INTERNATIONAL DISCUSSION ON SPECIFIED RISK MATERIALS

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Specified risk materials (SRM) in cattle carcasses are those tissues in infected animals that contain the vast majority (more than 99%) of infectious prions[1]. Canada's definition of SRM is consistent with guidelines of the World Organisation for Animal Health (OIE) apart from tonsils where the OIE recommends that they be excluded from animals of all ages. The list of tissues and the age cut-off defining SRM varies amongst countries (Table 1).

The removal of SRM from human food and animal feed has required considerable and costly changes by the cattle and beef industries of many countries. Canada's beef industry faces an additional challenge as a result of differences between Canada and the United States (US) in the list of tissues excluded from the animal feed chain. Both countries exclude the same list of tissues from the human food supply but not from the animal feed chain (Table 1). The impact of this is additional disposal costs and resulting competiveness issues. Although the US is now a negligible risk country for bovine spongiform encephalopathy (BSE), it continues to exclude SRM from human food (full list) and animal feed (partial list).

At the invitation of the Alberta Prion Research Institute, knowledgeable individuals with experience with SRM from industry, government and academia participated in a facilitated discussion about all aspects of SRM. Appendix A contains a list of participants. The participants were invited in their personal capacity and views expressed were not necessarily those of their respective affiliated organizations. The discussion was carried out under a modified version of the original Chatham House rule[2] that allowed the identification of the participants listed in the appendix, but not the attribution of specific comments.

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[1] SRM are defined in Canadian regulations as:

- the skull, brain, trigeminal ganglia (nerves attached to the brain), eyes, tonsils, spinal cord and dorsal root ganglia (nerves attached to the spinal cord) of cattle aged 30 months or older; and
- the distal ileum (portion of the small intestine) of cattle of all ages.

[2] Participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed.

SUMMARY OF DISCUSSION

Learning from Experience

Regulators in Canada and the US had the experience of others, especially those in the United Kingdom (UK), to draw upon as they formulated their approach to SRM regulations. The UK experience with BSE and Variant Creutzfeldt-Jakob Disease (vCJD) provided the primary evidence base for international SRM regulations, with increasing stringency applied as scientific knowledge evolved. The UK's BSE Inquiry Report[3] (16 volumes) was recommended as important reading for anyone seeking a good understanding of that experience and the lessons learned.

SRM regulations have two primary drivers: protection against human infection via food and protection from cattle infection via feed. Different countries took different approaches to protection and to the stringency of removal and disposal or alternate use, depending on national experience, culture and risk tolerance (see below). A key measure to protect human health is to remove the primary vector, potentially infectious tissues, from the food chain through the hygienic removal of SRM and banning their use in food. Herd protection is achieved by prohibiting SRM from being used in feed, the extent of the prohibition being dependent on the experience of the country. Canada introduced a precautionary feed ban in 1997, which was enhanced in 2007 as the Canadian experience evolved.

It was noted that the OIE has standards of reduced stringency for the control of SRM for countries that have negligible risk status. The OIE sets what are considered minimum standards, and countries can and do adopt more stringent regulations depending upon a number of national and international factors.

Current Considerations

A recent move to amend SRM regulations in the European Union was noted[4]. There was concern that any changes in standards be based on established scientific findings rather than on other pressures in the absence of solid evidence. It was noted that we should not forget history and the many lessons learned by the UK as it struggled with BSE and vCJD. The UK experience as well as new science need consideration in any action to reduce the stringency of SRM regulations. It was observed that France and Germany had voted against changing the EU regulations and that the UK had abstained[4]. The inference drawn was that different country experiences and interests in BSE and the SRM regulations are influencing decisions to move to new SRM regulations at this time.

There was discussion about information on newly-observed sources of infectivity, such as the complete intestine, that could influence risk assessment of re-emergence of BSE (and vCJD). The relatively recent recognition of atypical BSE (aBSE) was discussed. It was noted that information sufficient to adequately understand the risk of infectivity of aBSE in cattle or humans would likely be unavailable for another decade. The question thus arises as to whether atypical BSE should be regarded as having the same risk to humans as classical BSE until data indicate otherwise.

It was noted that the study of human appendices in the UK had indicated that about 1 in 2,000 individuals in the UK could have BSE prion infection. Risk estimates are not available for the possibility of emergence of a second wave of vCJD from a primary infection in those carriers or through secondary infection through blood or other tissue transfers.

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[3] http://webarchive.nationalarchives.gov.uk/20060715141954/http:/bseinquiry.gov.uk/index.htm

[4] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2015.116.01.0001.01.ENG

It was pointed out that our risk management procedures are unlikely to eradicate transmissible spongiform encephalopathies (TSEs) because of the potential for their spontaneous occurrence (as might be the case for aBSE), and the occurrence of different strains with varying infection potentials for humans and other animals. We need to expect that we will be managing, not eradicating, TSEs for the foreseeable future

Risk, Standards and Regulations

Risk

Risk assessment, risk management and risk communication are separate but interdependent activities. Risk is defined as a function of impact or magnitude of consequence (level of harm) of an action or event and the probability of the event occurring.

In the process of risk assessment, rigorously-measured estimates of either of the two pertinent factors are rarely available. When they are available, there will be uncertainties in the measures. Measures of probability of occurrence might be more precisely (or scientifically) derived than measures of impact. The latter will often be influenced by social or cultural values as well as specific measured data.

A level of risk can be established scientifically if the two component factors have been determined. It is important to avoid allowing uncertainties in the data to lead to bias in the assessment of risk. Because of uncertainties, assessments of risk are often controversial. This is particularly so when trade is at stake with factors such as economic interests and consumer acceptance coming into play.

Professionals who communicate with the public about risk should not underestimate their audience's ability to cope with uncertainty. Nevertheless, overemphasis of uncertainties will frustrate both policy makers and the public since in almost all situations decisions and actions will have to be taken in the face of uncertainties. We recognize that there can be bias in assessment in the face of uncertainties, bias in how information is understood by the public and bias in interpretation by specific groups of stakeholders. An important component of assuring confidence is to be open and transparent about the process and value assumptions used to make a risk assessment.

Public sector risk managers must deal with many issues beyond the estimate of risk itself. Their decisions will be influenced by a complex set of variables that include science, politics, cultural values, ethics and others. They face a plethora of questions, including: how much risk is acceptable and to whom is it acceptable; how do we balance health and economic values; do we understand the uncertainties well enough to develop a management scheme which protects values such as human health, animal health, vitality of trade, export markets and the like; to what extent should precaution be observed?

Risk and BSE

Within the safety system for cattle and meat, and for humans, there are four main components: what potentially-infected tissues should be removed from carcasses; what should be done with SRM; how can we effectively ensure that the national herd is free of disease; and, how can we ensure that food for human consumption is safe. The last issue has been addressed by removal and disposition of SRM, testing of animals going to slaughter and prevention of recontamination in the herd through restricting the uses of SRM.

In many jurisdictions, including Canada and the US, protection of human health focused on the animal vector through protection of animal health. Testing of all animals going to slaughter has a substantial cost without a complete guarantee of freedom from disease since no testing system is absolutely reliable. Hence testing of all cattle going to slaughter is not undertaken in either Canada or the US, while in the EU only cattle 72 months and older are tested. Countries monitor their respective cattle populations for BSE by testing certain classes of cattle.

For example in Canada, the focus of the surveillance program is on clinical suspects of all ages and a targeted sample of 4Ds (dead, down, dying, diseased) 30 months of age and older. While the EU's surveillance program focusses on the same classes of animals, in contrast with OIE recommendations as well as the surveillance programs in Canada and the US, the EU tests all cattle within the respective classes above the relevant cut-off age, for example all healthy slaughter cattle 72 months and older, and all fallen stock and casualty slaughter 48 months and older.

Surveillance

The BSE surveillance system relies on monitoring animals of different ages and states of health. The OIE has derived a standard for country surveillance systems that incorporates a number of factors, some of which are the size of the adult cattle population, the number in different age classes that are monitored and the numbers tested in different sub-populations (clinical suspects, casualty slaughter, fallen stock and healthy slaughter). With varying weights being given to the BSE risk of the different classes, a country can satisfy or exceed OIE guidance and minimum standards for surveillance by employing different combinations of numbers tested and class risks. A number of countries are now moving away from the testing of younger animals based on previous lack of detection of prions in those animals. The relatively small number of BSE-exposed persons in the United Kingdom that have developed vCJD suggests that animals with pre-clinical disease such as BSE infections in younger animals may not have accumulated sufficient infectious proteins to present a significant vCJD risk to humans.

BSE surveillance in Canada is a tool to monitor the BSE status of the cattle population as the key indicator of the effectiveness of the feed ban. As such, it is a targeted surveillance strategy that tests a targeted sample of all potentially eligible 4Ds 30 months of age and older.

It is noteworthy that surveillance of larger numbers of older and"4D" animals will favour detection of classical BSE and atypical BSE infections in older animals. Surveillance of older animals might not be as effective at identifying re-emergence of BSE from a new source of infection as would a system which monitored a wider range of age classes.

It's important to understand that the safety of Canadian beef and beef products is assured by a number of key factors: an extremely low prevalence of BSE as demonstrated through ongoing surveillance, which confirms that BSE is being effectively controlled in the cattle population through the ongoing implementation of the feed ban; ante mortem inspection of to ensure that only healthy cattle are slaughtered for human consumption; and, the hygienic exclusion of SRM from the human food supply at the time of slaughter. Collectively, these measures ensure that any potential public health risks posed by BSE through the consumption of meat and meat products from cattle in Canada is negligible. Although unwelcome, the finding of a BSE case can actually be a good indicator of a functional surveillance system.

International Standards and Regulations

Transparency in risk assessment is essential in effective risk communication. Process, data and decisions need to be accessible to interested parties. In the OIE the setting of standards or establishing country BSE risk status relies on assessment and recommendations by scientific and formulating bodies, followed by a two-thirds majority decision of the international OIE assembly. Dossiers developed during the process are open to legitimately interested or affected countries.

There was discussion around the intents of the OIE standards and classifications, which are to maintain the health of animals, to eliminate the classical infection and to avoid re-emergence of BSE through feed-borne routes. Restrictions on the use of processed SRM in human food protect against human infection. Restrictions in the use of SRM in animal feed, which are designed to protect the herd, add an extra level of security to the safety of the human food system.

In addition to the risk of human vCJD arising from direct infection by materials still associated with the original feed-borne BSE, there is need for vigilance for the potential for human infection occurring via materials associated with some re-emergent form of BSE. The potential that the atypical BSE forms could contribute to such an event is unknown at this time. The OIE will be reviewing the BSE chapter in order to take into consideration the recent findings regarding atypical BSE.

It was suggested that it will likely take at least a decade before sufficient information is collected to enable a proper risk assessment of this possibility. Participants expressed concern that a perceived reduction in risk has led to under-investment in the science necessary to develop proper risk assessments and potential management scenarios.

There were discussions about how long clinical cases of vCJD might continue to arise from the consumption of infected material from the original classical BSE outbreak. Uncertainty about this issue is increased by the fact that vCJD has been recognized only since 1996, and it is the only known zoonotic prion disease. Nevertheless, experience of transmission of CJD from contaminated human growth hormone suggests that the disease might remain occult for 30-40 years. Experience with kuru suggests that occurrence of clinical disease can occur more than 40 years after consumption of the infectious agent. The implication for both animals and humans is that vigilance for the next couple of decades is imperative, and changes to effective standards and regulations should be approached cautiously.

Experience in the UK has shown that at least three cases of vCJD and one vCJD subclinical infection have occurred through human blood transfusions. A recent study in the UK has shown that BSE prions could be detected in in appendices of people without clinical prion disease in numbers, which suggested that 1 in 2,000 people in the UK might have some level of BSE prion infection, presumably acquired through eating contaminated meat during the classical BSE outbreak[5].

Many questions arise from the appendix study. Might those harbouring prions have a subclinical disease that will manifest itself at a later time? Might the harboured prions cause infection if transferred to another human, say through blood? How does a risk assessor for the blood supply estimate probability of infection (note that the estimates continue to evolve[6])? Should it be based on the appendix study, or on the finding that only three people are known to have acquired prion disease after hundreds of thousands of units of blood have been transfused?

High uncertainty leads to questions about the degree of precaution warranted. Cultural values influence the desired degree of precaution. It would be a wise decision for the benefit of industry and for public health to invest in the science necessary to reduce the uncertainty. Attaining increasingly higher levels of risk reduction becomes increasingly expensive, and cost-benefit analyses need to be applied to decisions about SRM – what degree of protection at what cost will become a more important question over time.

Multiple layers or actions for protection will continue to be needed for the foreseeable future to protect the herd, human food, and human blood supply. It is arguable that regulations requiring the removal and safe disposal of SRM will exist well into the future. There might be some changes in what are regarded as safe uses, but the requirement for removal will likely always be there.

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[5] http://www.nature.com/news/one-in-2-000-uk-people-might-carry-vcjd-proteins-1.13962 accessed May 28, 2015

[6] https://www.gov.uk/government/publications/blood-borne-transmission-of-vcjd-re-examination-of-scenarios

Trade Issues

The effects of BSE are still being felt by the Canadian cattle industry that fully supports the management and control of BSE to support its long term market and trade goals.

Culture and societal risk tolerance often determine national standards. A country can be expected to have stringency for the safety of imported materials that is at least as high as for its domestic products. When processes for achieving the desired level of risk vary between countries, challenges in trade can be expected to follow. Acceptability of an exporting country's risk mitigation procedures will depend substantially on the importing country's experience with the disease as well as the attitude towards risk in the country. Under the World Trade Organization (WTO) Sanitary and Phytosanitary Agreement, food safety always trumps other WTO rules as a legitimate barrier to trade. However, restriction on trade might also have additional motivators hidden under the guise of food safety.

The biggest customer and competitor for Canada is the US. The differential cost of the more-stringent SRM removal and disposal regulations in Canada (estimated at $30 per head in excess of costs in the US) continues to be a competitiveness burden for Canadian industry. Canada will continue to be under a higher level of scrutiny for some time to come, having yet to achieve the negligible risk status that has been accorded to the US. Policy makers must consider the effects on trade as well as on food safety when establishing regulations. It is thus well to consider that SRM removal will be with us for the foreseeable future, and that the SRM regulations will vary among different countries. So part of industry planning for the foreseeable future should likely be a continuation of the SRM regulations with current stringency.

Willingness to work with experts in other countries and to build industry-to-industry interactions such as those promoted by Canada are important in lowering trade barriers. Transparency is important in dealing with risk aversion in trade relations, and Canada has been regarded positively by other countries because of its openness on the issues around BSE and Canadian regulations. This position has helped Canada in spite of the occurrence of BSE. Changes in disease status can affect trade status, as can alternate SRM regulations and surveillance regimes that might be perceived as introducing a higher level of risk. This could be most important for trading partners that already have a highly risk-averse culture.

Heightened perception of risk and high risk aversion are cultural values, and these traits appear to be higher in Southeast Asia and Europe than in other regions. Europe experienced a severe loss of consumer confidence at the appearance of BSE and vCJD, initially in the UK and then in other countries. A collapse in consumer confidence in Japan was associated with the detection of their first BSE case in 2001 and the resultant fear of vCJD. Very stringent measures with regard to SRM were put in place to restore consumer confidence just as much as to ensure food safety.

Experience and modelling have shown that classical BSE is declining exponentially in high-prevalence jurisdictions as a result of the reinforced or enhanced feed bans. The decline in both prevalence and the perception of risk has led to re-examination of SRM regulations in the EU with a view to some reduction in their stringency. Some countries, especially those that experienced a high prevalence of BSE or have high numbers of vCJD cases, did not seem inclined to reduce the stringency. Since Canada has had a recent case of cBSE, it would likely be unacceptable to trading countries for it to reduce stringency at this time.

What Happens to SRM

There appears to be near consensus that SRM should not be allowed into human food for a long period. While some feel that this should never be permitted again, opinions vary on how to approach that risk in the future.

The extent of tissue removal in SRM varies by country in that some prescribe more extensive removal than required by the OIE standards. The usage of SRM in animal feed also varies from country to country or region to

region. The specifics of usage in animal feed have been determined by a number of factors that include culture, experience with BSE, and trade implications, among others. Differences in SRM removal and SRM usage in the animal feed system lead to cost differentials that become important for industry where there is a large emphasis on international trade of the products. The industry in Canada is highly oriented to international trade.

Some large international retailers have developed and imposed a set of standards for their suppliers that can influence the behaviour of the production industry. This corporate approach can lead to consistency among suppliers across countries, but such standards are likely to be influenced not only by concern for food safety but also by concerns for marketability of product and market share.

There are a small number of acceptable ways to dispose of SRM that are not used in feed. Incineration is used in Europe and in some plants in North America. Using SRM as fuel in a co-generation plant is an adaptation of straight incineration. Incineration ash must be dealt with and there are high restrictions on its use at this time: encasement in cement, land-filling and, in very limited circumstances, in fertilizer. Incineration methods are likely to be cost-effective for commercial operations only if they are done on a large scale. Alkaline hydrolysis under high temperature and pressure is an acceptable means of disposal, but it is likely to be relatively expensive on a large scale.

Land-filling SRM in specifically selected sites is an approved method of disposal in some countries, including Canada. It has transportation costs and risks associated, but it is a method that allows for variable use and economies of scale. The issue of loss of long-term containment of infectivity within land fill sites has been raised, but there is no evidence available on the question. Land-filling is the cheapest acceptable method of disposal available at present, and might be into the foreseeable future. A thermal hydrolysis system has met OIE standards for reduction of infectivity, but it has not yet been developed into a large-scale process. Composting methods and other methods of anaerobic digestion accompanied by captured methane production have shown some promise for reducing infectivity. Additional research on the processes is an important area for investment, to improve efficiencies in processes and to find new uses for the end-products of the processes to make them more economically attractive.

The desire to find new methods of using SRM or SRM residues as a source of value-added products remains high. Progress in this field would offset the cost of dealing with SRM and possibly find additional income overall for the industry. This, in turn, would reduce pressure to ease stringency of SRM removal regulations. Two approaches to potentially generating new products from SRM were discussed.

One was through the use of fungi that would use SRM as a feedstock that could be broken down and reassembled into new protein biomass that no longer carried prion infectivity. It was noted that other organisms such as larval forms of some insects also have a prodigious capacity to generate protein biomass and might be used in a similar way. With appropriate selection or genetic manipulation of processing organisms, one could envisage driving such conversions in the direction of production of special high-values proteins and peptides.

A second method for development of new products utilized a chemical rather than a biological agent. In this methodology, small-molecule residues from acid or base catalyzed hydrolysis, or possibly thermal hydrolysis, are converted through chemical processes into building blocks for new polymers such as plastics. The products can be used in various conditions where there is need for industrial plastics. These processes have exciting potential and they invite thoughts for other approaches to make new value-added materials from SRM.

LAST WORDS AND LOOKING FORWARD

It is to be expected that prion diseases including BSE will be with us for a long time to come. Harmonization of SRM regulations is desirable for industry, regulators and consumers. Any moves to change policies and regulations in the absence of adequate science which supports such changes would not serve either area well. Despite the reduction in classical BSE and in associated vCJD, there is need for vigilance and continued

exploration of science in this relatively new and not completely understood field. Developments such as the recognition of atypical BSE and atypical scrapie, the spread of chronic wasting disease, along with our incomplete understanding of prion strain variability, transmissibility and infectiousness, underline the need for such vigilance.

Lessons learned over the past generation, taken with newer findings on disease pathogenesis and new developments in testing techniques could enable reliable early detection. This, in turn, will give rise to a positive future in dealing with SRM and prion diseases more generally. Recent progress in means of disposal and potential new uses of SRM also provide encouragement for a future that enables safer food and feed in conjunction with more favourable economic prospects for industry.

TABLE 1

A comparison of tissues defined as specified risk material (SRM) in Canada (CA), the United States of America (US), the European Union (EU), Japan (JP) and guidelines from the World Organisation for Animal Health (OIE)[7]

Tissue	CA	US	JP	OIE	EU
Tonsils	≥ 30 months	All ages			
Distal ileum	All ages				-
Last four metres of the small intestine and the caecum[8]; Mesentery including fat	-				All ages
Brain, eyes, skull and spinal cord	≥ 30 months		>30 months		>12 months
Vertebral column including the DRG	≥ 30 months		>30 months		

[7] Source: Noel Murray, Canadian Food Inspection Agency, and Shirou Mohri, Tohoku University, August 2015

[8] EU 2015/728 amended 999/2001 from May 2015 which excluded the intestines from duodenum to rectum in cattle of all ages

[9] Apart from the US these tissues are banned from both and human food and animal feed chains. In the US, while the full list of SRM is banned from human food, only a subset of these tissues is banned from animal feed. These tissues are referred to as cattle material prohibited in animal feed (CMPAF) and consist of the brain and spinal cord from cattle 30 months of age and older as well as the entire carcass of BSE positive cattle.

APPENDIX A

List of Participants

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Detwiler, Linda (Mississippi State University)
Djillali, Bachir (Canadian Food Inspection Agency)
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Hills, Bob (Health Canada)
Hope, James (Animal and Plant Health Agency – United Kingdom)
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MacDiarmid, Stuart (Massey University - New Zealand)
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