



The *EFSA Journal* (2005) 221, 1-45. Opinion on the assessment of the human and animal BSE risk posed by tallow with respect to residual BSE risk.

Opinion of the Scientific Panel on Biological Hazards of the European Food Safety Authority on the “Assessment of the human and animal BSE risk posed by tallow with respect to residual BSE risk”.

(Question N° EFSA-Q-2003-099)

Adopted on 27-28 April, 2005



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Summary

Summary of opinion

The European Food Safety Authority (EFSA) Biohaz Panel was invited to assess the validity of the outcome of a quantitative risk assessment (QRA) of the residual BSE risk in tallow. If the outcome was considered valid the previous Scientific Steering Committee (SSC) opinion “Revised opinion and report on the safety of tallow obtained from ruminant slaughter by-products (adopted on 28-29 June 2001, editorial clarifications introduced at the meeting of 6-7 September 2001)” should be reviewed and an advise should be given on how to interpret the results of the calculation in order to make an estimation of the number of potential BSE (cattle) and vCJD cases (human) expected per year in a population.

The general conclusions of the previous SSC Opinion are supported by the QRA. This should not be surprising since both are made on the same assumptions and many of the parameters fed into the QRA model, at this first stage of its evolution at least, must be regarded as expert opinion rather than factual data.

The QRA has provided a worst case mean estimate for the human exposure due to tallow made from a mixture of tissues with no specified bovine risk material removed sourced from cattle from a GBR IV (Geographical BSE (Bovine Spongiform Encephalopathy) Risk assessment) country with unreliable surveillance of 1.6×10^{-9} bovine oral ID₅₀ units per person per week. Multiplying this by 52 weeks per year results in an exposure of 8.3×10^{-8} bovine oral ID₅₀ units per person per year. Considering the estimate that the exposure of the UK population through food over the BSE epidemic was 0.004 bovine oral ID₅₀ units per person per year this worst case exposure due to tallow is 48,000 times less.

If we follow the cautionary advice of the original QRA working group and assume the species barrier between cattle and human is 1 then there might be on average 1 infected person in the European Union (EU) per period of time when the exposure is around 10^{-8} bovine CoID₅₀/person/period of time. This is calculated for an EU population of 450 million and under the assumption of a linear dose-response curve of infectivity at very low doses, an assumption considered valid by the WG

If the species barrier was given the value of 1000 obtained from the analysis carried out on the exposure of the British population to the BSE, this would mean that there might be on average 1 infected people in the EU per period of time when the residual exposure is 10^{-5} bovine CoID₅₀/person/period of time. Most other scenarios, such as tallow from fat tissues before and after splitting, GBRIII with reliable surveillance, etc..., have relative human exposures ten to one hundred fold smaller than this worst case.

For the veal calf exposure, the QRA has provided a mean exposure of 2.2×10^{-6} bovine oral ID₅₀ units per calf per 180 days due to tallow in milk replacers made from a mixture of tissues with no specified risk materials (SRMs) removed sourced from cattle from a GBR IV country with unreliable surveillance. In a veal calf population of 5 million this might be expected to give rise to ~ 5 infected veal calves



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per year. The risk in this unrealistic worst case sourcing scenario is lessened by a factor of 25 if cumulative dose of BSE infectivity operates over only a 7 day period (7/180). Most other scenarios – tallow from fat tissues before and after splitting, GBRIII with reliable surveillance, etc - have relative veal calf exposures ten to one hundred fold smaller than this worst case, and so would give rise to less than one infection in the EU per half year.

For the replacement calves the QRA has provided a mean estimate of exposure due to tallow in milk replacers made from a mixture of tissues with no SRMs removed sourced from cattle from a GBR IV country with unreliable surveillance of 1.4×10^{-7} bovine oral ID50 units per calve per 180 days. For the 20 million population calves receiving the 'replacement calf' milk replacer (not all are replacement calves, a large part being raised for beef production), this might be expected to give rise to ~ 1 infected calf per year. The exposure in this unrealistic worst case sourcing scenario is lessened by a factor of 25 if cumulative dose of BSE infectivity operates over only a 7 day period. Most other scenarios – tallow from fat tissues before and after splitting, GBRIII with reliable surveillance, etc - have relative replacement calf exposures ten to one hundred fold smaller than this worst case.

In general, the exposure levels calculated here in the case of tallow are so low that they can be regarded as minimal. However it should be stressed that not every scenario, every processing variation, every degree of cumulative dose or every intermediate species barrier value was considered. This QRA model is a working model with clear assumptions. It can be re-visited again and again by risk managers to explore alternative scenarios.

Key words: Tallow, BSE, Quantitative Risk Assessment, QRA, exposure assessment, GBR.



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1. Mandate and Terms of Reference

EFSA has received a formal mandate from DG SANCO of the European Commission requesting EFSA's Scientific Panel on Biological Hazards for an opinion on the quantitative assessment of the residual BSE risk in certain bovine derived products. The mandate also asks the Panel to revise the relevant SSC opinions on residual BSE risk in certain bovine derived products if their revision is indicated by the quantitative risk analysis (QRA).

1.1. Terms of Reference (ToR's)

The European Food Safety Authority (EFSA) is invited to:

a) Assess the validity of the outcome of a quantitative assessment of the residual BSE risk in bovine derived products, carried out for gelatine, tallow and dicalcium phosphate from bones, tallow from fat tissues and tallow from rendered mixtures of tissues, and for the presence of small amounts of meat-and-bone meal in feeding stuffs intended for ruminants.

b) If the outcome is considered valid, review the following SSC opinions in the light of the QRA:

- Updated [opinion](#) and report on the safety of dicalcium phosphate (DCP) and tricalcium phosphate (TCP) from bovine bones, used as an animal feed additive or as fertiliser (submitted to the SSC at its meeting of 6-7 March 2003) (EC, 2003a).
- Updated [opinion](#) on the safety with regard to TSE risks of gelatine derived from ruminant bones or hides (adopted by the SSC at its meeting of 6-7 March 2003) (EC, 2003b).
- [Opinion and report](#), assessment of the human BSE risk posed by bovine vertebral column including dorsal root ganglia (adopted on 16 May 2002) (EC, 2002).
- [Revised opinion and report](#) on the safety of tallow obtained from ruminant slaughter by-products (adopted on 28-29 June 2001, editorial clarifications introduced at the meeting of 6-7 September 2001) (EC, 2001a).
- [Report and Scientific Opinion](#) on mammalian derived meat and bone meal forming a cross-contaminant of animal feedstuffs adopted by the Scientific Steering Committee at its meeting of 24-25 September 1998 (EC, 1998).

c) Advise on how to interpret the results of the calculation in view of making an estimation of the number of potential BSE and vCJD cases expected per year in a population.



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1.2. Addressing the Mandate

Part (a) of the above ToR has been finalised and, while recognising that it would need continual review to take into account new data, the validity of the working QRA document was accepted by the Experts of the Scientific Panel on Biological Hazards. This working document including the assumptions and the calculations as carried out by a joint WG and the DNV Consultancy can now be used to guide an update of the SSC opinions listed above.

This opinion addresses parts (b) and (c) of the ToR's to provide the European Commission with updates of the requested opinions and concerns specifically the following opinion and report :

On the safety of tallow obtained from ruminant slaughter by-products (adopted on 28-29 June 2001, editorial clarifications introduced at the meeting of 6-7 September 2001) (EC, 2001a).

2. Tallow

2.1. Definition of Edible Tallow

Tallow refers to a wide range of animal fats and covers human edible products (meat products) produced from animals “fit for human consumption”¹ to “industrial use”² products manufactured from specified risk material (SRM). Within the context of this report, tallow is defined as fats obtained by extraction by melting or by processing of cattle (by-) products such as discrete adipose tissue masses³, trimmings, bones, certain slaughter offals, etc. This crude fat can be further purified by centrifugation, filtration, treatment with phosphoric acid or by thermal refining.

Edible tallows have low initial levels of impurity and, according to the European Fat Producers and Renderers Association (EFPRA, 2001a), are usually produced with final total impurity levels of <0.02% although the legal requirement is a maximum impurity level of 0.15%. This impurity is probably

¹ “Fit for human consumption” refers to material from animals that passed both *ante-* and *post mortem* inspection by a competent veterinary authority and that are certified and identifiable as fit for human consumption on the basis of the existing national and EU legislation. (Under certain conditions, this may imply that materials are considered fit for human consumption after a *post mortem* inspection following an unsatisfactory *ante mortem*.)

² “Industrial use” means that the end product is neither for direct nor for indirect human or animal consumption or use, including as a cosmetic nor as a pharmaceutical product.

³ Discrete adipose tissue is internal and external body fat removed during the slaughter and cutting process, in particular fresh fat from the heart, caul, kidneys and mesentery of bovine animals, and fat from cutting rooms. Discrete adipose tissue is not bone fat, nor is it fat rendered from multiple cattle tissues whether derived from animals fit for human consumption or from other sources. The safety of intestine-associated discrete adipose tissues is addressed in EC, (2001b).



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both mineral and organic but for the purposes of the QRA, in the absence of analytical data, it was assumed “proteinaceous” and a measure of the contamination of tallow by TSE infectivity. In current legislation, the production of edible tallow for human or animal consumption is only allowed from discrete adipose tissue, and not from a mixture of bone and other tissues or specified risk material. The current bovine SRMs are listed in Table 1⁴.

⁴ Ref EC, 2001b. This definition of SRM has been updated and now includes the mesentery, together with the entire intestine, of bovine animals.



residual BSE risk.

Table 1: Specified Bovine Risk Material in Europe (April 2004)

Cattle	European Union (without UK)	UK	Switzerland
Skull (including brain and eyes but excluding mandible)	>12 months*	-	>6 months
Entire head excluding tongue	-	> 6 months	>30 months
Tonsils	All ages	All ages	All ages
Spinal cord	>12 months	>6 months	>6 months
Vertebral column (including dorsal root ganglia - DRG – but excluding vertebrae of the tail and the spinous and transverse processes of cervical, lumbar and thoracic vertebrae and the median sacral crest and wings of the sacrum)	>12 months	>30 months	>30 months (includes tail)
Intestines (from duodenum to rectum) and mesentery	All ages	All ages	>6 months
Spleen	-	>6 months	>6 months
Thymus	-	>6 months	>6 months
Visible lymph nodes and nervous tissue	-	-	All ages

* Age of cattle from which the tissue/body part is considered SRM



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2.2. The Production of Tallow

The European Fat Processors and Renderers Association (EFPPRA) members produce tallow by fat melting and/or rendering of raw materials. These were the activities that were reviewed in the QRA of residual BSE risk and are shown diagrammatically in figure 1.

a) Fat melting

Cattle fatty tissues are usually melted for food and feed applications in dedicated processing facilities and the raw materials are fresh slaughter-fats (discrete adipose tissues) fit for human consumption (EFPPRA, 2001b). The tissues are gently heat-treated (<95 °C) to maintain the high quality of tallow and it is purified, mainly by separation and filtration, in order to reduce any residual insoluble impurities. *Premier Jus*, the highest quality of tallow, is produced for use in soups, sauces, margarine and frying and for the calf milk replacers industry. Commercial values of 0.02% insoluble impurities have been reported for tallow for use in foods and calf milk replacers.

b) Rendering (a mixture of) other tissues such as bones, trimmings, meat rests and slaughter offals into tallow

Rendering is a process of crushing, grinding, heating, optional steam sparging and pressing mixtures of cattle tissues fit for human consumption to extract fat. Tallow extracted by rendering a mixture of tissues at < 100°C is used for feed, petfood and industrial (non-food) applications. The tallow is purified to below 0.15% insoluble impurities. The extracted residue is referred to as greaves and can be further refined to produce meat and bone meal. Fats can also be obtained by pressing after rendering at "133°C/20/3 bars" of (a mixture of) high risk tissues⁵. A summary of these processing systems, their raw materials and products, is given in Table 2 (See: EC, 2001a, EFPPRA, 2001b; EFPPRA, 2001c). A good overview of current practices in processing fat is given in a recent article by Woodgate and van der Veen (2004).

2.3. Tallow Impurities

Crude tallow is stored in large holding tanks before sale and insoluble solids (up to 0.5%) may settle out on storage. Up to 85% of the impurities may be proteinaceous⁶,

⁵ These are animals by-products with a risk of spreading communicable diseases to animals and humans (i.e. cadavers, animals which has died with clinical signs of diseases, animals killed in the framework of disease eradication plan, slaughterhouses' condemned material). The highest risk materials are those with an unknown or TSE risk, or a risk related to contamination with banned substances or environmental toxins such as dioxin or polychlorobiphenyls. At present these materials must be disposed of as waste by incineration, co-incineration or as landfill (EC, 1999).

⁶ Analyses reported on by EFPPRA (2001b) and carried out in 1998 show much lower values. Crude protein levels in the impurities, determined for 6 samples, ranged from 5 to 16 %. The crude protein is calculated with the assumption that all nitrogen is present as protein molecules (which is not certain, because of the possible presence of NPN -Non Protein Nitrogen-) with 16%N (factor 6.25). In 1998 higher levels of impurities were common, prior to the current legislation requiring maximum impurity levels of 0.15%.



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although no reliable data are available on this level (EC, 2001a). The separation of fat from proteins and other impurities can be done by centrifugation or microfiltration using ceramics alone (earth filtering, clays, bentonite, montmorillonite, philipsite) or with co-adjuvants (celite). Further treatment of tallow with a phosphoric acid/water solution, followed by centrifugation, can improve residual nitrogen levels to less than 0.01%. Edible tallow (premier jus) has residual insoluble impurities of max 0.02%.

All these processes are usually done at a temperature around or over 80°C and the refinement of the fat achieved by the filtration and centrifugation steps will depend upon the quality of the raw materials and the production process. No data are available for the evaluation of these processes for the removal or inactivation of TSE infectivity.

2.4. Deodorisation

Edible fat is sparged with steam under pressure to de-aerate and de-gum the viscous liquid and then heated to 240 degrees C under vacuum to remove unpleasant smells (EFPPRA, 2001b). The total residence time is 1 hour and the fat is thoroughly mixed during this process. The volatile matter removed by the steam is condensed separately to produce a Fatty Acid Distillate: this distillate is not used for human food. The deodorised fat is stored at about 65 degrees C under a nitrogen atmosphere prior to use. This process will significantly reduced levels of TSE infectivity (D. Taylor, pers. comm. May 2001) although this reduction was not taken into account in the QRA because of the lack of inactivation data for this treatment.

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Table 2: Production, sources and use of tallow

Type of tallow produced	Edible tallow, Premier jus, FFA max 0,50% (legally max 0,75%) Edible tallow, others, FFA max 1,25% Tallow for refining, FFA max 3,0%	Rendered ruminant tallow, FFA max 1% to max 15%
Type of industry	Fat processors	Renderers
Legislation	Council directive 92/5/EEG as amended	Regulation 1774/2002 as amended
Intended use (tallow)	Human or animal use	Animal or industrial use
Source Animal class	Approved fit for human consumption	Approved fit for human consumption (cat.3 : low risk material)
Animal by-product class	Fit for human consumption	Fit for animal consumption : low risk material (dead animals banned from feed as from 1 March 2001)
Type animal by -products	Fresh slaughterfats from bovines : fatty tissues from the kidney area, « mesogastrium » mesentery and cutting fats (minimal) readily removed during slaughter in the slaughterhouse or cutting plants (fat content fatty tissue from kidney area : 80% fat)	Animal byproducts from bovine, ovine and caprine All other ruminant tissues (SRM excluded) : cutting fats, bones, etc.
Bones as raw material	Bones are not used as raw material	Bones are used as raw material. In specific cases, bones are processed separately to produce bonemeal (40% protein) and bonefat (e.g. bone processors)
Species dedicated	Always applied	Is occurring in specific cases
Other products produced	Wet greaves, proteinwater, greavesmeal (80% protein)	Meat meal, meat and bone meal, bonemeal (protein 40-60%), greavesmeal (80% protein)
Tallow production process	1. <u>Wet melting process (premier jus)</u> Mincing, direct steam injection (95°C), purification by decantation, centrifugation and filtration (bag filters, aid free) 2. <u>Dry melting process</u> Mincing, indirect heating (e.g. 135°C ; disc dryer), purification by decantation, pressing, centrifugation and filtration	1. <u>Dry rendering process</u> : the tallow is separated from the proteins after indirect drying ; mincing, indirect heating (e.g.135°C disc dryer), purification by decantation, pressing, centrifugation and filtration. Pre- or post-sterilisation can be applied. 2. <u>Wet rendering process</u> : the tallow is separated from the proteins before removal of the water ; mincing, heating, purification by decantation, centrifugation and filtration. Pre- or post-sterilisation can be applied.
Sterilisation 133°C/20'/3 bars	Only applied on animal protein destined for feed (temporary banned)	For both methods pre sterilisation on raw material or post sterilisation on purified tallow and/or meal is used. The sterilisation of animal proteins destined for petfood and tallow from LRM destined for feed/petfood is not required (derogations on sterilisation 1999/534/EC are applied in practice).
Residual insoluble impurities	No legal requirements for the moment, but 0.15% becomes mandatory from 1/1/2006 on. For commercial reasons a maximum of 0.02% is mostly applied	Max 0.15%
Applications tallow	<u>Food</u> : soups, sauces, margarine, frying medium <u>Feed</u> : mainly calf milk replacers <u>Petfood</u> : petfood ingredient	<u>Feed</u> : feed ingredient <u>Petfood</u> : petfood ingredient <u>Industrial</u> :oleochemistry, cosmetics, soaps, detergents, fuel
Remarks	For commercial reasons this tallow is refined or deodorised (e.g. removal of FFA, odour, colour and impurities). Refined tallow FFA max. 0,30%	

Notes (EFPR, 2001c): Dry rendering is a process where proteins and fats are dried together and the fat is removed after drying. Fat removal is normally done by pressing. To obtain a clean fat further centrifugation is performed.

Wet rendering is a process where proteins and fats are separated before the drying process. The separation is done by pressing or centrifugation. The wet defatted protein fraction is dried separately. The fat fraction is separated from the process water by centrifugation and the process water (glue water) is normally concentrated and dried together with the protein fraction. Further fat cleaning is done by centrifugation (or filtration).

In as well the dry and the wet rendering process sterilisation can take place at the beginning of the process (pre-sterilisation) or the final products, meal and fat can be sterilised in steam atmosphere.

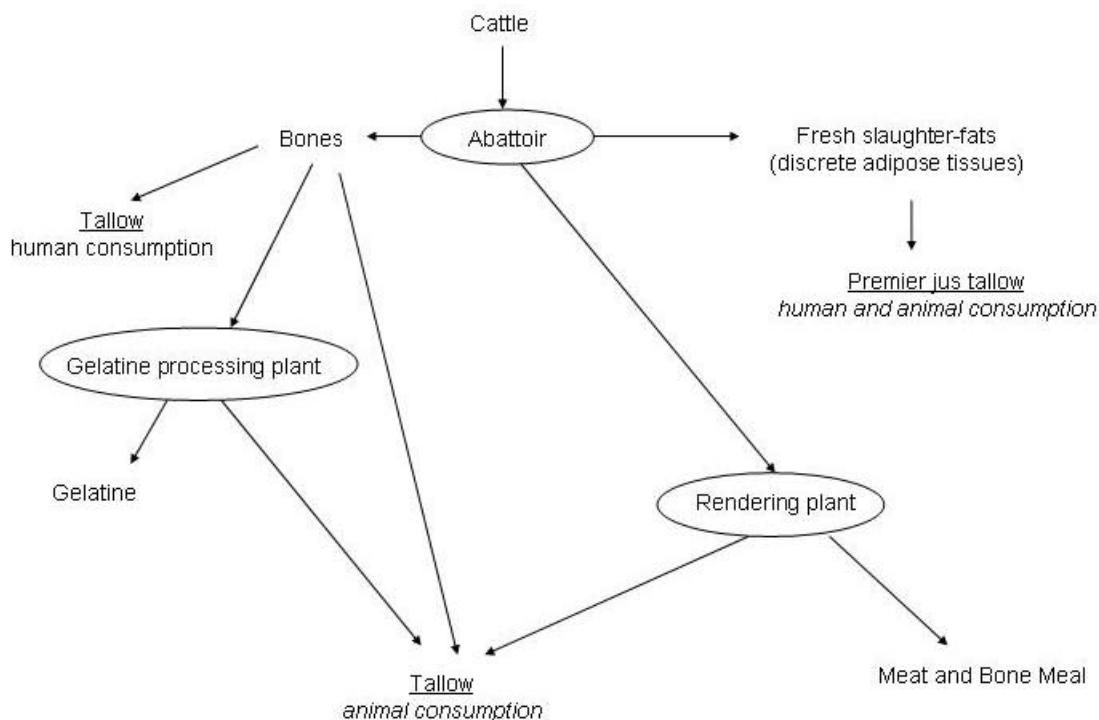
Depending on the nature of the raw material pre-sterilisation might give technical problems due to cooking out of glue from the proteins or from creating fines.

Glue will give difficulties during drying and fines will give difficulties cleaning the fat by centrifugation (or filtration).

A post-sterilisation process can therefore sometimes but not always be changed to a pre-sterilisation process as this might give technical problems. Furthermore a pre-sterilisation process will give a darker coloured fat due to the heating process in contact with the proteins.

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Figure 1: The Rendering Process and the production of tallow



3. Conclusions of the SSC opinion (EC, 2001a) relevant to the quantitative assessment of residual BSE risk

The SSC was asked to address the following question in its mandate for the Opinion and Report on “The safety of tallow obtained from ruminant slaughter by-products” (revised and adopted 28-29th June 2001) (EC, 2001a):

“Under what conditions can industrially produced tallow obtained from ruminant slaughter be safely used for food, feed or other applications ?”

The SSC considered the factors influencing TSE risk in tallow and, based on a qualitative assessment of that risk, summarized the various safety criteria that needed to apply to the production of tallow from ruminant slaughter by-products to minimize exposure of humans and ruminants to BSE. The safety criteria were considered for countries with different geographical BSE risk and are reproduced for ruminant slaughter by-products in Table 3 and in the italicized text below.

Table 3. Summary overview of safety criteria for tallow obtained from ruminant slaughter by-products

TALLOW FROM MELTING DISCRETE ADIPOSE TISSUES FROM ANIMALS FIT FOR HUMAN CONSUMPTION		TALLOW FROM RENDERING OTHER TISSUES FROM ANIMALS FIT FOR HUMAN CONSUMPTION		TALLOW FROM CERTAIN TISSUES FROM ANIMALS NOT FIT FOR HUMAN CONSUMPTION
<i>GBR LEVEL I</i>	<i>GBR LEVELS II, III, AND IV</i>	<i>GBR LEVEL I</i>	<i>GBR LEVELS II, III AND IV</i>	
	<p>If specified risk materials removed* and if either:</p> <ul style="list-style-type: none"> - discrete fat tissues that were intended for or associated with animal products intended for human consumption and that were handled as such (see Section 2.a. of the text) or: - Other discrete adipose tissues not intended for direct human consumption as such, with the exception of certain digestive tract-associated discrete adipose tissues as described in the SSC opinion of 28-29 June 2001⁷, and provided the fat collection procedure is able to prevent contamination with potentially BSE infected materials and provided dedicated manufacturing lines are used. <p>Filtration to 0.02% insoluble impurities</p> <p>Tallow for all uses (e.g., food, pet food, feed, milk replacers, industrial uses, tallow derivatives, cosmetics, ...)</p>		<p>If specified risk materials removed *:</p> <ul style="list-style-type: none"> - Filtration to maximum 0.15% insoluble impurities and (except for exclusive industrial applications) pre-sterilisation at "133°C/20'/3bars": <p>Tallow for restricted uses including pet food and feed (with the exception of calf and lam feed) but excluding food (see text).</p>	<p>If specified risk materials removed and provided that the "Fallen stock" opinion of 25 June 1999 is respected:</p> <ul style="list-style-type: none"> - Filtration to max. 0.15% insoluble impurities. <p>Tallow for restricted uses such as industrial ones.</p>

(*) It is noted that, with respect to the production of tallow and with regard to the risk of intra-species recycling of TSEs, the list of specified risk materials is different for small ruminants and cattle. This may imply that in practice most fatty tissues of small ruminants may pose a risk if transformed into feed, if the presence of TSE infectivity cannot be excluded. (EC, 2001b)

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3.1. General principles

- a. *There is no evidence that tallow derived from ruminant animals would constitute a TSE risk. The SSC considers that possible TSE risks associated with tallow will result from protein impurities that may be present in the end product, because it is expected that TSE agents, if present in the product, would be associated with these impurities.*
- b. *As the safety of most products⁸ can currently not (yet) be assessed exclusively on the basis of the infectivity reduction capacity of a production process alone, consideration needs also to be given to safety criteria such as the geographical source of the raw materials, the individual animal source of the by-products, the presence of specified risk materials, the risk of (cross-) contamination, the level of residual impurities and the intended use.*

In this opinion the tallow production has been assessed in three parts: (1) sourcing of the animals and the tissues, (2) the fat extraction processes and (3) the possible sterilisation processes.

1. Sourcing of the animals and the tissues.

The SSC considers that the main protection against TSE infection of tallow is safe sourcing of animals and materials based on the recommendations made in the various SSC opinions on product safety, geographical risk, specified risk materials and avoidance of cross-contamination. The risk associated with raw materials from animals fit for human consumption, following ante- and post mortem inspection⁹ and after careful removal of the specified risk materials is considered to be sufficiently low for them to be used for the production of tallow.

For certain raw materials, inclusion or contamination with infectious materials cannot be excluded, as parts of specified risk materials might accidentally be mixed with the raw materials. This risk is considered to be negligible for discrete fat tissues that are intended for or associated with products destined for human consumption and that are handled as such, for example: fat and certain bones sold on the meat, discrete fat tissues removed during meat cutting or from carcass parts approved for human consumption and entering a dedicated storage, transport and production line.

The risk of inclusion or contamination with infectious materials is considered to be higher for slaughter by-products that initially are not intended for direct human consumption. These are, for example: slaughter by-products such as bones and certain slaughter offals. The risk is expected to be higher for bones and (mixtures of) slaughter offals (by-

⁸The SSC is aware of the limitations of the currently available methods and techniques for the assessment of (residual) TSE infectivity in products and tissues. These are detailed in the attached report or discussed in other opinions of the SSC, for example the opinion of 13-14 April 2000 on *Oral exposure of humans to the BSE agent: infective dose and species barrier.*

⁹If and where appropriate: including a rapid BSE test.

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products) as compared to discrete adipose tissues (provided the intestine-associated risks are excluded¹⁰.)

2. *Fat extraction processes.*

A priori the fat extraction procedure excludes most proteinaceous material and hence probably most infectivity, unless there is selective partitioning of infectivity into the fat phases during extraction. There is little evidence for or against this possibility. Filtration steps in the process may trap some infectivity, if infectivity follows the bulk of proteinaceous material. However it is probable that significant reduction of infectivity occurs during processing by reducing the non fat matter during the filtration and purification stages.

3 *Sterilisation processes*

Some TSE strains are not completely inactivated at 133°C during 20 minutes even when fully hydrated. When dehydrated greater survival of infectivity at higher temperatures is found. In general, TSEs are more readily inactivated by wet than dry heat. This may be because hydrated infective agent is more susceptible to inactivation than dehydrated (or otherwise fixed) agent. The hydration state of protein, or specifically TSE infectivity, after the fat extraction procedure is not known, nor is it known how it might change when exposed to wet heat sterilisation at 133°C. If the extraction procedure dehydrates (or otherwise fixes) the infectivity then it is more likely to survive.

c. *The SSC points out that the list of specified risk materials is different for small ruminants and cattle. This may imply that in practice most fatty tissues of small ruminants may pose a risk if transformed into feed for certain animal species, if the presence of BSE infectivity cannot be excluded.¹⁰ and if a risk of propagation of scrapie exists.*

d. *For all countries¹¹, sourcing of raw materials from animals declared fit for human consumption following appropriate ante- and post-mortem inspection will reduce TSE risk for humans and animals.*

For countries where the presence of BSE is highly unlikely (GBR level I), additional conditions regarding minimal production processes, purification levels or removal of specified risk materials such raw materials will not result in an additional (TSE) risk reduction. For other countries, the additional exclusion of specified risk materials will further significantly reduce the possible risk of residual TSE infectivity being present in tallow.

e. *Given the fact that animals and materials that carry an actual or suspected TSE risk should be disposed of, the SSC, in the line of its opinion on "Fallen stock" opinion of 24-25 June 1999, considers that purified tallow derivatives can be considered to be safe provided the production process uses the*

¹⁰Ref. EC, 2001b; EC, 2001c

¹¹ Ref. EC, 1999 on "Fallen stock", which recommends the exclusion of fallen stock also in GBR I countries, to avoid recycling of unrecognised first cases.

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appropriate, validated and scientifically most up-to-date methods and processes in terms of eliminating and inactivating the TSE agent. The material should in addition be sourced respecting the recommendations made in the SSC opinion of 25 June 1999 on "Fallen stock"

- f. *The SSC considers that separate storage, transport and use of industrial tallow is needed to avoid possible mixed uses or contamination with food or feed-grade tallow. Also, if the intended end use cannot be verified and controlled to exclude any human or animal consumption or use, then the conditions outlined for food-standard tallow should apply also for tallow for industrial or technical use.*

3.2. Specific recommendations

a. Tallow obtained from melting discrete adipose tissues sourced from animals fit for human consumption.

- *The SSC considers that tallow derived from discrete fat tissues that were intended for or associated with carcass parts intended for human consumption and that were handled as such, is as safe as meat and can therefore be used for all applications. Such raw materials are, for example: fat and certain bones sold on the meat, discrete fat tissues removed during meat cutting or from carcass parts approved for human consumption. Dedicated storage, transport and production lines for these raw materials will further minimise the risk of contamination with TSE agent.*
- *Other discrete adipose tissues not intended for direct human consumption as such can also safely be used for all applications, with the exception of certain digestive tract-associated discrete adipose tissues as described in the SSC opinion of 28-29 June 2001¹², and provided the fat collection procedure is able to prevent contamination with potentially BSE infected materials and provided dedicated manufacturing lines are used.*
- *The SSC considers that the current practice adhered to by most European tallow industries to purify the tallow derived from these source materials to a maximum level of insoluble impurities of 0.02%, will reduce the residual risk, if any, to a negligible level.*

Notes:

- *For uses which imply a contact with skin or open wounds (e.g., as a constituent of ointments) the use of a food-standard tallow is recommendable.*
- *The Scientific Steering Committee has examined the existing licensed uses in the E.U. of tallow and is not aware of any licensed use of tallow as an injectable product or for possible parenteral pharmaceutical applications. If it were to be used as such, the SSC would need to issue an additional opinion.*

¹² Ref EC, 2001b.

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b. **Tallow obtained from rendering other tissues sourced from animals fit for human consumption.**

These tissues can be safely used for the production of tallow in feed (but excluding calf feed¹³), petfood, as well as industrial/technical tallow, under the following conditions.

- *The produced tallow should be purified to levels below 0.15% insoluble impurities. Because of the higher risk of inclusion or contamination with infectious materials pointed out in section 1, a sterilisation process (see hereafter) should in addition be applied if the tallow is used as feed or petfood¹⁴.*

So far, only the "133°C/20'/3 bars" process, applied as a pre-sterilisation to a mixture of fresh tissues has been validated in terms of TSE infectivity clearance. Tallow derived (pressed and filtered) from such pre-sterilised material (or by a process that has been validated to be equivalent in terms of TSE inactivation) can be considered to pose no risk, although it is recognised that the end-product is likely to be of a minor quality.

No validated and operationally exploitable results are available on the clearance achieved by other processes, for example post-sterilisation of fats (e.g., 133°/20'/3 bars; the current deodorization processes). Although it is recognised that post-sterilisation processes have some clearance capacity, they should first be validated before they can be accepted as equivalent to pre-sterilisation.

Tallow derived from (a mixture) of tissues other than discrete adipose tissues and not submitted to a pre-sterilisation should therefore, pending the validation of the TSE infectivity clearance capacity of post-sterilisation processes, only be used for certain industrial applications and for the production of tallow-derivatives.

The SSC recommends that research is done on the TSE clearance capacity of processes, for example of post-sterilisation.

c. **Tallow obtained from rendering other tissues sourced from animals possibly not fit for human consumption.**

If the animals from which the raw material is derived are not fit for human consumption, tissues can be safely used for the production of industrial or technical tallow provided the recommendations on sourcing, heat/pressure treatment and removal of specified risk materials specified in the SSC opinion of 25 June 1999 on "Fallen stock"¹⁵ are complied with. It should in addition be purified to max. 0.15% insoluble impurities.

¹³ Tallow in calf feed (including in milk replacers) is excluded here because of the high amounts of such tallow that may be consumed by the young animals and because the susceptibility to infection of young animals may be higher.

¹⁴ See EC, 1999 signalling the evidence that the agent of FSE in cats is identical to BSE in bovines and considering anecdotal reports of individuals eating processed pet food as a source of meat and protein.

¹⁵ Complete title: *The risks of non conventional transmissible agents, conventional infectious agents or other hazards such as toxic substances entering the human food or animal feed chains via raw material from fallen stock*



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4. The QRA and the approach to updating the Opinion

Since 2001 little new research data has come to light that might substantially alter these conclusions of the SSC but it was felt that its advice might change if a quantitative analysis of the residual BSE risk of tallow from animal by-products were considered. Therefore a quantitative assessment of the residual BSE risk in bovine-derived products has been prepared (EFSA QRA Report, 2004). Herein we review the SSC safety criteria for the production of tallow from bovine slaughter by-products in the light of the EFSA QRA.

Quantitative risk assessment of food-borne pathogens has emerged as a powerful methodology for estimating how likely, and at what level, an individual or population will be exposed to a microbial hazard. The quantitative assessment of residual BSE risk in tallow posed by cattle-derived products to humans and animals required information for the following input variables:

- 1) The species barrier.
- 2) The possible infectious load of the cattle by-products.
- 3) The prevalence of BSE positive animals that become slaughtered for food.
- 4) The typical size of the batch of raw materials entering the production chain.
- 5) The effects of processing on infectious load
- 6) The size of batch of the end product.
- 7) The amount consumed per intake.

Two main scenarios were considered by the QRA WG : the residual risk due to i) cross-contamination of discrete fats, and ii) the production of tallow from a mixture of by-products and offals. The reasoning behind these scenarios is outlined below.

- i) The possible residual risk results from contamination of fats.

For fats from fat tissues, the risk of contamination will depend upon the type of fats used, fats removed before splitting of the carcass versus cutting fats obtained from other parts of the carcass after splitting, the slaughtering method and the precautions taken during slaughtering and the techniques used for the subsequent processes such as cutting, fat removal, de-boning, etc.

- a) The fat tissues are removed as a dedicated process at the slaughterhouse, before splitting of the carcass. The abdominal contents (stomach, spleen, complete intestine and associated mesentery) are sent directly from the slaughter place to the gut room and the risk of inclusion of mesenteric fat and intestine material (e.g., ileum) is (very) low.
- b) The fat tissues can be obtained from other sources or by using other techniques (e.g., discrete adipose tissues like kidney fats and cutting fats, after removal of the intestine). Some contamination cannot be excluded *a priori* for

and dead animals (including also: ruminants, pigs, poultry, fish, wild/exotic/zoo animals, fur animals, cats, laboratory animals and fish) or via condemned materials.

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the adipose fat tissues obtained during the cutting and deboning stages because the carcass pieces may have been spiked with spinal cord, brain, marrow particles or fluids. This contamination will be proportional to the amount of spinal cord spilled and to the weight of the cutting fats as a fraction of the total carcass weight after splitting. For example, a reasonable range for spinal cord spillage would be 1 to 10% of its total weight and a reasonable fraction of cutting fats as proportion of the carcass weight after splitting would be approximately 10%.

c) Accidental inclusion of distal ileum with the mesenteric fat tissue was considered. However, in the EU, the risk of contamination with ileum is currently substantially reduced because:

- All the intestine including the distal ileum, and all the mesentery, is now classified as SRM. The entire intestine, including the ileum and mesentery generally, remains intact and is disposed of as SRM. The omental fat is removed from the stomach in the green offal room.
- The intestines, including the distal ileum, can not be confused with the fat tissues recovered for processing, i.e. the omental fat (or caul fat). The accidental inclusion of distal ileum, as an intact part of the intestines, with other discrete adipose tissues is not plausible.
- In certain situations, particularly if fat is being collected for processing for human consumption, the omental fat will be removed from the rumen in the abattoir itself. This is generally done on the evisceration table and so the accidental contamination of this discrete adipose tissues with the ileum is unlikely.

ii) Tallow from a mixture of by-products and offals

The following scenarios have been envisaged:

- a) No specified risk materials (SRMs) are removed with the exception of the parts sold for human consumption, the hide, the manure, the hooves, etc., and all by-products and offals are rendered.
- b) Specified risk materials are removed (spleen, ileum, skull, spinal cord, etc), with the exception of the vertebral column.

In a worst case scenario, in a poorly regulated abattoir, the WG considered that contamination of this material might occur by accidental inclusion in a batch of 1 spinal cord and 1 ileum as well as of contamination with brain and DRG tissue residues from 1 BSE positive animal. This is highly unlikely to occur in a well-supervised slaughter house. The ileum, the vertebral column and spinal cord are quite visible materials and unlikely to be missed. Additionally, in certain abattoirs, the spinal cord is removed by aspiration and its accidental inclusion within these materials is again highly unlikely.

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c) All specified risk materials are removed including the vertebral column. It is assumed that the BSE infectivity that could be contained in this material consists of the possible accidental inclusion in a batch of 1 ileum per batch as well as of contamination with brain and DRG tissue residues from 1 BSE positive animal.

d) As above, but *in addition* it is assumed that bone marrow is infectious.

5. Analysis of the Residual Risk quantification in relation to production of tallow according to tissue sourcing and processing of fats

The range of possible conditions addressed for the sourcing of tallow are described in the (EFSA QRA Report, 2004). Here, as requested in the mandate, we consider revision of the specific recommendations of the Opinion (EC 2001a) with respect to tallow from fat tissues and tallow from rendered mixtures of tissues as summarised in Table 3. The purpose of the revision of the Opinion with respect to the QRA Report is to establish the conditions under which tallow can be authorized for use in food and feed. The QRA considers only cattle infected with BSE, not sheep and goats. Therefore any mention of animals or ruminants in the text of this opinion refers to cattle only and not to any other animal.

5.1. Tallow produced from GBRI countries

The Opinion (EC2001a) considered that as a general principle for all countries, sourcing of raw materials for animals declared fit for human consumption reduced the TSE risk for humans and animals. For GBRI countries it has been recommended that “fallen stock” be excluded from use for sourcing raw materials. The Report (EFSA QRA Report, 2004) considers, consistent with the Opinion therefore, that the residual risk in products from animals sourced from GBRI countries is negligible if “fallen stock” continuous to be excluded from use for sourcing raw materials. It therefore does not consider there is further risk associated with sourcing of tissues for tallow from such countries.

5.2. Tallow produced from melting discrete adipose tissues of cattle fit for human consumption sourced from a GBRI II, III, IV countries for food and feed

In the SSC Opinion (EC, 2001a), the conditions of production and usage of tallow assume that specified risk materials are removed, the fat collection procedure is able to prevent contamination with potentially BSE-infected materials, that dedicated manufacturing lines are used and that filtration to 0.02% insoluble impurities is achieved. One of the purposes of the quantitative risk assessment was to pose “what if” scenarios of non-compliance with these requirements and gauge the effect on risk to humans and cattle.

In the QRA Report, spinal cord spilled following carcass splitting is considered the major source of infectivity possibly contaminating the discrete adipose tissues of animals fit for human consumption. Thus if the fat is collected before splitting, the risk of infectivity being present is eliminated. For fat tissues obtained after carcass splitting potential contamination may result from spilled spinal cord. The QRA Report

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also considers that contamination of fats from inclusion of certain SRM (distal ileum/mesenteric fat) is substantially reduced by current practices. Omental fat, which is removed from the carcass with the viscera before splitting, poses the same zero risk as for direct adipose tissue when removed in this manner. We concur with the QRA Report report that accidental contamination with the ileum is unlikely. No quantitative assessment of risk is available for omental fat so no change to the SSC opinion is possible.

The residual infectivities calculated for tallow produced for food from fat tissues fit for human consumption by filtration to 0.02% are shown in the EFSA QRA Report (2004) in tables I.13 to I.18 and Table 7 Summary of Human Exposure to BSE infectivity which is reproduced in Annex 1 of this Report. If fat is collected both before and after splitting and considering a worst case (e.g. GBR IV country, Annex 1) it is estimated that there is a 97.5 percent probability/confidence (p97.5%) that the value of the residual risk is less than or equal to 1.3×10^{-9} CoID50 units per person per week. If fat is collected before and after splitting from a GBR III country (unreliable surveillance) it is estimated that there is a 97.5 percent probability/confidence that the value of the residual risk is less than or equal to 1.8×10^{-10} CoID50 units per person per week. Reliable surveillance decreases this risk by 10 fold (4×10^{-11}).

The residual infectivities calculated for feed (Veal calves - 180 day exposure period and Replacement calves 60 day exposure period) from fat tissues fit for human consumption by filtration to 0.02% are shown in the EFSA QRA Report (2004) shown in tables I.31 to I.36 and Table 8 “Summary of Residual BSE Risk results for Exposures to Cattle BSE infectivity”. Table 8 is reproduced in Annex 2 of this Report. For all countries, irrespective of GBR, fats obtained before carcass splitting carry a zero risk. If fat is collected both before and after splitting from a GBR IV country, it is estimated that there is a 97.5 percent probability/confidence that the value of the residual risk is less than or equal to 2×10^{-6} CoID50 units (veal) and 1×10^{-7} CoID50 units (replacement) if surveillance is unreliable. Reliable surveillance provides a 10 fold improvement in risk. Relative to GBRIII, these values of exposure risk are reduced by a further 10 fold respectively.

The interpretation of these exposure estimates is discussed in Section 6.

5.3. Tallow produced from rendering other tissues of animals fit for human consumption sourced from a GBR II, III, IV countries for feed (with the exception of calf and lamb rations)

As previously recommended in the Opinion (EC, 2001a) the conditions of production assume that specified risk materials are removed, filtration to 0.15% insoluble impurities and pre-sterilisation at 133C/20'/3bars (except for some industrial cases) are carried out.

The QRA Report provides data on scenarios for the production of tallow from a mixture of tissues for calf feed which is not authorized (only from discrete adipose tissues) and therefore does not directly give assessments for the use of tallow from rendering for feed of adult cattle, sheep etc., and for use in pet food. The QRA model

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would need to be run with data acquired to reflect a specific use in feed or pet food. Nevertheless, the values provided in the QRA Report for production of calf feed from a mixture of tissues (5.3.2) provide a comparison with the legitimate production of calf feed from discrete adipose tissues (5.2).

5.3.1. Tallow from Bones

Tallow from bones collected at slaughterhouses, cutting plants or meat processing plants may be used for food and feed. Tallow from bones as a by-product of the gelatine industry may only be used for feed. These results are given in Annex 1 and discussed below.

For country scenario GBRIII, the median value (P50) of the residual risk is zero for all three options with reliable surveillance and with unreliable surveillance it is estimated to be less than 1×10^{-13} CoID50. The P97.5 values are 7×10^{-11} with reliable surveillance and 2×10^{-10} CoID50 with unreliable surveillance. The results for a GBRIV country scenario are a factor of 10 or more greater than those for GBRIII, with the median value (P50) of the residual risk estimated to be 7×10^{-11} if the skull and vertebral column is not removed, reducing to 5×10^{-12} with removal of the skull and vertebral column (both for unreliable surveillance).

From the mean values it can be seen that the residual risk for a GBR III country is between 1 and 2 orders of magnitude greater than that for a GBRII country, with a GBRIV country being about one order of magnitude greater than a GBRIII. We refer to annex 5 for a discussion on the meaning of that difference.

The P97.5 value of the residual risk from tallow produced from bovine bones is estimated to be a weekly consumption of 4×10^{10} CoID50 units for a GBRIV country with the skull removed and 5×10^{11} CoID50 units with both the skull and vertebral column removed if there is reliable surveillance. If there is not reliable surveillance these values increase to 1×10^9 and 2×10^{10} CoID50 units respectively

The interpretation of these exposure estimates is discussed in Section 6.

5.3.2. Tallow from Mixture of Tissues

The P50 values for tallow made from a mixture of by-products and offals are zero for most scenarios, necessitating the use of the mean value to characterise the results (Tables I.19 to I.24, Annex 1, QRA Report). It can be seen that the residual BSE risks are very dependant on the degree to which SRMs are removed. If all SRMs are removed the residual BSE risk ranges from 4×10^{-15} for a GBRIII country to 6×10^{-12} CoID50 units for a GBR IV country with reliable surveillance. If no SRMs are removed the BSE risk increases by about a factor of 100. The maximum residual BSE risks are for a GBR IV country with unreliable surveillance when no SRMs are removed; even with this scenario the residual BSE risk is estimated to be about 1×10^8 CoID50 units per week for 97.5% of the time.

The interpretation of these exposure estimates is discussed in Section 6.



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5.4. Tallow produced from tissues of animals not fit for human consumption for restricted industrial uses

As previously recommended in the opinion (EC, 2001a) the conditions of production assume that specified risk materials are removed, filtration to a maximum of 0.15% insoluble impurities and that *the “Fallen stock Opinion of 25th June 1999” is respected*. Tallow from certain tissues from animals not fit for human consumption would have very restricted use (ie mostly industrial grease, etc) and this would not change. *The Fallen stock Report 1999 says:; From 1 April 1997, Decision 96/449/EC4 requires that all mammalian animal waste must be processed in accordance with the following minimum parameters which have been demonstrated as being effective to a certain amount for the inactivation of the agents of scrapie and BSE:- maximum particle size 50 mm; - temperature > 133°C; - time 20 minutes; - pressure (absolute) 3 bar, in a batch or continuous system*. Some products derived from mammalian animal waste are exempt from this new rendering standard, such as petfood produced with low risk material, feed for fur animals, rendered fats, gelatine etc., and, in general, products which can be guaranteed not to enter any food or feed chain. In the case of fallen cattle, sheep and goats either the specified risk materials must be removed or the whole carcass must be destroyed. *So, even for industrial use, tissues for tallow must be non-SRM and pre-sterilised*.

6. How to interpret the results of the calculation in view of making an estimation of the number of potential BSE and vCJD cases expected per year in a population (TOR 3)?

This is by far the most difficult aspect of the mandate to address and was the subject of most discussion within the work group.

6.1. How to interpret the results of the calculation in view of making an estimation of the number of vCJD cases expected per year in a population?

The exposure of the UK population to BSE infectivity was assessed as part of the review of the Over Thirty Month Rule (OTMR). The OTMR review provides a basis for comparison and interpretation of the results of the QRA because they used the same methodology (Comer and Huntly, 2004).

In the OTMR review, the exposure to infectivity in food was assessed by considering the routes by which infective material could be incorporated into food for human consumption including contamination with infected tissues in the abattoir, embolism following slaughter, dorsal root ganglia (DRG) in meat, the use of mechanically recovered meat (MRM) and failure of specified risk material (SRM) controls. Combining these data with the latest results on the timing and tempo of BSE infectivity in CNS or peripheral bovine tissues allowed estimation of the potential exposure of humans to infectivity from any infected animal. These values were then combined with estimates of the numbers of infected animals by incubation period and year to estimate that a total of 54 million bovine oral ID₅₀ units entered the human food chain from 1980 to 2001 in the UK, falling rapidly following the introduction of SRM controls from a peak of about 11 million units in 1993 to about 1 bovine oral ID₅₀ units in 2004 (Comer and Huntly, 2004).



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For comparison with the results of this QRA, these exposure levels need to be divided by 10 and a value of 5 million bovine oral ID₅₀ units consumed by the UK population should be used as the Comer and Huntly calculations were made using a 10-fold higher estimation of the titre of clinical BSE bovine CNS. This would indicate that the average exposure of the population (assumed to be 60 million) over the 20 year period would have been 0.004 bovine oral ID₅₀ units per person per year.

To assess the significance of these exposures for people it is necessary to take account of the cattle to human species barrier. In the QRA Report, the QRA WG recommended that in the absence of data, the cattle to human species barrier should be set at 1, a worst-case scenario. This can now be revised in the light of these new estimates of exposure and of the size of the UK vCJD epidemic. There have been a total 154 cases of vCJD in the United Kingdom (CJDSU website: 4th February 2005, <http://www.cjd.ed.ac.uk/>), and it now seems that there has been a slow down in the numbers of vCJD cases (Clarke & Ghani, 2004). Current estimates of the total size of the vCJD epidemic have reduced significantly from the high numbers thought possible a few years ago to an upper limit of 550 in a recent report (Clarke & Ghani, 2004). In fact Clarke and Ghani give a best estimate of 70 future deaths, and state that *“even in the worst case scenario, when non-MM homozygous individuals are equally susceptible but have longer mean incubation period than MM homozygous individuals, the best estimate of the potential scale of the epidemic is unlikely to exceed 400 future cases.”* Using this upper estimate gives an indication that the species barrier for methionine homozygous individuals may be of the order of 4,000, *indicating that the BSE infectious agent may not be as infectious to people as was once feared.*

In consideration of the TOR: how can the output of the QRA be interpreted in terms of potential human infections? If we follow the cautionary advice of the original QRA WG and assume the species barrier is 1 then there might be on average 1 infected person in the EU per period of time when the residual exposure is around 10⁻⁸ bovine CoID₅₀/person/period of time. This assumes a linear dose-response curve of infectivity at very low doses (see below) and an EU population of 450 million. Therefore any residual exposure equal or higher than 10⁻⁸ bovine CoID₅₀/person/period of time represents a risk to infect people.

If the species barrier was given the value obtained from the analysis carried out on the exposure of the British population to the BSE agent (see above), around 1000-4000, this would mean that there might be on average 1 infected people in the EU per period of time when the exposure risk is 10⁻⁵ bovine CoID₅₀/person/period of time. With this much more optimistic scenario, it could be considered that any residual exposure equal or higher than 10⁻⁵ bovine CoID₅₀/person/period of time represents a risk to infect people.

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The QRA has provided a worst case mean estimate for the human exposure due to tallow made from a mixture of tissues with no SRMs removed sourced from cattle from a GBR IV country with unreliable surveillance of 1.6×10^{-9} bovine oral ID₅₀ units per person per week (see Annex 1, Table, Human exposure to BSE infectivity). Multiplying this by 52 weeks per year results in an exposure of 8.3×10^{-8} bovine oral ID₅₀ units per person per year. Considering the estimate that the exposure of the UK population through food over the BSE epidemic was 0.004 bovine oral ID₅₀ units per person per year this worst case exposure due to tallow is 48,000 times less. Most other scenarios like tallow from fat tissues before and after splitting, GBRIII with reliable surveillance, etc... have relative human exposures ten to one hundred fold smaller than this worst case.

6.2. How to interpret the results of the calculation in view of making an estimation of the number of BSE cases expected per year in a population ?

The QRA provides residual exposure levels expressed in CoID₅₀ per animal per period of exposure for cattle. Since the results show exposure levels that are very small, the question has been raised of how such low levels of exposure can be interpreted.

In the opinion on “Oral exposure of humans to the BSE agent : infective dose and species barrier” (EC, 2000), the SSC “assumed for the time being a linear dose response curve down to the low dose range”, as a “conservative assumption”. However, in risk assessment studies related to drinking water, Gale (1998, 2001) questioned the assumption of a linear dose response. In other words, he questioned the use of the negative exponential dose-response curve that is very similar to a linear low-dose extrapolation (Gale 1998). The reason is that it “is a worst-case in assuming that there is no threshold dose for prions”. He argued that two possible mechanisms have been discussed for a co-operative effect of prions (which are a requirement for a crystalline aggregate of prions such that individual molecules cannot initiate infection, and the fact that the conversion of PrP^{sen} to PrP^{res} proceeds through a co-operative interactive effect between individual PrP molecules within the two-dimensional plane of the lipid bilayer membrane) ; and that a cooperative effect would mean a threshold. While this co-operative mechanism may or may not operate at the molecular level, its consequences for the whole animal are difficult to predict. This is important because whether or not it does produce a threshold effect has a huge impact on the meaning of very low residual exposure level, and hence on this risk assessment.

In order to get a better idea of what happens in the whole animal, we tried to compare the outputs of the QRA for cattle, assuming a linear dose response relationship, with the observed data in different countries that have had BSE cases. We chose 5 different situations : countries with large cattle population, different status of GBR, surveillance and the risk of infection (risk of MBM cross contamination, use of DCP in animal feed, use of tallow). The results and method are given in the Annex. By inspection, the observed data are in the same range of values as the computed data assuming a linear dose response relationship.

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For this reason, and in agreement with previous opinions, we considered a linear dose response curve down to the low dose range is appropriate in order to interpret the results of the QRA.

From a practical point of view, this implies that one can derive an estimate of the number of animals being infected, given the assumptions introduced in the QRA, by multiplying the mean residual exposure level, expressed in CoID50 per animal per period of time by the population size exposed, and divide the number obtained by 2 (because the CoID50 infects only half of the animals exposed). If we apply this calculation to the EU adult (over 2 years of age) cattle population, that is around 45 million individuals, this means that there might be on average 1 infected case of BSE in the EU per period of time when the residual risk is around 10^{-7} CoID50/animal/period of time. For this reason, it can be considered that any residual risk equal or higher than 10^{-7} CoID50/animal/period of time represents a risk of infection in cattle.

Milk replacers are fed to young animals. Considering the Eurostat data, about 30 million calves are raised each year and about 5 millions are veal calves. From these data we can make the assumption that each year, a maximum 5 millions are fed milk replacer dedicated to veal calves and a maximum 20 million are fed milk replacer dedicated to replacement calves ; the others are suckled.

The QRA has provided a mean estimate for the veal calf exposure due to tallow in milk replacers made from a mixture of tissues with no SRMs removed sourced from cattle from a GBR IV country with unreliable surveillance of 2.2×10^{-6} bovine oral ID₅₀ units per calve per time period (180 days) (see Annex 2, Table, Residual BSE risk for exposures to cattle). In a veal calf population of 5 million this might be expected to give rise to ~ 5 infected veal calves per year. The risk in this unrealistic worst case sourcing scenario is lessened by a factor of 25 if cumulative dose of BSE infectivity operates over only a 7 day period (7/180). Most other scenarios – tallow from fat tissues before and after splitting, GBRIII with reliable surveillance, etc - have relative veal calf exposures ten to one hundred fold smaller than this worst case, and so would give rise to less than one infection in the EU per half year.

The QRA has provided a mean estimate for the replacement calve exposure due to tallow in milk replacers made from a mixture of tissues with no SRMs removed sourced from cattle from a GBR IV country with unreliable surveillance of 1.4×10^{-7} bovine oral ID₅₀ units per calve per time period (180 days) (see Annex 2, Table, Residual BSE risk for exposures to cattle). For the 20 million population calves receiving the 'replacement calf' milk replacer (not all are replacement calves, a large part being raised for beef production), this might be expected to give rise to ~ 1 infected calf per year. The risk in this unrealistic worst case sourcing scenario is lessened by a factor of 25 if cumulative dose of BSE infectivity operates over only a 7 day period (7/180). Most other scenarios – tallow from fat tissues before and after splitting, GBRIII with reliable surveillance, etc - have relative replacement calf exposures ten to one hundred fold smaller than this worst case.



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7. Summary and Conclusions

7.1. General comments on the QRA Report (EFSA QRA Report, 2004)

- The general conclusions of the Opinion are supported by the QRA. This should not be surprising since both are made on the same assumptions and many of the parameters fed into the QRA model, at this first stage of its evolution at least, must be regarded as expert opinion rather than factual data. While the Work Group were asked to flag any errors or inconsistencies with the QRA Report or the tallow Opinion and Report, the complete revisions of these documents were not attempted.
- The QRA Report should be considered a dynamic document and, consequently, its content and data need to be revised periodically. The Work Group noted some scientific and political developments relevant to the QRA that had occurred since its inception that should be taken into account during any future assessments. These developments included the expansion of the 15 member states to 25, developments in the resolution of the geographical BSE risk assessment methodology and a re-evaluation of the age susceptibility of cattle to BSE infection (Arnold and Wilesmith, 2004).
- Risk estimates were dependent on the time period over which exposure was considered. These time intervals similarly depended on the likelihood of a cumulative dose effect in cattle and humans, which in turn was inferred by extrapolation from research data in rodent models of prion disease. Future reviews of the QRA of residual BSE risk of cattle by-products would benefit from more data in this area.

7.2. General comments on the Tallow Opinion and Report

- The estimates of risk for tallow production and uses as specified in the Opinion are low and comparisons made with production of tallow using other scenarios of tissue source do not greatly effect the assessment. This may have implications for relaxation of rules.
- In general, the exposure levels calculated here in the case of tallow are so low that they can be regarded as minimal. However it should be stressed that not every scenario, every processing variation, every degree of cumulative dose or every intermediate species barrier value was considered. This is a working model with clear assumptions. It can be re-visited again and again by risk managers to explore alternative scenarios (see below COM questions, 7.3 and 7.4).
- The estimates of such low levels of hazard have such uncertainty that even a 10-fold difference in risk between different scenarios may have a limited significance. Further simulations were executed to investigate this significance (see Annex 4).

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7.3. Answers to questions and scenarios of tallow production specified by COM

Question: What effect does filtration of the tallow have on risk ?

Answer: Does it matter if the tallow is purified to 0.02% or 0.15%? From the assumptions made in the QRA Report because of the lack of experimental data, these filtration steps are pre-determined to make a constant 6.67-fold (1% impurities to 0.15%) or 50-fold (1% impurities to 0.02%) reduction in infectivity titre in the tallow fraction. The filtration is essentially to improve the physical properties of the tallow and, at this level of contamination (or any level), its effect is probably negligible given the assumptions of the QRA WG are correct. While, on average, changing the level of filtration from 0.15% to 0.02% nominally lowers the risk 7.5-fold, this is not significant in the context of these extremely low and uncertain overall risk estimates. Additionally, because of the simple way in which this part of the process was modelled, the probability/confidence of the exposure level being greater than zero is not affected by this step in tallow production.

Question: What difference does it make to the risk of tallow made from discrete fat if the carcass is split first or not split before its removal ?

Answer: In the QRA, spinal cord split following carcass splitting was considered the only source of infectivity contaminating the melting discrete adipose tissues of animals fit for human consumption. Thus, if the fat is collected before splitting there is no risk of infectivity being present, regardless of whether or not SRMs are removed (above, Section 3.2). This contrasts with a maximal residual risk with P97.5 value of $\sim 1.3 \times 10^{-9}$ CoID50 units per person per week for a GBRIV country with unreliable surveillance (Table I.18, Annex 1 of the EFSA QRA Report, 2004).

Question: Does heat treatment of the tallow at 133°C at 3 bar effect the overall risk of the product for cattle, for humans ?

Answer: From the assumption made in the QRA Report based on limited experimental data, these steam/pressure treatments are pre-determined to make a constant reduction of 1.0-3.0 logs of infectivity. The omission of this recommended inactivation step would increase the exposure by 1000-fold. The practical impact of that omission needs to be considered for particular cases by the risk manager.

Question: What effect does the GBR status of the source cattle have on the exposure risk from tallow derived from those animals ?

Answer: From several comparisons, the relative residual risk for a GBR III country is between 1 and 2 orders of magnitude greater than that for a GBR II country, with a GBR IV country being about one order of magnitude greater than a GBR III.

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7.4. Further questions and answers relating to this Tallow Report from COM after adoption of the Opinion and Report by the EFSA Bio-Hazards Panel (April 28th 2005).

Question: Cumulative dose; should an accumulative effect over a longer period of time (a year or even a lifetime) be considered by risk managers when evaluating the outcome of the QRA? At 0.15% filtration and assuming a cumulative evaluation of the estimations, the risk for vCJD has been estimated under certain scenarios in Table A. Do experts still consider the outcome of the QRA for human food very favourable taking the estimations in Table A into account or even possibly an accumulative effect and the average lifespan of 70 years?

Table A

Scenario :	0.02% filtration		0.15% filtration	
	Dose 16 (CoID50/week)	vCJD infections per year ¹⁷	Dose	vCJD infectio ns per year
discrete adipose tissue, GBRIII, reliable surveillance				
97.5 percentile	4.3×10^{-11}	0.5	3.3×10^{-10}	3.7
Mean	5×10^{-12}	0.06	3.8×10^{-11}	0.44

Or

Scenario : Tallow from bones, skull & vertebral column included, filtration 0.15% GBRIII, unreliable surveillance	
Mean CoID50/week	2.4×10^{-10}
Mean CoID50/week	1.3×10^{-8}
Cases per year	2.9

In this case, if the filtration of 0.02% with a risk-reduction of 7.5 was applied, no cases would be seen per year.

¹⁶ These levels of hazard are derived from the Tables in Annex 1 of this Opinion and Report.

¹⁷ This is calculated, assuming a linear dose-response curve at very low dose, as the product of (dose per week) x (weeks per year) x (population of EU) divided by 2 (to account for the fact that an ID₅₀ unit is equivalent to a ½ probability of infection) : eg., $(3.3 \times 10^{-10} \text{ CoID}_{50}/\text{week}) \times (52 \text{ weeks}) \times (450 \cdot 10^6) / 2 = 3.7$.

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Answer (ref. EFSA QRA Report, 2004): The typical batch size of the end-product investigated determines how many ‘typical edible portions’ can be made with one (contaminated) batch. If the size of a typical edible portion is known, it is also possible to determine the infection risks per typical edible portion and/or roughly estimate how many people or animals would actually be (repeatedly) exposed to contaminated meals or medicines (e.g. gelatine capsules).

An accumulative infectivity scenario may be valid if the interval of administration is not too long (probably less than about 2 to 3 days) and if the repeated doses are sufficiently high so that an infective dose is reached - the repeated individual doses must be higher than the capacity of an individual to inactivate the infectivity during the interval of administration. From laboratory results it appears that the clearance period is approximately 24-48 hours in rodent models (Diringer, et al, 1998); beyond that, macrophages are again capable to take up their clearance function. Further research in this area is needed. The working group considered that summation of daily intakes over a period of one week would reasonably simulate the possible cumulative effect of repeated doses.

The EFSA WG also considered more recent work by McLean and her colleagues (Gravenor et al., 2003) who concluded that “a fixed total [prion] dose has a significantly reduced probability of causing infection if the material is presented as multiple challenges, and as the time between challenges lengthens a trend exists for the risk of infection with prion disease to increase with repeated doses, it does so to a lesser degree than is expected if challenges combine independently or in a cumulative manner”. This work, and that of Diringer et al. (1998) analysed transmission data using rodent models of scrapie and since mice are mono-gastric the EFSA WG thought it might not be strictly applicable to ruminants or humans. Hence we echoed the original sentiment of the QRA WG that “further research was needed” but considered the cumulative effects for cattle and humans over the whole exposure period (for veal and replacement calves) or one year (humans). This is the rationale for quoting human exposure per year (section 6.1) and cattle exposure per time period (60, 180 days) (Section 6.2). Our lack of data on the effect of cumulative dose in humans and cattle, and possible variation in susceptibility with age in either species, needs to be acknowledged when transforming exposure estimates per year into “number of infections” per year.

Question: Reading the 5th paragraph of section 6.1 gives the impression that the WG is agreeing to a species barrier of at least 1000. Is this correct? When a linear dose response is applied (multiplying the risk with the EU population and expressing per year) the risk is not negligible under certain scenarios if no species barrier is assumed.

Answer (ref. EFSA QRA Report, 2004): “The TSE/BSE ad hoc Group, however, recommends that for quantitative risk assessments, the cattle-to-human species barrier for oral transmission is put equal to 1, because there are no experimental data available to support a range of values higher than 1. Oral transmission experiments have a relatively low success rate and positive transmissions are often detected in the detection limit zone. From such results, it is hard to attempt to



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propose a range of values that would cover the species barrier by oral transmission. A species barrier of 1 is a worst case assumption and should be adjusted if and when more data become available.”

The EFSA WG also considered more recent work by Lasmezas et al, (2005) who calculated a species barrier of 7-20 and the appraisal of the Clarke & Ghani work by Comer that appears as section 5.1 in the text of the Tallow Report. By implication we have considered a species barrier of greater than or equal to 1000 as a more realistic scenario than that originally considered by the SSC QRA WG. Not every scenario or every intermediate species barrier value was considered. This is a working model with clear assumptions. It can be re-visited again and again by risk managers to explore alternative scenarios.



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Annex 1: Summary of Human Exposure to BSE Infectivity (CoID50 per week)

a) Median and 97.5 percentile values (0.02% filtration)

Case	GBR II		GBR III		GBR IV	
	Reliable	Unreliable	Reliable	Unreliable	Reliable	Unreliable
1 Tallow from bones (filtration 0.02%)						
1.1 skull and vertebral column removed - P50	0	0	0	1.4E-13	1.2E-12	5.0E-12
P97.5	0	0	5.1E-12	1.7E-11	4.6E-11	1.5E-10
1.2 only skull removed - P50	0	0	0	0.0E+00	1.0E-11	4.7E-11
P97.5	0	0	4.4E-11	1.5E-10	4.1E-10	1.4E-09
1.3 skull and vertebral column not removed - P50	0	0	0	0.0E+00	1.4E-11	7.1E-11
P97.5	0	0	7.1E-11	2.4E-10	6.4E-10	2.1E-09
2 Tallow from fat tissues (filtration 0.02%)						
2.1 Carcass fats before splitting - P50	0	0	0	0	0	0
P97.5	0	0	0	0	0	0
2.2 Fats before and after splitting - P50	0	0	0	0	0	3.6E-11
P97.5	0	0	4.3E-11	1.8E-10	4.4E-10	1.3E-09
3 Tallow from mixture of tissues tissues (0.02%)						
3.1 No SRMs removed - P50	0	0	0	0	0	1.9E-10
P97.5	0	0	2.0E-10	1.3E-09	3.6E-09	1.1E-08
3.2 SRMs removed, except vertebrae - P50	0	0	0	0	0	8.2E-12
P97.5	0	0	9.4E-12	5.8E-11	1.6E-10	5.1E-10
3.3 All SRMs removed - P50	0	0	0	0	0	2.8E-12
P97.5	0	0	3.3E-12	1.8E-11	4.9E-11	1.6E-10
4 Gelatine from bovine bones (acid & alkaline)						
4.1 skull and vertebral column removed - P50	0	0	0.0	0	0.0E+00	1.7E-09
P97.5	0	0	2.1E-09	8.0E-09	2.0E-08	6.4E-08
4.2 only skull removed - P50	0	0	0	0	0.0E+00	1.5E-08
P97.5	0	0	1.4E-08	6.7E-08	1.9E-07	6.0E-07
4.3 skull and vertebral column not removed - P50	0	0	0	0	0	2.1E-08
P97.5	0	0	2.3E-08	1.2E-07	3.2E-07	9.2E-07
5 Gelatine from bovine bones (heat pressure)						
5.1 skull and vertebral column removed - P50	0	0	0	0.0E+00	0.0E+00	1.7E-11
P97.5	0	0	2.1E-11	7.7E-11	1.9E-10	6.3E-10
5.2 only skull removed - P50	0	0	0	0.0E+00	0.0E+00	1.5E-10
P97.5	0	0	1.5E-10	6.8E-10	1.8E-09	5.8E-09
5.3 skull and vertebral column not removed - P50	0	0	0	0.0E+00	0	2.1E-10
P97.5	0	0	2.1E-10	1.2E-09	3.0E-09	9.3E-09

b) Mean values (0.02% filtration)

1	Tallow from bones (filtration 0.02%)						
1.1	skull and vertebral column removed - Mean	7.5E-15	1.9E-14	5.6E-13	2.1E-12	6.2E-12	2.3E-11
1.2	only skull removed - Mean	2.1E-13	2.8E-13	5.9E-12	2.0E-11	6.0E-11	2.2E-10
1.3	skull and vertebral column not removed - Mean	4.1E-13	4.6E-13	9.8E-12	3.3E-11	9.5E-11	3.4E-10
2	Tallow from fat tissues (filtration 0.02%)						
2.1	Carcass fats before splitting - Mean	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00
2.2	Fats before and after splitting - Mean	4.0E-14	2.2E-13	5.0E-12	1.8E-11	5.2E-11	1.8E-10
3	Tallow from mixture of tissues tissues (0.02%)						
3.1	No SRMs removed - Mean	1.9E-12	2.0E-12	4.4E-11	1.5E-10	4.6E-10	1.6E-09
3.2	SRMs removed, except vertebrae - Mean	4.2E-14	2.4E-13	1.8E-12	6.1E-12	1.9E-11	6.7E-11
3.3	All SRMs removed - Mean	4.0E-15	8.0E-14	6.7E-13	2.1E-12	6.3E-12	2.2E-11
4	Gelatine from bovine bones (acid & alkaline)						
4.1	skull and vertebral column removed - Mean	3.2E-12	1.6E-11	2.5E-10	8.7E-10	2.5E-09	8.7E-09
4.2	only skull removed - Mean	9.7E-12	1.3E-10	2.3E-09	8.0E-09	2.3E-08	8.3E-08
4.3	skull and vertebral column not removed - Mean	1.1E-11	1.2E-10	3.7E-09	1.3E-08	3.7E-08	1.3E-07
5	Gelatine from bovine bones (heat pressure)						
5.1	skull and vertebral column removed - Mean	2.8E-14	1.5E-13	2.5E-12	8.7E-12	2.5E-11	8.8E-11
5.2	only skull removed - Mean	1.2E-13	2.1E-12	2.8E-11	8.9E-11	2.5E-10	8.5E-10
5.3	skull and vertebral column not removed - Mean	1.2E-13	1.3E-12	3.4E-11	1.3E-10	3.8E-10	1.3E-09

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c) Median and 97.5 percentile values (0.15% filtration)

Case	GBR II		GBR III		GBR IV	
	Reliable	Unreliable	Reliable	Unreliable	Reliable	Unreliable
1 Tallow from bones (filtration 0.15%)						
1.1 skull and vertebral column removed - P50	0	0	0	1.0E-12	9.0E-12	3.8E-11
P97.5	0	0	3.8E-11	1.3E-10	3.4E-10	1.2E-9
1.2 only skull removed - P50	0	0	0	0	7.5E-11	3.5E-10
P97.5	0	0	3.3E-10	1.1E-9	3.1E-9	1.1E-8
1.3 skull and vertebral column not removed - P50	0	0	0	0	1.1E-10	5.3E-10
P97.5	0	0	5.3E-10	1.8E-9	4.8E-9	1.6E-8
2 Tallow from fat tissues (filtration 0.15%)						
2.1 Carcass fats before splitting - P50	0	0	0	0	0	0
P97.5	0	0	0	0	0	0
2.2 Fats before and after splitting - P50	0	0	0	0	0	2.7E-10
P97.5	0	0	3.2E-10	1.3E-9	3.3E-9	1.0E-8
3 Tallow from mixture of tissues tissues (0.15%)						
3.1 No SRMs removed - P50	0	0	0	0	0	1.4E-9
P97.5	0	0	1.5E-9	9.5E-9	2.7E-8	8.4E-8
3.2 SRMs removed, except vertebrae - P50	0	0	0	0	0	6.2E-11
P97.5	0	0	7.0E-11	4.3E-10	1.2E-9	3.8E-9
3.3 All SRMs removed - P50	0	0	0	0	0	2.1E-11
P97.5	0	0	2.5E-11	1.3E-10	3.7E-10	1.2E-9

d) Mean values (0.15% filtration)

1 Tallow from bones (filtration 0.15%)						
1.1 skull and vertebral column removed - Mean	5.7E-14	1.5E-13	4.2E-12	1.6E-11	4.7E-11	1.7E-10
1.2 Only skull removed - Mean	1.5E-12	2.1E-12	4.4E-11	1.5E-10	4.5E-10	1.6E-9
1.3 skull and vertebral column not removed - Mean	3.1E-12	3.5E-12	7.3E-11	2.5E-10	7.1E-10	2.6E-9
2 Tallow from fat tissues (filtration 0.15%)						
2.1 Carcass fats before splitting - Mean	0	0	0	0	0	0
2.2 Fats before and after splitting - Mean	3.3E-13	1.6E-12	3.8E-11	1.4E-10	3.9E-10	1.4E-9
3 Tallow from mixture of tissues tissues (0.15%)						
3.1 No SRMs removed - Mean	1.4E-11	1.5E-11	3.3E-10	1.1E-9	3.5E-9	1.2E-8
3.2 SRMs removed, except vertebrae - Mean	3.2E-13	1.8E-12	1.4E-11	4.6E-11	1.4E-10	5.0E-10
3.3 All SRMs removed - Mean	3.0E-14	6.0E-13	5.0E-12	1.5E-11	4.7E-11	1.7E-10

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**Annex 2: Summary of Residual BSE Risk Results for Exposures to Cattle
(CoID50 units per exposure period)**

a) Median and 95 percentile values

Case	GBR II		GBR III		GBR IV	
	Reliable	Unreliable	Reliable	Unreliable	Reliable	Unreliable
1 Tallow from fat tissues - Veal calves (Total CoID50 units over 180 day exposure)						
1.1 Carcass fats before splitting - P50	0	0	0	0	0	0
P97.5	0	0	0	0	0	0
1.2 Fats before and after splitting - P50	0	0	0	0	0	6.5E-08
P97.5	0	0	5.7E-08	2.3E-07	5.7E-07	1.6E-06
2 Tallow from fat tissues - Replacement calves (Total CoID50 units over 60 day exposure)						
2.1 Carcass fats before splitting - P50	0	0	0	0	0	0
P97.5	0	0	0	0	0	0
2.2 Fats before and after splitting - P50	0	0	0	0	0	4.2E-09
P97.5	0	0	3.7E-09	1.5E-08	3.7E-08	1.1E-07
3 Tallow from mixture of tissues tissues - Veal calves (Total CoID50 units over 180 day exposure)						
3.1 No SRMs removed - P50	0	0	0	0	0	3.4E-07
P97.5	0	0	3.4E-07	2.0E-06	5.4E-06	1.6E-05
3.2 SRMs removed, except vertebrae - P50	0	0	0	0	0	1.5E-08
P97.5	0	0	1.3E-08	7.2E-08	2.3E-07	6.7E-07
3.3 All SRMs removed - P50	0	0	0	0	0	5.3E-09
P97.5	0	0	5.3E-09	2.8E-08	6.8E-08	2.1E-07
4 Tallow from mixture of tissues tissues - Replacement calves (Total CoID50 units over 60 day exposure)						
4.1 No SRMs removed - P50	0	0	0	0	0	2.2E-08
P97.5	0	0	2.2E-08	1.3E-07	3.5E-07	1.0E-06
4.2 SRMs removed, except vertebrae - P50	0	0	0	0	0	9.8E-10
P97.5	0	0	8.6E-10	4.6E-09	1.5E-08	4.4E-08
4.3 All SRMs removed - P50	0	0	0	0	0	3.5E-10
P97.5	0	0	3.4E-10	1.8E-09	4.4E-09	1.4E-08
5 Dicalcium phosphate - Adult milk cows (CoID50 units per year)						
5.1 skull and vertebral column removed - P50	0	0	0.0	0.0E+00	1.1E-06	4.4E-06
P97.5	0	0	3.9E-06	1.1E-05	2.7E-05	9.0E-05
5.2 only skull removed - P50	0	0	0	0	8.4E-06	4.2E-05
P97.5	0	0	3.7E-05	1.0E-04	2.6E-04	8.6E-04
5.3 skull and vertebral column not removed - P50	0	0	0	0	1.1E-05	6.1E-05
P97.5	0	0	5.8E-05	1.7E-04	4.0E-04	1.3E-03
6 Dicalcium phosphate - Beef cattle (CoID50 units per year)						
6.1 skull and vertebral column removed - P50	0	0	0.0	0.0E+00	3.1E-07	1.3E-06
P97.5	0	0	1.1E-06	3.3E-06	7.9E-06	2.7E-05
6.2 only skull removed - P50	0	0	0	0	2.5E-06	1.3E-05
P97.5	0	0	1.1E-05	3.0E-05	7.6E-05	2.5E-04
6.3 skull and vertebral column not removed - P50	0	0	0	0	3.2E-06	1.8E-05
P97.5	0	0	1.7E-05	5.1E-05	1.2E-04	3.9E-04

b) Mean values

1	Tallow from fat tissues - Veal calves (Total CoID50 units over 180 day exposure)						
1.1	Carcass fats before splitting - Mean	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00
1.2	Fats before and after splitting - Mean	9.1E-11	3.1E-10	6.1E-09	2.2E-08	6.9E-08	2.5E-07
2	Tallow from fat tissues - Replacement calves (Total CoID50 units over 60 day exposure)						
2.1	Carcass fats before splitting - Mean	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00
2.2	Fats before and after splitting - Mean	5.9E-12	2.0E-11	4.0E-10	1.4E-09	4.5E-09	1.6E-08
3	Tallow from mixture of tissues tissues - Veal calves (Total CoID50 units over 180 day exposure)						
3.1	No SRMs removed - Mean	2.5E-09	5.1E-09	7.0E-08	2.3E-07	6.5E-07	2.2E-06
3.2	SRMs removed, except vertebrae - Mean	8.9E-11	1.4E-10	2.4E-09	9.0E-09	2.6E-08	9.4E-08
3.3	All SRMs removed - Mean	3.3E-12	4.0E-11	7.5E-10	2.9E-09	8.4E-09	3.1E-08
4	Tallow from mixture of tissues tissues - Replacement calves (Total CoID50 units over 60 day exposure)						
4.1	No SRMs removed - Mean	1.6E-10	3.3E-10	4.6E-09	1.5E-08	4.2E-08	1.4E-07
4.2	SRMs removed, except vertebrae - Mean	5.8E-12	9.0E-12	1.6E-10	5.8E-10	1.7E-09	6.1E-09
4.3	All SRMs removed - Mean	2.1E-13	2.6E-12	4.9E-11	1.9E-10	5.5E-10	2.0E-09
5	Dicalcium phosphate - Adult milk cows (CoID50 units per year)						
5.1	skull and vertebral column removed - Mean	5.5E-09	1.9E-08	3.8E-07	1.4E-06	4.1E-06	1.5E-05
5.2	only skull removed - Mean	6.9E-08	1.7E-07	3.9E-06	1.3E-05	3.8E-05	1.4E-04
5.3	skull and vertebral column not removed - Mean	5.8E-08	3.7E-07	5.9E-06	2.1E-05	5.9E-05	2.1E-04
6	Dicalcium phosphate - Beef cattle (CoID50 units per year)						
6.1	skull and vertebral column removed - Mean	1.6E-09	5.6E-09	1.1E-07	4.2E-07	1.2E-06	4.3E-06
6.2	only skull removed - Mean	2.0E-08	5.1E-08	1.1E-06	3.8E-06	1.1E-05	4.0E-05
6.3	skull and vertebral column not removed - Mean	1.7E-08	1.1E-07	1.7E-06	6.2E-06	1.7E-05	6.3E-05



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Annex 3: Linear dose-response at very low dose

The table below compares the observed number of cases of BSE in the UK, Germany, France and Spain with the numbers of cases estimated from the calculations of the QRA exposure levels assuming a linear dose-response curve for very low titres of infectivity.

Method:

- to define the type of situation in a certain country and a certain period of time
- to define a sub period of time for which the detection of the animals born in these birth cohorts were correctly detectable 4 to 8 years later (good surveillance) (for example we can detect since 2000 in France the animals born between 1993 and 1996)
- to compare the number of animals detected in these birth cohorts to the number estimated from the QRA on the basis of the adult cattle population size (without distinguishing dairy and beef in a first simple approach), and situation of the country at that time

Computation of the estimated number

The estimated average number of cattle receiving an infectious unit is based on the computation done by DNV (mean number CoID50/yr) * (number cattle at risk) / 2

- The mean number CoID50/yr is taken from the QRA report on pages 54 and 58-59
- The number of cattle at risk is taken from the EU report TSE 2003 ; It comes from Eurostat mean of May-June and December 2003

Observed number of positive cattle

We need to keep two things in mind in order to interpret these observed numbers:

- Roughly only one third to one fourth (depending on countries) of the infected cattle can be detected with the test, because the others are culled or die before being BSE positive.
- All cattle infected from a given birth cohort and positive at the time of death or slaughter could not be detected because the period with "good surveillance" has been too short (2001-2004); for example, a large part of those animals infected from the birth cohort 1993 were dead or slaughtered before 2001, when the tests became used largely; only the infected animals of the cohorts 1995 and 1996 are pretty well detected in Germany, France and Spain. Concerning the United Kingdom, until recently, most of the surveillance was based on clinical surveillance only. There might be an underestimate.

So we need to multiply the number of animals detected positive by at least 3 but maybe 6 or 10 in order to get an idea of the real number of infected animals in each birth cohort, the cohorts with the best surveillance being 1995 and 1996.

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Table : Comparison of observed versus estimated number of BSE cases

Situation	Country	UK	UK	Germany	France	Spain
	Period	1990-1995	1997-2000	1990-2000	1990-1995	1990-1995
	Type	GBR IV – Unreliable surveillance	GBR IV – Unreliable surveillance	GBR III – Unreliable surveillance	GBR III – Unreliable surveillance	GBR III – Unreliable surveillance
	SRM	SRM removed, but not vertebral column	All SRM removed	No SRM removed	No SRM removed	No SRM removed
QRA P58-59	MBM cross-contam. food Mean Residual risk CoID50/yr :	Possible	Not possible	Possible	Possible	Possible
	Intensive 0.1% conta. Extensive 0.1% conta.	1.5 E-05 3.0 E-06	0 (4.8 E-06) 0 (9.7 E-07)	3.6 E-05 7.5 E-06	3.6 E-05 7.5 E-06	3.6 E-05 7.5 E-06
	<i>Estimated number of infected animals if linear dose-response</i> μ (See Philip Comer)	If all were: -Intens. -Extens. 38/yr 8/yr	0 0	108/yr 23/yr	198/yr 41/yr	63/yr 13/yr
p54	DCP : Use of DCP Mean Residual risk CoID50/yr :	Possible	Possible	Possible	Possible	Possible
	Dairy cow Beef cow	1.4 E-04 4.0 E-05	1.5 E-05 4.3 E-06	2.1 E-05 6.2 E-06	2.1 E-05 6.2 E-06	2.1 E-05 6.2 E-06
	<i>Estimated number of infected animals if linear dose-response</i> μ (See Philip Comer)	If all were: -Dairy -Beef 350/yr 100/yr	38/yr 11/yr	63/yr 19/yr	116/yr 34/yr	37/yr 11/yr
p54	TALLOW Use of tallow – from fat tissues – collected before and after splitting Mean Residual risk CoID50/60day Replacement calves (only 20% of adult population)	Possible	Possible	Possible	Possible	Possible
		1.6 E-08	1.6 E-08	1.4 E-09	1.4 E-09	1.4 E-09
	<i>Estimated number of infected animals if linear dose-response</i> μ (See Philip Comer)	0.008/yr	0.008/yr	0.0008/yr	0.0015/yr	0.0005/yr
Data	Sub Period with efficient surveillance 4-8 years later	1989-1995	1997-1999	1993-1999	1993-1995	1993-1995
	Adult cattle * (approximate)	4 919 000 (5 000 000)	4 919 000 (5 000 000)	6 170 000 (6 000 000)	10 817 000 (11 000 000)	3 530 000 (3 500 000)
	Number of positive cases observed from 2001 through 2004, born in : (EU report page 33, updated with 2004 by Commission)	1993: 571 1994: 875 1995: 789	1997: 44 1998: 30	1993: 3 1994: 15 1995: 82 1996: 131 1997: 43	1993: 58 1994: 178 1995: 288	1993: 33 1994: 35 1995: 88

NOTES IN TABLE

* Eurostat mean of May-June and December 2003; does not distinguish dairy from beef cattle! μ Computation : (MEAN number CoID50/yr) * (number cattle at risk) / 2 ; for TALLOW, number of calves = 20% of adult cattle

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Annex 4: Comparison of output distributions

Some examples are given to demonstrate the fact that the comparison of distributions of the output of a QRA should be interpreted carefully if only done by comparison of statistics of the distributions like the mean value or the 95 th percentiles or median. Specific for the outputs described below is also the fact that the distributions are extremely skewed which also has an influence.

The figures 1,3 and 5 show ascending cumulative distribution plots of outputs of different scenarios. On the Y axis the confidence of having a result equal or lower to the value on the X axis can be determined. The X axis describes the amount of CoID50 exposure per time period, hence a bigger exposure (eg a higher risk) shifts the graph to the right.

When comparing two output distributions the confidence that output A is bigger than output B is determined by drawing iteratively random values from both outputs and check at each iteration whether the sampled value from A is bigger than the sampled value from B. The number of times that this criteria is fulfilled divided by the total number of iterations give the confidence that A is bigger than B. Enough iterations are conducted to provide a stable estimate. Similarly the confidence in having a not zero exposure can be determined by drawing randomly from a distribution and calculate the proportion of iterations where the value is larger than zero.

To have an idea however how much the exposure differs between two scenarios, graphs are added (fig 2,4 and 6) where, on the Y axis the confidence is shown that the exposure (on the X axis) differs between >0 and 10 times, between 10 and 100, between 100 and 1000, etc... The approach to create this graphs are similar as described above.

All examples below illustrate that, as the output of a QRA are distributions, it is very informative to look at the whole distribution instead of comparing means and or percentiles.

Example 1: *GBRIV scenario 2* versus *GBRIV scenario 3*, both unreliable surveillance. The mean values of the exposure ($2.2 \cdot 10^{-10}$ versus $3.4 \cdot 10^{-10}$) are more or less equal and the confidence in the exposure being not zero is 94% for both options. In addition, the confidence that the exposure in scenario3 is higher than in scenario 2 is 55% which confirms the fact that they are equal (see fig 1 showing the cumulative ascending distribution for both scenarios).

This is confirmed in fig 2 where it is shown that the confidence in the risk in sc3 being between more than 0 and 1 times the risk in scenario 2 is the highest of all (43%).

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Fig 1: ascending cumulative distribution plots of the CoID50 exposure in GBRIV scenario 2 versus a GBRIVscenario 3, both unreliable surveillance

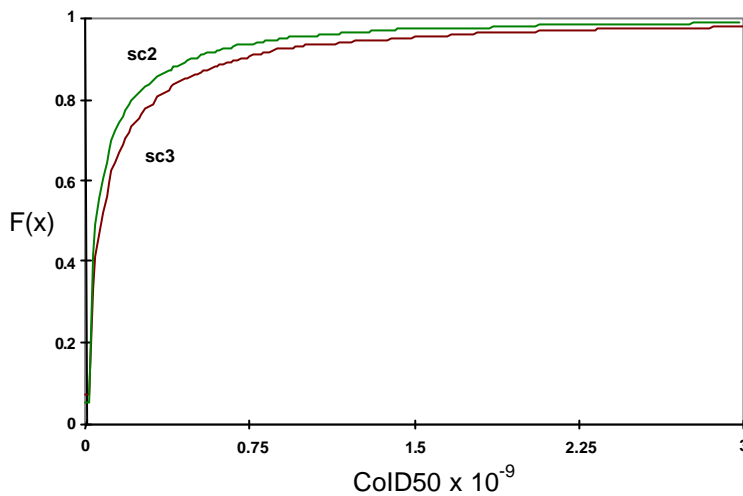
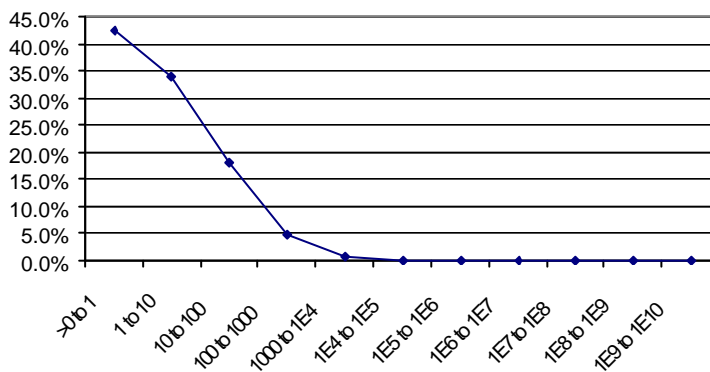


Fig 2: confidence in having a N times bigger exposure in GBRIV scenario 3 than in a GBRIVscenario 2, both unreliable surveillance



Example 2: *GBR IV unreliable surveillance scenario3 versus GBR III unreliable surveillance scenario3*

The mean exposure differs 10 times (3.4 10⁻¹⁰ versus 3.3 10⁻¹¹).

However the confidence in having a non zero exposure for the GBR III case is only 47% which indicates that there is 53% confidence that there is no exposure.

The confidence that the exposure is bigger in GBRIV unreliable surveillance scenario 3 than in GBR III unreliable surveillance scenario3 is 81%.

In fig 4 it is shown how much the exposure differs (eg. 25% confidence that it is between 0 and 10 times, 35% confidence between 10 and 100 times, 30% between 100 and 1000 times etc...).

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Fig 3: ascending cumulative distribution plots of the CoID50 exposure in GBR IV unreliable surveillance scenario 3 versus GBR III unreliable surveillance scenario

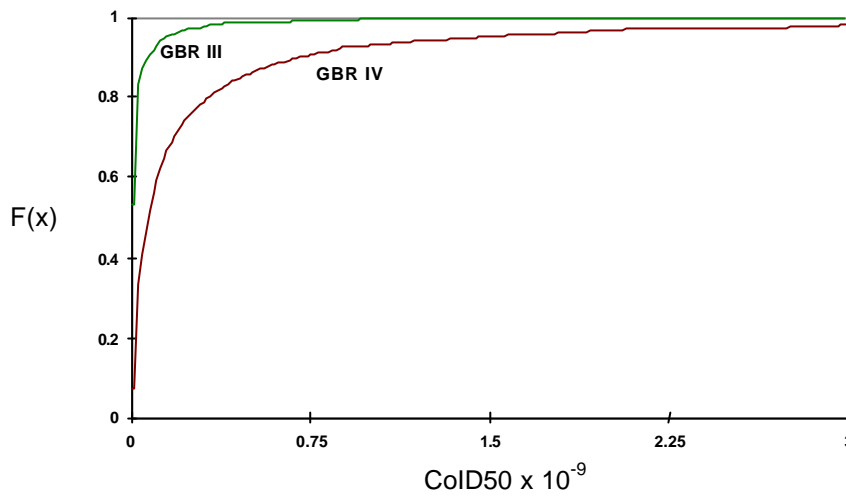
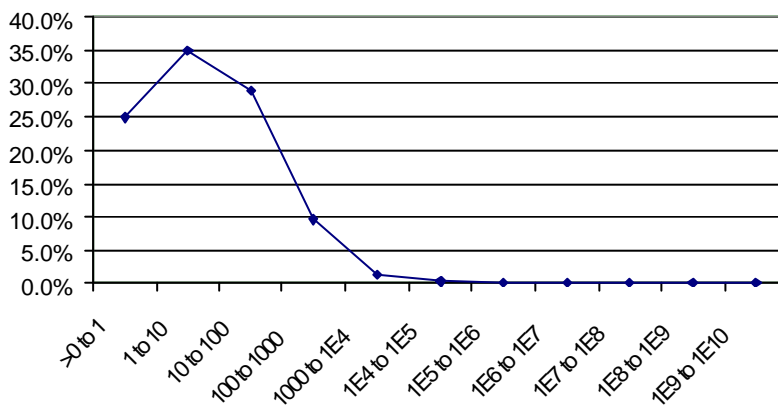


Fig 4: confidence in having a N times bigger exposure in GBR IV unreliable surveillance scenario 3 than in a GBR III unreliable surveillance scenario



Example 3: *GBRIV reliable surveillance scenario1* versus *GBRIV unreliable surveillance scenario3*

Figures are given below. Although the mean difference is 100 times the confidence in a bigger exposure in *GBRIVunrelsc3* > *GBRIVrelsc1* is 88%. Figure 6 shows that there is still a 10% probability that the risk is between 1000 and 10,000 times higher. The confidence that the exposure is not zero is high for both scenarios (94% for scenario 3 and 85% for scenario 1).

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Fig 5: ascending cumulative distribution plots of the CoID50 exposure in GBRIV reliable sc1 versus GBRIV unreliable sc3

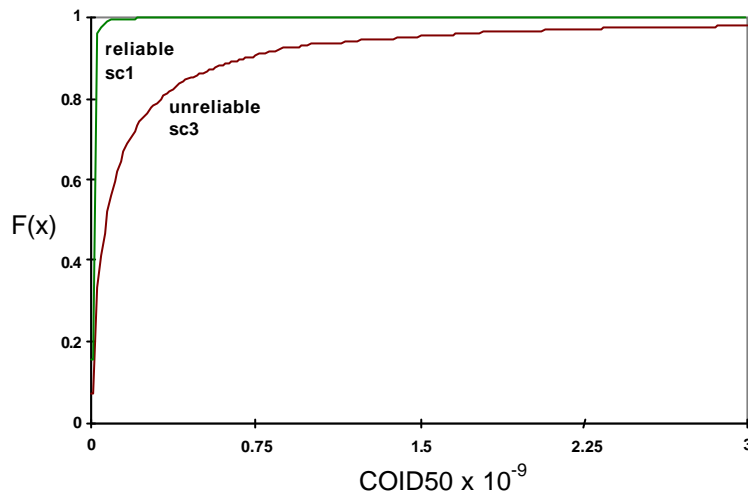


Fig 6: confidence in having a N times bigger exposure in GBRIV unreliable sc3 than in GBRIV reliable sc1

