August 30, 2010

VIA email

To: Centers for Disease Control and Prevention
1600 Clifton Road N.E., Mail Stop A-46
Atlanta, CA 30333

From: SRI International
Office for Biosafety
333 Ravenswood Avenue
Menlo Park, CA 94025

Re: Comments on the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, (42 CFR Part 73).

Currently botulinum and ricin toxin are listed on the HHS and USDA select agent and toxin lists, and users of these agents must follow the select agent regulations. We agree these procedures should be followed for injections of viable select agents into animals. However, we are requesting that the CDC and USDA consider the health hazards and security risks of select agent toxins, when injected into animals. We believe that animals containing toxins are not hazardous to people handling them. Once the toxin is injected, it is replication incompetent (if it ever was) and cannot be excreted and cannot be cultured. No toxin can be retrieved from these animals for nefarious purposes.

When botulinum neurotoxins are administered intraperitoneal into mice, the toxin rapidly accumulates in neural tissues where it induces toxic effects within a few hours and to a lesser extent may accumulate in liver tissue. Pharmacokinetic studies in mice and rats (following intravenous administration) reveal a half-life in blood of 1-4 hours depending on the toxin serotype [1-3]. Following intraperitoneal administration, toxin levels in blood are assumed to be much lower. Since the toxin preparation itself is cell-free, the toxin cannot be propagated in vivo and cannot be transmitted from animal to animal or animal to person.

In neural tissues the toxin binds irreversibly to synaptotagmin receptors located on the cell surface of neurons [4]. Upon binding, the toxin is translocated into the cells where the toxin is broken down into its constituent heavy and light chains [4]. The light chain is responsible for

toxicity by interfering with formation of vesicles responsible for secreting the neurotransmitter acetylcholine at neuromuscular junctions causing flaccid paralysis of skeletal muscles [4]. Because of the irreversible binding of toxin to cell surface receptors and intracellular dissociation of the toxin, the toxin cannot be recovered once bound to neurons. The rapid pharmacokinetics reveals that the toxin cannot be readily isolated from peripheral blood following dose administration. Additionally, there are no reports of people who have been intoxicated with botulinum neurotoxin following bites or scratches from animals that have been dosed with toxin or after contact with bedding from toxin-exposed animals.

We are requesting that both CDC/HHS and USDA consider this proposal: Once toxins are injected into an animal, the animal and the project study should be exempted from select agent requirements.

1. Ravichandran E, Gong Y, Al Saleem FH, Ancharski DM, Joshi SG, Simpson LL. 2006. An initial assessment of the systemic pharmacokinetics of botulinum toxin. *J Pharmacol Exp Ther* 318(3):1343-51.
2. Al-Saleem FH, Ancharski DM, Ravichandran E, Joshi SG, Singh AK, Gong Y, Simpson LL. 2008. The role of systemic handling in the pathophysiologic actions of botulinum toxin. *J Pharmacol Exp Ther* 326(3):856-63.
3. World Health Organization. http://www.who.int/csr/delibepidemics/clostridiumbotulism.pdf
4. Huang W, Foster JA, Rogachefsky AS. 2000. Pharmacology of botulinum toxin. *J Am Acad Dermatol* 43(2 Pt 1):249-59.

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