of serotype – with a combination of the *eae* and *vtx2* genes simultaneously**
- **All other VTEC isolates, which are positively known to have been isolated from human disease with bloody diarrhoea and/or HUS**

Comment:

These VTEC **isolates** will be at a relatively limited number, because we do not have clinical data on all our VTEC isolates.

ad Note: 1C353.

It should be emphasised that *nucleic acid sequences encoding* subunits of verocytotoxin, cannot be used for synthesis of complete holotoxin and cannot be used in relation to biological terror against humans, and hence represent no danger to public security.

Furthermore, PCR for the *vtx* genes is performed daily in many routine laboratories and it is completely unrealistic to control these amplified partial sequences.

Nucleic acid sequences encoding subunits or parts of verocytotoxin should therefore be excluded from the list.

Regarding

d. "toxins", as follows, and "sub-unit of toxins" thereof:

6. shiga toxin;

9. verocytotoxin and shiga-like ribosome inactivating proteins;

Comment:

Bullits 6. and 9. are identical and should be combined into one bullit.

References

1. **Caprioli, A., S. Morabito, F. Scheutz, H. Chart, E. Oswald, M. Brigotti, L. Monnens, A. Aspan, R. M. La Ragione, C. Low, and D. Newell.** 2006. Pathogenesis of Verocytotoxin/Shiga Toxin-producing *Escherichia coli* Infection. *Emerg.Infect.Dis.* **12**.
2. **Scheutz, F. and S. Ethelberg.** 2008. Nordic Meeting on detection and surveillance of VTEC infections in humans, p. 1-30. Statens serum institut, Statens serum institut.

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