別紙様式第2-1

No. 12

# 医薬品 研究報告 調査報告書

| 識別番号・報告回数 | | | 報告日 | 第一報入手日 | 新医薬品等の区分 | 機構処理欄 |
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| | | | | 2007. 5. 22 | 該当なし | |

| 一般的名称 | 白血球除去人赤血球浮遊液 | 研究報告の公表状況 | ABC Newsletter. 2007 May 4. | 公表国 米国 |
|---|---|---|---|---|
| 販売名(企業名) | 白血球除去赤血球「日赤」(日本赤十字社)<br>照射白血球除去赤血球「日赤」(日本赤十字社) | | | |

**研究報告の概要**

○イスラエルはvCJD及び肝炎に関する供血延期基準を変更
イスラエルで血液事業を行っている赤盾ダビデ社(Magen David Adom:MDA)は、変異型クロイツフェルト・ヤコブ病(vCJD)に関する供血延期基準を変更し、1980年以降にフランス居住歴がある人の供血を可能とした。イギリスでウシ海綿状脳症(「狂牛病」)の流行が始まった1980年から10年間のうちにイギリス、アイルランド、ポルトガルに居住歴のある人は、引き続き供血延期となる。vCJDの発生リスクはイギリスで600/100万、アイルランドで17/100万、ポルトガルで20/100万であるのに対し、フランスではわずかに1.7/100万であり、リスク要因としてはあまりにも小さい。このため、MDAは(保健省の承認を得て)フランス系移民及び旅行者に対し制限を緩和することを決定した。
加えてMDAは、輸血を受けた人、B型肝炎やC型肝炎患者と一緒に住んでいた人、入れ墨を入れた人、胃や小腸の生検を含む内視鏡検査を受けた人の供血延期期間を1年から6ヵ月に短縮した(内視鏡検査を受けた人の供血延期は、生検に使用された内視鏡が完全に滅菌されずに再使用された場合、ウイルス感染症やvCJDを伝播しうるとの理論的可能性による)。
また、動物に噛まれた人は、噛んだ動物が不明であったり検査を受けていない場合、これまでの12ヵ月後ではなく2ヵ月後から供血が可能となる。

**使用上の注意記載状況・その他参考事項等**

白血球除去赤血球「日赤」
照射白血球除去赤血球「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

| 報告企業の意見 | 今後の対応 |
|---|---|
| イスラエルで血液事業を行っている赤盾ダビデ社は変異型クロイツフェルト・ヤコブ病に関する供血延期基準を変更し、1980年以降フランスに居住歴がある人の供血を可能にしたとの報告である。 | 日本赤十字社は、輸血感染症防止のため輸血歴のあるドナーを無期限に献血延期としている。vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より英国滞在歴1日以上の方からの献血を制限している。さらに、血液製剤の保存前白血球除去を導入し、平成19年1月16日には全ての輸血用血液への保存前白血球除去の導入が完了した。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。 |

**On the Difference between What People Say and What They Do About Risk**

"If you ask me based on findings, (if people are) afraid of food recalls, the answer is no. So people aren't really concerned or scared, but the funny thing is that sales are still down."

*– Dr. Sylvain Charlebois, of the University of Regina, on a study he helped conduct of the Canadian food safety system. The study sought to understand the consumer's perception of food recalls. According to Dr. Charlebois, people are loath to admit they are scared, and the numbers bear that out. Canadian Leader-Post, 4/12/07*

Strike at Southern California Red Cross (continued from page 5)

The job action was not expected to threaten the local blood supply. Southern California already imports about 40 percent, and Red Cross officials said it was possible more might be shipped in as a result of the walkout.

Both Red Cross and union officials called for the public to continue donating blood. The union distributed lists of local hospitals where people could give blood, and the Red Cross directed people to the national Red Cross blood donation Web site, www.givelife.org (Sources: Associated Press, 4/30/07; *Los Angeles Times*, 5/3/07) ♦

## Israel Changes Blood Donor Deferral Criteria for vCJD, Hepatitis

Israel's national blood service Magen David Adom (MDA) has changed its variant Creutzfeldt-Jakob disease (vCJD) donor deferral criteria to allow anyone who lived in France from 1980 to become a blood donor in Israel. Those who lived in England, Ireland and Portugal for a decade after 1980, when England's bovine spongiform encephalopathy ("mad cow") epidemic began, are still barred from donating blood in Israel and Europe.

MDA blood services director Eilat Shinar, MD told *The Jerusalem Post* last month (4/16/07) that the prevalence of vCJD is around 600 per million in England and between 17 and 20 per million in Ireland and Portugal, but only 1.7 per million in France and thus too small to be a risk factor. For this reason, the European authorities and subsequently MDA (with Health Ministry approval) decided to liberalize the policy for French immigrants and tourists, Dr. Shinar said.

In addition, MDA shortened the deferral period from one year to six months for people who received a blood transfusion, lived with a patient who had hepatitis B or C, had a tattoo done or underwent an endoscopic examination including a biopsy of the stomach or small intestine. (Deferral for endoscopic examinations is based on the fact that the reuse of endoscopes used for biopsy theoretically can transmit viral infections or vCJD if not thoroughly sterilized).

Finally, anyone who was bitten by an unidentified and untested animal now can donate blood in Israel two months after the bite instead of the previous 12 month deferral. ♦

別紙様式第2-1

No. 11

# 医薬品 研究報告 調査報告書

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| 一般的名称 | 白血球除去人赤血球浮遊液 | 研究報告の公表状況 | Seitz R, von Auer F, Blümel J, Burger R, Buschmann A, Dietz K, Heiden M, Hitzler WE, Klamm H, Kreil T, Kretzschmar H, Nubling M, Offergeld R, Pauli G, Schottstedt V, Volkers P, Zerr I. Biologicals. 2007 Jun;35(2):79-97. Epub 2007 Feb 21. | 公表国 |
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| 販売名(企業名) | 白血球除去赤血球「日赤」(日本赤十字社)<br>照射白血球除去赤血球「日赤」(日本赤十字社) | | | ドイツ |

**研究報告の概要**

○vCJDが血液供給へ及ぼす影響

変異型クロイツフェルトヤコブ病(vCJD)は、現状では剖検によってのみ確定診断が可能な、不治の神経変性疾患である。現在までの罹患者約200名のほとんどは、感染牛肉が広く食物環に入り込んだ英国在住者である。英国の3症例によってvCJDが輸血により感染する可能性が示された。BSEおよびvCJDは英国以外の複数の国に広がっているため、異なる国及び地域に特異的な評価を実施することが賢明であると思われる。本レビューは、当該リスクの評価及び予防的手段の検討においてドイツで採用された方法を説明するものである。これは、ウシの飼料連鎖およびヒトの食物環から、汚染物質が確実かつ恒久的に除去できるとの基本前提をとるものである。一方でこのモデルは輸血を介したvCJDの伝播が永続化するような可能性があるかどうかという疑問を新たにもたらす。しかし、実際の集団データを基にしたモデル計算は、そのようなことはないであろうことを示唆した。また、輸血経験者を供血者から排除することは、輸血の安全性向上にほとんど寄与しないが、血液供給には多大な影響を及ぼすと考えられた。したがって、ドイツでは輸血経験者の排除は推奨されなかった。

| 報告企業の意見 | 今後の対応 |
|---|---|
| ドイツにおいて、vCJDが血液供給へ及ぼす影響について実際の集団データを基にモデル計算を行ったところ、輸血を介した伝播がvCJDを永続化するような可能性はなく、輸血経験者を供血者から排除しても輸血の安全性向上にはほとんど寄与しないが、血液供給には多大な影響を及ぼすと考えられたとの報告である。 | 日本赤十字社は、輸血感染症防止のため輸血歴のあるドナーを無期限に献血延期としている。vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より英国滞在歴1日以上の方からの献血を制限している。さらに、血液製剤の保存前白血球除去を導入し、平成19年1月16日には全ての輸血用血液への保存前白血球除去の導入が完了した。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。 |

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8

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Review

# Impact of vCJD on blood supply

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**Abstract**

Variant Creutzfeldt–Jakob disease (vCJD) is an at present inevitably lethal neurodegenerative disease which can only be diagnosed definitely post mortem. The majority of the approximately 200 victims to date have resided in the UK where most contaminated beef materials entered the food chain. Three cases in the UK demonstrated that vCJD can be transmitted by blood transfusion. Since BSE and vCJD have spread to several countries outside the UK, it appears advisable that specific risk assessments be carried out in different countries and geographic areas. This review explains the approach adopted by Germany in assessing the risk and considering precautionary measures. A fundamental premise is that the feeding chain of cattle and the food chain have been successfully and permanently cleared from contaminated material. This raises the question of whether transmissions via blood transfusions could have the potential to perpetuate vCJD in mankind. A model calculation based on actual population data showed, however, that this would not be the case. Moreover, an exclusion of transfusion recipients from blood donation would add very little to the safety of blood transfusions, but would have a considerable impact on blood supply. Therefore, an exclusion of transfusion recipients was not recommended in Germany.


*Keywords:* Bovine spongiform encephalopathy; Variant Creutzfeldt–Jakob disease; Blood supply; Risk assessment

*Abbreviations:* AFSSAPS, Agence Française de Sécurité Sanitaire des Produits de Santé (French medicinal products authority); BSE, bovine spongiform encephalopathy (degenerative neurological disease in cattle caused by prions); CJD, Creutzfeldt–Jakob disease (TSE disease in humans, transmissible via medicinal products (iatrogenic) or occurring sporadically); FFP, "fresh frozen plasma"(plasma for transfusion); GBR, "geographical BSE risk": classification of countries into one of four risk classes (GBR I–IV) by the Scientific Steering Committee of the European Commission; GSS, Gerstmann-Sträussler-Scheinker syndrome (a human TSE); HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus (agent of AIDS); i.c., intracerebral; IU, infectious unit; i.v., intravenous; M, methionine; PMCA, protein misfolding cyclic amplification (method for amplification of $PrP^{Sc}$ in vitro); PrP, prion protein; $PrP^{c}$, cellular, physiological form of the prion protein (c = cellular); $PrP^{Sc}$, pathological form of the prion protein (Sc = Scrapie); RBCC, red blood cell concentrate; SCMPMD, Scientific Committee on Medicinal Products and Medical Devices of the European Commission; SRM, specified risk material (bovine materials in which the BSE agent can be detected in high concentrations (brain, spinal cord etc.)); SSC, Scientific Steering Committee of the European Commission; TSE, transmissible spongiform encephalopathy (disease of the brain, generic term for neurological disorders caused by prions); UK, United Kingdom (Great Britain and Northern Ireland); V, valine; vCJD, variant Creutzfeldt–Jakob disease (human TSE caused by the BSE agent, first described in 1996).

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## 1. Introduction

A working group was formed in 2001 by request of the German Federal Ministry of Health that consisted of staffs from the Paul-Ehrlich-Institut, the Robert-Koch-Institut and the Federal Ministry of Health, as well as external experts. The task of this working group has been to assess the risks for the blood supply in Germany with regard to vCJD and to prepare reports outlining a strategy. The spread of bovine spongiform encephalopathy (BSE) among cattle is believed to be the origin of the problem, followed by the transition to humans via the food chain. Since the epidemical course shows geographical differences, every country needs to assess its specific vCJD risk as a condition for developing a reasonable national blood supply strategy. The group published reports[1] in 2001 and in 2006 [1]. This review summarizes the current view of the group of the impact of vCJD on blood supply.

## 2. The Occurrence of BSE

Feeding of ruminant material to cattle has most probably caused the occurrence of BSE, a disease of cattle that was first diagnosed in the UK in 1986 [2]. Technological changes (pressure and temperature conditions) in the manufacture of meat and bone meal and other products are considered to be the cause for the occurrence of BSE in the UK beginning in 1985, since the inactivation of the BSE pathogen was no longer sufficiently effective [3]. This assumption is confirmed by the course of the epidemic in the UK where a decline in the number of cases was observed during the mid-1990s with a time lag representing the incubation time of 4–5 years for BSE following the ban on the feeding of meat and bone meal and the regulations on the disposal of BSE-infected animal carcasses [4] (Table 1). While in the first few years it was assumed that there was only one strain of BSE in cattle, several authors have described atypical BSE cases in the past few years [5–7]. These cases do not represent a uniform strain and are characterized by an altered molecular weight of the accumulated $PrP^{Sc}$, a different anatomical distribution pattern of the pathological changes and the $PrP^{Sc}$ deposits, and partly by the occurrence of amyloid plaques. All cases of atypical BSE described so far have been found in animals older than 8 years. The cases described in France show a biochemical similarity with the cases of scrapie in sheep. Therefore, the possibility that these might be scrapie infections in cattle is discussed.

Through animal trade and trade of feeding stuff components produced from animal carcasses and slaughtering by-products (bone meal, fats for milk replacers, grieves etc.), BSE spread from the UK to other European countries and countries outside Europe (e.g. Canada, Japan, Israel). First Ireland (1989), then Switzerland (1990) and France (1991) reported cases of BSE. During the mid-1990s, Portugal (1994), the Netherlands (1997), Belgium (1997), Luxemburg (1997), and Liechtenstein (1998) reported cases. Toward the end of the 1990s, it became clear that almost all countries with extensive exchange of goods within the European single market during the previous decade were affected by BSE. It was, therefore, not surprising that BSE was diagnosed in some cattle of Denmark, Germany, and Spain in the year 2000 and also in Austria, the Czech Republic, Finland, Greece, Italy, Slovakia, and Slovenia in 2001. Since 2002, BSE has also been diagnosed in Polish cattle. Cases of BSE in cattle imported from the UK were reported as early as the early 1990s by several European countries (Portugal 1990, Germany 1992, Denmark 1992, Italy 1994). Three BSE cases have so far occurred in the United States, of which one animal had been imported from Canada. The two indigenous cases were of the atypical BSE type of which the origin is still unknown.

In addition to animal trade and trade with animal products, however, intrinsic national factors influenced the occurrence and spread of BSE. Since by the 1980s most EU member states had changed their animal carcass disposal methods and processed side products from abattoirs without the removal of risk materials under pressure and temperature conditions that were not sufficient for the inactivation of the BSE pathogen, this pathogen was continuously spread, thus increasing the number of BSE cases. Moreover, only passive monitoring systems based on the reporting of clinical symptoms were in place; BSE rapid tests were not yet available.

Organs and tissues of BSE infected cattle in which the pathogen has been detected are called "specified risk materials" (SRM). SRM of naturally infected animals may, especially toward the end of the incubation period and during the development of clinical BSE symptoms, contain the pathogen in very high concentrations. Using biological detection systems for the BSE pathogen, which include a species barrier, e.g. intracerebral infection into mice, $10^5$ infectious units/g SRM (brain) were determined, while a 1000-fold increased infectivity titer is assumed for transmissions within a species [8–10]. The Scientific Steering Committee (SSC) of the European Commission set up an SRM list for cattle (e.g. skull including brain and eyes, tonsils, spinal cord) (SSC 1998[2]), which served as a basis for various European policies for the exclusion of SRM in the food and feed chains. Since the spread of the BSE crisis in Europe, the definition of specified risk materials has been revised several times (a comprehensive overview of the European legislation can be found in Table 2 of [1]). According to the latest amendment, the tissues designated as SRM must be subjected to safe removal and must not enter the food chain. The following tissues are designated as SRM: "The skull excluding the mandible and including the brain and eyes, the vertebral column excluding the vertebrae of the tail, the spinous and transverse processes of the cervical, thoracic and lumbar vertebrae and the wings of the sacrum, but including the dorsal root ganglia, and the spinal cord of

[1] The reports published by this group in German language in the years 2001 and 2006 can be found in the internet: http://www.pei.de.

[2] Scientific Steering Committee (SSC), 1998. Listing of Specified Risk Materials: a scheme for assessing relative risks to man—Opinion of the SSC adopted on 9 December 1997 (Re-edited version adopted by the SSC during its Third Plenary Session of 22–23 January 1998).

Table 1
Number of BSE cases reported

| Country | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Austria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Belgium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 6 | 3 | 9 | 46 | 38 | 15 | 11 | 1 |
| Canada | 0 | 0 | 0 | 0 | 1* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 1 |
| Czech Republic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 4 | 7 | 8 |
| Denmark | 0 | 0 | 0 | 1* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 6 | 3 | 2 | 1 | n.d. |
| Finland | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | n.d. |
| France | 0 | 0 | 5 | 0 | 1 | 4 | 3 | 12 | 6 | 18 | 31 | 161 | 274 | 239 | 137 | 54 | n.d. |
| Germany | 0 | 0 | 0 | 1* | 0 | 3* | 0 | 0 | 2* | 0 | 0 | 7 | 125 | 106 | 54 | 65 | 32 |
| Greece | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | n.d. |
| Ireland | 15 | 14 | 17 | 18 | 16 | 19 | 16 | 73 | 80 | 83 | 91 | 149 | 246 | 333 | 183 | 126 | 69 |
| Israel | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Italy | 0 | 0 | 0 | 0 | 0 | 2* | 0 | 0 | 0 | 0 | 0 | 0 | 48 | 38 | 29 | 7 | 3 |
| Japan | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 4 | 5 | 7 |
| Liechtenstein | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | n.d. |
| Luxembourg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| The Netherlands | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 20 | 24 | 19 | 6 | n.d. |
| Poland | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 5 | 11 | 18 |
| Portugal | 0 | 1* | 1* | 1* | 3* | 12 | 15 | 31 | 30 | 127 | 159 | 149 | 110 | 86 | 133 | 92 | 37 |
| Slovakia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 6 | 2 | 7 | n.d. |
| Slovenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 2 | 1 |
| Spain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 82 | 127 | 167 | 137 | 75 |
| USA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Switzerland | 0 | 2 | 8 | 15 | 29 | 64 | 68 | 45 | 38 | 14 | 50 | 33 | 42 | 24 | 21 | 3 | 3 |
| United Kingdom | 7228 | 14407 | 25359 | 37280 | 35090 | 24438 | 14562 | 8149 | 4393 | 3235 | 2301 | 1443 | 1202 | 1144 | 611 | 343 | 151 |

Source and information on up-to-date statistics: Office International des Epizooties, as of 9 January 2006 (www.oie.int). *Cases in imported animals.
[a] Data for 2005 still incomplete. n.d., not done.

bovines aged over 12 months, and the tonsils, the intestines from the duodenum to the rectum and the mesentery of bovines of all ages; the skull including the brain and eyes, the tonsils and the spinal cord of ovine and caprine animals aged over 12 months or which have a permanent incisor erupted through the gum, and the spleen of ovine and caprine animals of all ages." Because of the significant decrease in the number of BSE cases in the European Union, the age limit for the collection and safe removal of SRM for the spinal cord of bovine animals was raised to 24 months and a raise of the test age is being discussed.[3]

The SSC has developed a procedure by which the geographical BSE risk (GBR) in a member state or non-European country can be evaluated. In its opinion, published in July 2000,[4] it laid down the following criteria for classifying one of four risk levels:

- Structure and dynamics of the bovine population,
- BSE surveillance,
- Cullings in connection with BSE cases,
- Imports of bovine animals and meat and bone meal (MBM),
- Feeding,
- Ban on the feeding of meat and bone meal (MBM bans),
- Regulations concerning specified risk material (SRM bans),
- Removal of animal carcasses.

The risk levels are defined in Table 2.

At that point in time (2000), Argentina, Australia, Chile, Norway, New Zealand, and Paraguay were classified as GBR level I, Austria, Finland, Sweden, Canada, and the United States as GBR level II, whereas the UK and Portugal were classified as GBR level IV. All other countries, including Germany, were classified as GBR level III. Germany's classification as GBR level III caused heated discussions in Germany, since up to that time the country had been considered to be absolutely BSE free. In actuality, all countries rated into BSE level III indeed identified BSE cases in their own countries within the following months.

Since 2001, the GBR has been assessed for various other countries, e.g. candidate countries for accession to the EU. Almost all countries were classified as GBR level III, since insufficient monitoring had been carried out to guarantee satisfactory statistical safety. A number of countries evaluated in 2000 were later re-evaluated, which led to the classification of Austria, Canada, USA, Mexico and South Africa to GBR level III. In March 2003, Canada's second BSE case was discovered (the first case was diagnosed in 1993), and in June 2005, the first BSE case was confirmed in the USA.[5]

[3] See the "BSE road map" for more details, http://europa.eu.int/comm/food/food/biosafety/bse/roadmap_en.pdf

[4] Final Opinion of the Scientific Steering Committee on the Geographical Risk of Bovine Spongiform Encephalopathy (GBR). Adopted on 6 July 2000.

[5] The results and opinions of the Scientific Steering Committee (SSC) and the European Food Safety Authority (EFSA) can be found in http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html and http://www.efsa.eu.int respectively.

Table 2
GBR levels as defined by the SSC

| GBR level | Presence of one or more cattle clinically or pre-clinically infected with the BSE agent in a geographical region/country |
|---|---|
| I | Highly unlikely |
| II | Unlikely but not excluded |
| III | Likely but not confirmed or confirmed, at a lower level |
| IV | Confirmed, at a higher level |

The member states and third countries were also classified into five BSE status categories.[6] The classification in status categories was based on criteria similar to those of the SSC. However, in this context the number of diagnosed BSE cases served as an important additional factor. Consequently, other points of combating BSE laid down in this EU regulation refer to the status category of the appropriate country, such as the required extent of the safe retrieval and removal of SRM.

Following the steady decrease of BSE cases in the UK in the past few years, the number of BSE cases reported per one million bovine animals older than 30 months has fallen below 1,000, enabling a re-evaluation of the UK. The application was given a favorable opinion by the European Food Safety Authority (EFSA), and it was suggested that the UK be classified as BSE risk status III. A change in the BSE risk status represents a significant relief for the UK regarding international trade of bovines and bovine animal products.

## 3. BSE in Germany

Passive BSE surveillance has been performed in Germany for years, i.e. all bovine animals that died or became clinically sick due to disorders of the central nervous system and were suspected to have suffered from BSE were examined. The brains of such animals were subjected to histopathological examination, and any samples with abnormal results were also examined for plaques of $PrP^{Sc}$ by immunohistochemical examination and/or scrapie associated fibril (SAF) extraction with subsequent immunoblot. These examinations did not reveal any BSE cases in German cattle.

The first BSE rapid test, the Prionics Check Western blot developed by Prionics (Switzerland), became available in mid-1999. Even though the test had not yet been approved, it was already used in some European countries. A series of examinations using this BSE test for 5,000 beef cattle was carried out between March and May 1999 in North Rhine-Westphalia, Germany. All these animals showed negative results, reinforcing the hope of a BSE-free Germany.

In preparation for transposing the Commission Decision 2000/374/EC, which established random BSE monitoring of bovine animals, a few voluntary BSE examinations were carried out in cattle samples starting in mid-November of 2000. These examinations revealed the first indigenous German BSE case in Schleswig-Holstein confirmed by the National Reference Laboratory on 26 November 2000. This was followed by the introduction of rapid test examinations throughout Germany within a short period of time. After the extensive introduction of BSE rapid tests in December 2000 for all slaughtered cattle as well as for fallen stock (first over 30, then over 24 months old; since June 2006 again over 30 months old), 390 BSE cases were identified in following years (reference date: 16 January 2006) (Table 1). The number of cases reported annually is steadily declining, despite a slight increase from 2003 to 2004.

Altogether, these data indicate that the BSE "epidemic" in Germany may have already exceeded its peak before the first case was even diagnosed. Simultaneous to the introduction of the BSE rapid test, a total ban on feeding protein-containing products and fats derived from warm-blooded land animals to ruminants throughout Europe was imposed in the year 2000. In Germany, this ban was extended to the feeding of all productive livestock as defined in the Futtermittelgesetz (Act on Feeding-Stuffs).

While during the first two years of BSE monitoring in Germany the disease was predominantly diagnosed in animals born in 1995 and 1996, BSE has been increasingly identified in animals born in later years (particularly in 1998/99) since 2004. This suggests that after a significant entry of BSE infectivity into the feeding-stuff chain in 1995/96, a reduction must have occurred, followed by a second increase in the pathogen content around 1998/99. It is still unknown what caused these two BSE waves. Until the end of 2004, BSE was diagnosed in ten bovine animals born in 2000. Then, in April 2005, BSE was diagnosed for the first time in a bovine born in May 2001, i.e. after the implementation of the total feed ban of MBM from warm-blooded land animals to productive livestock in Germany. A second case followed in June 2005 when a BSE infection was diagnosed in an animal born in March 2001. It must be assumed that these two cases were caused by a contamination with the pathogen beyond the feed ban. In this context, it must be mentioned that in the UK, 95 cases born after the reinforced feed ban of August 1996 (so-called BARB-BSE cases) were diagnosed up to April 2005 (source: DEFRA-statistics). Two explanations must be considered as the cause for the occurrence of such cases:

1. The routes of infection have not yet been fully identified, and a transmission cannot be excluded 100% despite a strict adherence to the feed ban.
2. In isolated cases, MBM was fed to animals even after the feed ban came into force. This is very difficult to prove after so many years, and would imply that the control mechanisms might have to be made even more restrictive.

## 4. BSE in small ruminants

The theoretical risk of transmission of the BSE pathogen to small ruminants has been scientifically discussed for some

[6] Regulation (EC) No 999/2001 of the European Parliament and the Council of 22 May 2001 (Official Journal of the European Communities of 31 May 2001, L147, p. 1) laying down rules on prevention, control and eradication of certain transmissible spongiform encephalopathies.