SCIENTIFIC OPINION

Assessment of listing and categorisation of animal diseases within the framework of the Animal Health Law (Regulation (EU) No 2016/429): paratuberculosis

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Abstract

Paratuberculosis has been assessed according to the criteria of the Animal Health Law (AHL), in particular criteria of Article 7 on disease profile and impacts, Article 5 on the eligibility of paratuberculosis to be listed, Article 9 for the categorisation of paratuberculosis according to disease prevention and control rules as in Annex IV and Article 8 on the list of animal species related to paratuberculosis. The assessment has been performed following a methodology composed of information collection and compilation, expert judgement on each criterion at individual and, if no consensus was reached before, also at collective level. The output is composed of the categorical answer, and for the questions where no consensus was reached, the different supporting views are reported. Details on the methodology used for this assessment are explained in a separate opinion. According to the assessment performed, paratuberculosis can be considered eligible to be listed for Union intervention as laid down in Article 5(3) of the AHL. The disease would comply with the criteria in Sections 3, 4 and 5 of Annex IV of the AHL, for the application of the disease prevention and control rules referred to in points (c), (d) and (e) of Article 9(1). The animal species to be listed for paratuberculosis according to Article 8(3) criteria are several species of mammals and birds as susceptible species and some species of the families Bovidae, Cervidae and Leporidae as reservoirs.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

The background and Terms of Reference (ToR) as provided by the European Commission for the present document are reported in Section 1.2 of the scientific opinion on the ad hoc methodology followed for the assessment of the disease to be listed and categorised according to the criteria of Article 5, Annex IV according to Article 9, and 8 within the Animal Health Law (AHL) framework (EFSA AHAW Panel, 2017).

1.2. Interpretation of the Terms of Reference

The interpretation of the ToR is as in Section 1.2 of the scientific opinion on the ad hoc methodology followed for the assessment of the disease to be listed and categorised according to the criteria of Article 5, Annex IV according to Article 9, and 8 within the AHL framework (EFSA AHAW Panel, 2017).

The present document reports the results of assessment on paratuberculosis according to the criteria of the AHL articles as follows:

- Article 7: paratuberculosis profile and impacts
- Article 5: eligibility of paratuberculosis to be listed
- Article 9: categorisation of paratuberculosis according to disease prevention and control rules as in Annex IV
- Article 8: list of animal species related to paratuberculosis.

2. Data and methodologies

The methodology applied in this opinion is described in detail in a dedicated document about the ad hoc method developed for assessing any animal disease for the listing and categorisation of diseases within the AHL framework (EFSA AHAW Panel, 2017).

3. Assessment

3.1. Assessment according to Article 7 criteria

This section presents the assessment of paratuberculosis according to the Article 7 criteria of the AHL and related parameters (see Table 2 of the opinion on methodology (EFSA AHAW Panel, 2017)), based on the information contained in the fact-sheet as drafted by the selected disease scientist (see Section 2.1 of the scientific opinion on the ad hoc methodology) and amended by the AHAW Panel.

3.1.1. Article 7(a) Disease Profile

Paratuberculosis is a chronic intestinal infection caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP). The disease was originally described as a peculiar case of bovine tuberculosis more than a century ago (Johne and Frothingham, 1895), but was later characterised as an independent entity when B. Bang infected calves with intestinal smears of diseased cows (Bang, 1906). MAP primarily affects domestic and wild ruminants and has a worldwide distribution (Sweeney, 2011). The main clinical features are: initially intermittent diarrhoea that becomes persistent and profuse. It leads to increased loss of plasma proteins, malabsorption of nutrients and water and therefore weight loss and declining milk production.

The progressing MAP infection has severe consequences in the subclinically infected and, especially, the clinically affected animals, leading to reduced milk yield (Lombard et al., 2005; Raizman et al., 2007), weight loss (Benedictus et al., 1987; Hutchinson, 1996), infertility (Johnson-Ifearulundu et al., 2000; Kostoulas et al., 2006a) and eventually premature removal from the herd. MAP is also suspected of being involved in the aetiology of Crohn's disease (CD) (e.g. Uzoigwe et al., 2007). This potential implication, if confirmed, adds importance to control efforts aiming to prevent transmission through milk consumption and other products of animal origin.

MAP control has been largely hampered by the absence of diagnostic tests that can effectively detect animals at the early infection stages. The sensitivity for most of the existing humoral tests increases with disease progression and only animals in the advanced stages are effectively identified through testing. Beaver et al. (2017) have confirmed earlier work by Van Schaik et al. (2003a,b)

demonstrating that faecal shedding generally precedes a positive humoral response by showing that spikes in faecal shedding of MAP predicted high serum enzyme-linked immunosorbent assay (ELISA) values up to 2 months later (Van Schaik et al., 2003b; Beaver et al., 2017). Various classification systems have been proposed to describe the various stages of MAP infection. Most of them depend on disease progression. For example, Whitlock and Buergelt (1996) described four stages: (i) silent infection, (ii) subclinical disease, (iii) clinical disease and (iv) advanced clinical disease (Whitlock and Buergelt, 1996). Animals in the first stage remain undetected with standard diagnostics, while a small percentage (15–25%) of animals in the second stage can be detected. Most of the animals in the third and fourth stage test positive.

An alternative classification considers the different stages of MAP infection in combination with the purpose of testing (i.e. prevalence estimation, control, eradication, etc.) and can be more helpful for a control-oriented approach (Nielsen and Toft, 2008). Animals can be (i) infected that carry MAP intracellularly and some of them control the infection, whereas others proceed to next stages; (ii) infectious that shed sufficient load of MAP to infect a susceptible herd mate; (iii) affected with chronic or intermittent diarrhoea and/or suboptimal productivity. MAP-infected animals are primarily of relevance for prevalence estimation; MAP-infectious animals when transmission should be avoided in a control scheme and MAP affected when the target is animals that should be removed from a herd because of their poor productivity and hence negative input.

3.1.1.1. Article 7(a)(i) Animal species concerned by the disease

Susceptible animal species

An extensive but not exhaustive list of susceptible animal species (from which MAP has only been isolated, and species from which MAP has been isolated and clinical signs associated with MAP infection have been reported) is shown in Table 1. Among domestic ruminants, cattle, sheep and goat are commonly affected (Nielsen and Toft, 2009), while it has also been reported in farmed zebu cattle (Fernandez-Silva et al., 2014), llamas (Belknap et al., 1994), alpacas (Ridge et al., 1995), fallow and red deer (Machackova et al., 2004). Natural infections are reported from mouflon in Austria and the Czech Republic, and chamois in Austria. Studies of Cervidae indicate that at least fallow deer can be infected with MAP subsequent to natural exposure, as demonstrated by histopathology. MAP has also been isolated from fallow deer, red deer and roe deer in various countries of Europe (Nebbia et al., 2000; Machackova et al., 2004; Deutz et al., 2005; Carta et al., 2013), but histopathological investigations were not carried out in these studies. Hence, although carriage was demonstrated, disease may not have been present. Tryland et al. (2004) reported serological responses against MAP in moose in Norway, but methods to detect MAP or pathological changes were not applied. Wild boars have also tested positive for MAP in tissue culture (Pribylova et al., 2011a; Carta et al., 2013), but in neither of the studies were histopathological changes described.

Among lagomorphs, MAP infections have been established in rabbits, but there is insufficient data to determine if infections can occur in hares. MAP infection can be maintained in a wild lagomorph population (Judge et al., 2006). The high proportion of infected foxes may be a result of the high number of infected rabbits, which may be consumed by the foxes. Among free-ranging carnivores, only a few studies have been carried out. It is highly likely that MAP infections occur in fox, but less certain whether the infection can be established in other carnivore species. Only a limited number of rodent-studies on MAP infections have been carried out, which is surprising considering their generally huge population size and often close proximity to farmed animals. It is not possible to determine whether natural infections occur among rodents based on these studies (Florou et al., 2008).

Table 1: Farmed (F) or free-ranging (R) animal species from which *Mycobacterium avium* subsp. *paratuberculosis* (MAP) has been isolated (I) and susceptible species (S) from which MAP has been isolated and clinical signs associated with paratuberculosis have been reported. Reporting of experimental (E) and/or natural (N) MAP infection is also listed as well as the extinction risk of each species according to the red list of the International Union for Conservation of Nature (IUCN)

F/R	Order	Family	Species	I,S	E/N[a]	IUCN[b]	Reference
F	Artiodactyla	Bovidae	Cattle (*Bos taurus*)	S	E,N	NE	Nielsen and Toft (2009)
F			Goats (*Capra aegagrus hircus*)	S	E,N	NE	
F			Sheep (*Ovis aries*)	S	E,N	NE	
F			Zebu cattle (*Bos indicus*)	S	N	NE	Chiodini et al. (1984b)
F			American bison (*Bison bison*)	S	N	NT	Buergelt and Ginn, 2000
F		Camelidae	Llama (*Lama glama*)	S	N	LC	Kramsky et al. (2000)
F			Alpaca (*Vicugna pacos*)	S	N	NE	Ridge et al. (1995)
F		Cervidae	Fallow deer (*Dama dama*)	S	N	LC	Machackova et al. (2004)
F			Red deer (*Cervus elaphus*)	S	N	LC	
F			Elk (*Cervus elaphus canadensis*)	S	N	LC	Manning et al. (1998)
R	Aves		Buzzard (*Buteo buteo*)	I	N	LC	Beard et al. (2001b)
R			Crow (*Corvus corone*)	I	N	LC	
R			Feral pigeon (*Columbia livia*)	I	N	–	
R			House sparrow (*Passer domesticus*)	I	N	LC	
R			Jackdaw (*Corvus monedula*)	I	N	LC	
R			Pheasant (*Phasianus colchicus*)	I	N	LC	
R			Rook (*Corvus frugilegus*)	I	N	LC	
R			Wood pigeon (*Columba palumbus*)	I	N	LC	
R			European starling (*Sturnus vulgaris*)	I	N	LC	Corn et al. (2005)
R			Common snipe (*Gallinago gallinago*)	I	N	LC	
R			Chicken (*Gallus gallus*)	S	E	LC	Larsen et al. (1972)
R			Diamant sparrow (*Emblema guttata*)	S	N	–	Miranda et al. (2009)
R	Carnivora	Canidae	Fox (*Vulpes vulpes*)	S	N	LC	Beard et al. (2001b)
R			Dog (*Canis lupus*)	S	N	LC	Kukanich et al. (2013)
R		Felidae	Feral cat (*Felis catus*)	I	N	–	
R		Mephitidae	Stripen skunk (*Mephitis mephitis*)	I	N	LC	Corn et al. (2005)
R		Mustelidae	Badger (*Meles meles*)	I	N	LC	Daniels et al. (2003)
R		Ursidae	European brown Bear (*Ursus arctos*)	I	N	LC	Kopecna et al. (2006)

F/R	Order	Family	Species	I,S	E/N[a]	IUCN[b]	Reference
R			Stoat (*Mustela erminea*)	I	N	LC	Daniels et al. (2003)
R			Weasel (*Mustela nivalis*)	I	N	LC	
R		Procyonidae	Raccoon (*Procyon lotor*)	I	N	LC	Corn et al. (2005)
R	Lagomorpha	Leporidae	Hare (*Lepus* spp.)	I	N	−	Beard et al. (2001a)
R			European brown hare (*Lepus europaeus*)	I	N	LC	Corn et al. (2005)
R			Mountain hare (*Lepus timidus*)	S	N	LC	Deutz et al. (2005)
R			Rabbit (*Oryctolagus cuniculus*)	S	E,N	NT	Greig et al. (1999)
R			Eastern cottonail (*Sylvilagus floridanus*)	I	N	LC	Corn et al. (2005)
R	Rodentia		Bank vole (*Clethrionomys glareolus*)	I	N	LC	Beard et al. (2001b)
R			Field vole (*Microtus agrestis*)	I	N	LC	
R			House mouse (*Mus domesticus*)	I	N	LC	
R			Mouse (not further specified) (*Mus* spp.)	S	E	−	Deutz et al. (2005)
R			Wood mouse (*Apodemus sylvaticus*)	I	N	LC	Beard et al. (2001a)
R			Yellow-necked mouse (*Apademus flavicollis*)	S	N	LC	Deutz et al. (2005)
R			Rat (*Rattus norvegicus*)	I	N	LC	Florou et al. (2008)
R			Hispid cotton rat (*Sigmodon hispidus*)	I	N	LC	Corn et al. (2005)
R			Norway rat (*Blarina brevicauda*)	I	N	LC	Corn et al. (2005)
R			Hamster (*Mesocricetus* spp.)	S	E	−	Larsen and Miller (1978)
R			Guinea pig (*Cavia porcellus*)	I	E	−	Merkal et al. (1982)
R	Artiodactyla	Bovidae	Water buffalo (*Bubalis bubalis*)	S	N	EN	Sivakumar et al. (2006)
R			Bison (*Bison bison*)	S	E,N	NT	Buergelt and Ginn (2000)
R			Alpine ibex (*Capra ibex*)	S	N	LC	Ferroglio et al. (2000)
R			Chamois (*Rupicapra rupicapra*)	S	N	LC	Deutz et al. (2005)
R			Yak (*Bos grunniens*)	S	N	NE	Geilhausen (2002)
R			Rocky mountain goat (*Oreamos americanus*)	S	N	NE	Williams et al. (1983)
R			Pygmy goat (*Capra hircus*)	S	E,N	NE	Ayele et al. (2001)
R			Dwarf goats (*Capra aegagrus hircus*)	S	N	NE	Manning et al. (2003)
R			Stone buck (*Capra aegagraus ibex*)	S	N	NE	Chiodini et al. (1984a)

F/R	Order	Family	Species	I,S	E/N[a]	IUCN[b]	Reference
R			Mouflon sheep (*Ovis orientalis*)	S	N	VU	Pribylova et al. (2011b)
R			Bighorn sheep (*Ovis canadensis*)	S	E,N	LC	Greig et al. (1999)
R			Aoudad (Barbary sheep) (*Ammotragus lervia*)	S	N	VU	Ayele et al. (2001)
R			Cameroon sheep (*Ovis aries cameroon dwarf*)	S	N	NE	
R			Antelope kudu (*Tragelaphus strepsiceros*)	S	N	LC	
R			Saiga antelope (*Saiga tatarica*)	S	N	CR	Dukes et al. (1992)
R		Camelidae	Bactrian camel (*Camelus bacterianus*)	S	N	CR	Ayele et al. (2001)
R			Dromedary camel (*Camelus dromedarius*)	S	N	–	Amand (1974)
R			Guanacos (*Lama guanicoe*)	I	N	LC	Salgado et al. (2009)
R		Cervidae	Fallow deer (*Dama dama*)	S	N	LC	Marco et al. (2002)
R			Red deer (*Cervus elaphus*)	S	E,N	LC	Tryland et al. (2004)
R			Roe deer (*Capreolus capreolus*)	S	N	LC	Tryland et al. (2004)
R			Sika deer (*Cervus nippon*)	I	N	LC	Ayele et al. (2001)
R			Axis deer (*Axis axis*)	I	N	LC	
R			Key deer (*Odocoileus virginianus clavium*)	S	N	NE	Quist et al. (2002)
R			Mule deer (*Odocoileus hemionus*)	S	E,N	LC	Williams et al. (1983)
R			Pudu (*Pudu pudu*)	I	N	–	Ayele et al. (2001)
R			White-tailed deer (*Odocoileus virginianus*)	S	E,N	LC	Williams et al. (1983)
R			Moose (*Alces alces*)	S	N	LC	Tryland et al. (2004)
R			Reindeer (*Rangifer tarandus*)	I	N	VU	Tryland et al. (2004)
R			Elk (*Cervus canadensis*)	S	N	NE	Ayele et al. (2001)
R			Tule elk (*Cervus elaphus nannodes*)	S	N	LC	
R			Rocky mountain elk (*Cervus elaphus nelsoni*)	S	E,N	–	Williams et al. (1983)
R		Suidae	Wild boar (*Sus scrofa*)	I	N	LC	Boadella et al. (2011)
R			Pigs (*Sus* spp.)	I	E	–	
R	Didelphimorphia	Didelphidae	Opossum (*Didelphis virginiana*)	I	N	LC	Corn et al. (2005)
R	Cingulata	Dasypodinae	Armadillo (*Dasypus novemcinctus*)	I	N	LC	
R	Perissodactlya	Equidae	Pygmy ass (*Equus asinus* f. dom.)	S	N	–	Ayele et al. (2001)

F/R	Order	Family	Species	I,S	E/N[a]	IUCN[b]	Reference
R			Horses (*Equus ferus caballus*)	I	E	–	Larsen et al. (1972)
F			Mules (*Equus mule*)	S	E	–	Chiodini et al. (1984a)
R	Primates (Non-human)		Mandrill (*Papio sphinx*)	S	N	–	Zwick et al. (2002)
R			Stumptail macaque (*Macaca arctoides*)	S	N	VU	McClure et al. (1987)
R			Common marmoset (*Callithrix jacchus*)	S	N	LC	Fechner et al. (2017)
R			Rhesus macaques (*Macaca mulatta*)	S	N	LC	Singh et al. (2011)
R			Cottontop tamarins (*Sanguinus oedipus*)	S	N	CR	Munster et al. (2013)
R			Black-and-white ruffed lemurs (*Varecia variegata*)	S	N	CR	Munster et al. (2013)
R	Oligochaeta	Lumbricidae	Earthworms (*Lumbricus* spp.)	I	N	–	Fischer et al. (2004)

(a): Hines et al. (2007) provided an extensive review and proposed guidelines for experimental challenge models of MAP infection.
(b): NE: not evaluated; LC: least concerned; NT: near threatened; VU: vulnerable; EN: endangered; CR: critically endangered.
An explicit description of these terms can be found at: http://www.iucnredlist.org/about/introduction

Reservoir animal species

Wildlife and domestic species can serve as potential reservoirs since interspecies transmission has been documented. However, their potential role in the epidemiology of paratuberculosis depends on (i) whether paratuberculosis is endemic in a region or not (i.e. under endemic disease conditions within herd/flock transmission is the main way of disease persistence) and (ii) the husbandry type (i.e. whether systems allow for interface between domestic and wildlife carriers through, for example, co-grazing). Stevenson et al. (2009) genotyped 164 MAP isolates from seven European countries representing 19 different host species, and provided evidence of interspecies transmission between wildlife and domestic ruminants and among wildlife species, adding further support to the reservoir role of wildlife (Stevenson et al., 2009). Only ruminants (Bovidae, Cervidae) and lagomorphs show evidence of disease as determined by the presence of gross or microscopic lesions with associated acid fast bacteria, thus species have the capacity to excrete MAP and spread disease to other susceptible species primarily through further faecal contamination of the environment, so potentially, they could constitute wildlife reservoirs. By definition, to constitute a wildlife reservoir the infection would need to be sustained within the species population. Evidence is available for vertical and horizontal transmission within natural rabbit populations which could contribute to the maintenance of Map infections within such populations (Stevenson et al., 2009). Rabbits can also serve as a reservoir in the UK due to the high prevalence of MAP infection and the high excretion rates (Greig et al., 1999; Judge et al., 2006).

3.1.1.2. Article 7(a)(ii) The morbidity and mortality rates of the disease in animal populations

Morbidity

Parameter 1 – Prevalence/incidence

A recent review aiming to identify potential sources of MAP exposure for humans (Waddell et al., 2016) found 148 research papers on the prevalence and/or presence of MAP in farmed, pets and wild animals. Earlier, Nielsen and Toft (2009) summarised the prevalence of paratuberculosis for dairy cattle, sheep and goats in Europe. The latter authors concluded that, for each species, prevalence estimates at the animal level are not comparable. Indeed, the use of different tests among studies that targeted different conditions, lack of knowledge on the accuracy of the used diagnostic tests in several studies, differences in the source populations – and hence likely differences in the distribution of the various infections stages within these populations – and finally variable sampling designs and poor

reporting do not allow for a direct comparison of the prevalence estimates. An extensive list of the apparent and true prevalence estimates at the animal level is given in Tables 2, 3, 4 and 5. The apparent prevalence is defined as the number of test-positive among tested subjects, whereas the true prevalence is based on a conversion correcting the apparent prevalence for the diagnostic sensitivity and diagnostic specificity (Houe et al., 2004).

Recent work on the within herd dynamics of MAP infection in dairy cattle (Al-Mamun et al., 2016) assumed that latently infected animals progress to low shedders and low shedders to heavy shedders with a yearly incidence rate of 0.47 and 0.28, respectively (Van Schaik et al., 2003a). The proportion of calves infected at birth from latently infected, low-shedding and high-shedding animals is estimated to be 0.15 (Sweeney et al., 1992), 0.15 and 0.17 (Crossley et al., 2005), respectively. In another study, the proportion of infected cows with detectable MAP-specific IgG antibodies increased from 0.33, for cows 2 years of age, to 0.94 for cows 5 years of age (Nielsen et al., 2013). However, it should be noted that most of the aforementioned estimates depended on the opinion of experts due to the scarcity of valid data on the duration of the latent infection period. Studies that determine the age-specific proportion of detectable infected animals can be used to provide indirect estimates of the age-specific incidence rate for paratuberculosis and thus insight in the infection dynamics of MAP.

MAP prevalence in sheep worldwide is unknown as the disease is not notifiable in many countries and the study of MAP in species other than cattle has relatively low priority. However, prevalence varies between countries and geographical regions ranging from 2% to 32% of sheep flocks affected (Begg and Whittington, 2010). MAP has been diagnosed in sheep in the southern hemisphere in Australia, New Zealand and South Africa, and in the northern hemisphere in Great Britain, Norway, Austria, Greece, Spain, Portugal, Morocco and Jordan (Windsor, 2015).

In goats, MAP had been diagnosed in most goat rearing/farming countries including Austria, France, Portugal, Spain, Greece, Great Britain, Croatia, Norway, Switzerland, Turkey, South Africa, Australia New Zealand, Canada, the USA and Chile. The disease resembles that in sheep and it appears that prevalence may be increasing but prevalence estimates vary widely (Djønne, 2010; Windsor, 2015).

There have been a few isolated reports of paratuberculosis in deer prior to 1970, but since then it has been reported frequently in many countries in a range of deer species in the wild and in parks, zoos and enclosures. It has also been diagnosed on deer farms in the UK, Ireland, Denmark, Germany and Belgium, Hungary, Asia, Canada, the USA, Argentina, Australia and New Zealand. Serological surveillance for paratuberculosis on 627 of New Zealand's deer farms has been carried out since 2000, using blood samples submitted as part of the national tuberculosis eradication scheme indicate a national herd infection prevalence of approximately 63%. A non-random sample of 115 New Zealand deer herds of unknown infection status reported in 2006 that 43% had pooled faecal samples culture-positive for MAP (Mackintosh and Griffin, 2010). By passive surveillance, Mackintosh et al. (2004) estimated approximately 6% of herd prevalence of the infection in farmed deer in New Zealand (Mackintosh et al., 2004). MAP infection was identified in over 600 farms by the examination of suspect 'tuberculosis' lesions in deer slaughtered plants, thus the true prevalence is expected to be higher.

Concerning other ruminant species, paratuberculosis has been reported in riverine buffalo (*Bubalus bubalis*) in India, where the prevalence of infection was over 40% in some populations, and in Italy with a low prevalence; it has also been reported widely in many populations of camels in Asia, the Middle East, Africa and the former Soviet Union. The disease appears to be uncommon in llamas but has been occasionally reported in alpacas in Australia, the UK and New Zealand (Mackintosh and Griffin, 2010).

Table 2: Animals that tested positive (T+) of the animals tested (N), apparent (AP) and true prevalence (TP) of MAP in cattle by region/country

Country	Region	Type of test	N	T+	AP (%)	TP (%)	Reference
Austria	All	ELISA	756	144	19.0	100.0	Dreier et al. (2006)
Austria	Four regions	ELISA	11,028	664	6.0	47.0	Gasteiner et al. (1999)
Belgium		ELISA	13,317	116	0.87 (0.71,1.03)	0.0	Boelaert et al. (2000)
France	Yonne	ELISA	8,793	292	3.3	22.0	Petit (2001)
Germany	Saxony	ELISA	3,454	151	4.4	31.0	Donat et al. (2005)

Country	Region	Type of test	N	T+	AP (%)	TP (%)	Reference
Germany	Arnsberg	ELISA	536	79	14.7	98.0	Bottcher and Gangl (2004)
Germany	Arnsberg	Tissue culture	517	7	1.35		
Germany	Bavaria	ELISA	2,748	41	1.5	0.0	
Germany	Bavaria	ELISA	2,748	25	0.15	6.0	
Germany	Bavaria	ELISA	2,748	662	24.1	100.0	
Italy	Latium	ELISA	19,627	472	2.4	100.0	Lillini et al. (2005)
Italy	Lombardia	ELISA	38,478	982	2.55		Arrigoni et al. (2008)
Italy	Veneto	ELISA	27,135	949	3.5	17.0	Robbi et al. (2003)
Italy	Umbria	ELISA	788	44	5.6	9.7 (7.0; 12.4)	Cenci-Goga et al. (2010)
Norway		ELISA	9,456	728	7.7	83.0	Tharaldsen et al. (2003)
Rep. of Ireland	Imported	ELISA, Faecal culture	225 221	8 9	3.6 4.0	19.0	O'Doherty et al. (2002)
Slovenia	All	ELISA	11,513	47	0.41	0.0	Ocepek et al. (2002)
Slovenia	All	ELISA	12,082	140	1.16	0.0	
Slovenia	All	ELISA	38,469	1305	3.4	16	
Slovenia	All	ELISA	9,388	41	0.4	3.0	
Spain		ELISA	61,069	1374	2.53 (Dairy) 1.59 (Beef) 2.44 (Mixed) 2.25 (Total)	3.02 (Dairy) 2.07 (Beef) 3.84 (Mixed) 2.95 (Total)	Dieguez et al. (2007)
Sweden	All	Faecal culture	4,000	0	0.0	0.0	Sternberg and Viske (2003)
Switzerland	Plat. de Diesse	ELISA	565	29	5.1	30	Meylan et al. (1995)
Switzerland	All	ELISA	1,663	12	0.7	0.0	Stark et al. (1997)
Switzerland		F57 PCR	101	20	19.8		Bosshard et al. (2006)
The Netherlands	All	ELISA	15,822	400	2.5	2.0	Muskens et al. (2000)
Turkey		IS900 PCR	96	0	0.0		Ikiz et al. (2005)
Turkey	Elazig	IS900 PCR	500	25	5.0		Cetinkaya et al. (2000)
United Kingdom	SW England	IS900 PCR	1,297	46	3.5 (2.6; 4.7)		Cetinkaya et al. (1996)
United Kingdom	SW England	IS900 PCR of T+ from IS900 PCR	1,297	34	2.6 (1.8; 3.6)		
Brazil		ELISA	128	41	32		Ristow et al. (2007)
Brazil		Culture	24	10	41		
Canada	Nova Scotia	ELISA	814	27	3.3		Tiwari et al. (2006)
Canada	Prince Edward Island	ELISA	816	11	1.3		

Country	Region	Type of test	N	T+	AP (%)	TP (%)	Reference
Canada	New Brunswick	ELISA	804	23	2.9		
Canada	Ontario	ELISA	1,530	34	2.2		
Canada	Manitoba	ELISA	1,204	54	4.5		
Canada	Saskatchewan	ELISA	1,530	41	2.7		
Canada	Alberta	ELISA	1,500	105	7.0		
Canada	Alberta	Tissue culture	984	158	16.1		McKenna et al. (2004)
USA	Georgia	ELISA	637	61	9.58		Pence et al. (2003)
USA	Florida	ELISA	4,491	768	17.1		Braun et al. (1990)
USA	Wisconsin	ELISA	4,990	364	7.3	4.79	Collins et al. (1994)
USA	Michigan	ELISA	3,886	268	6.9		Johnson et al. (2001)
USA	20 States		31,745	794	2.5		Wells (1996)
Egypt		Faecal culture, PCR, Microscopic examination	160	75	50		Salem et al. (2005)

ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction.

Table 3: Animals that tested positive (T+) of the animals tested (N), apparent (AP) and true prevalence (TP) of MAP in sheep by region/country

Country	Region	Test	N	T+	AP (%)	TP (%)	Reference
Austria	All	ELISA	169	1	0.6	0.0	Khol et al. (2006)
Austria	All	Tissue culture	169	1	0.6		
Cyprus		ELISA	3,429	340	9.9 (8.9; 10.9)	24.6	Liapi et al. (2011)
Norway	All	Faecal culture	369	1	0.3	0.0	Mork et al. (2003)

ELISA: enzyme-linked immunosorbent assay.

Table 4: Animals that tested positive (T+) of the animals tested (N), apparent (AP) and true prevalence (TP) of MAP in goats by region/country

Country	Region	Test	N	T+	AP (%)	TP (%)	Reference
Austria	All	Faecal/Tissue culture	80	0	0.0		Khol et al. (2006)
Austria	All	ELISA	80	0	0.0	0.0	
Cyprus		ELISA	4,582	362	7.9 (7.2; 8.7)	23.1	Liapi et al. (2011)
Greece		Milk ELISA	1,200			10.0	Angelidou et al. (2014)
Norway	All	Faecal culture	662	7	1.1	0.0	Mork et al. (2003)
Portugal	Lisbon	ELISA	2,351	41	1.7		Mendes et al. (2004)

ELISA: enzyme-linked immunosorbent assay.

Table 5: Animals that tested positive (T+) of the animals tested (N), apparent (AP) and true prevalence (TP) of MAP in mixed sheep and goat flocks by region/country

Country	Region	Test	N	T+	AP (%)	TP (%)	Reference
Portugal	Lisbon	ELISA	2351	41	1.7		Mendes et al. (2004)
Slovenia	All	ELISA	12578	440	3.5		Ocepek et al. (2002)

ELISA: enzyme-linked immunosorbent assay.

Parameter 2 – Case-morbidity rate (% clinically diseased animals out of infected ones)

The case-morbidity rate is not known. Partly, it is not known if cure can take place or some animals are naturally resistant, partly the long incubation period makes assessment challenging while many infected animals are culled before a causative diagnosis is made, but culling is based on impact of the disease agent (e.g. reduced milk yield). Therefore, the case-morbidity rate considering the natural life of domestic animals can be higher than what can be observed in their production life.

At any point in time, it is believed that 50–70% of MAP infected animals are undetectable; a fraction referred to as the invisible part of the 'iceberg' (Whitlock and Buergelt, 1996). Recently, Schukken et al. (2015) in a long-term follow-up study, including of test negative apparently healthy dairy cows at routine slaughter, from three infected dairy farms demonstrated that the prevalence of positive samples was 1.4% for serological samples, 2.2% in faecal samples and 16.7% in tissue samples.

A common feature of mycobacterial infections is the long latent infection period. Under endemic disease conditions, most animals acquire MAP early in their life. Infected animals may not experience progression of the infection during their productive life because they are resistant or will be prematurely removed. Hence, animals in a herd can be: uninfected or potentially latently infected animals where infection will never evolve; latently infected where infection will evolve within their expected life-time; and animals where the infection is progressing with a predominant anti-inflammatory or humoral immune response (Nielsen, 2009).

Sheep, goats, deer and South American camelids presents with ill thrift and progressive chronic weight loss as the primary clinical sign of disease with poor production; affected animals may also display exercise intolerance and in only 10–20% of clinical cases will intermittent soft faeces, clumping of faces or even persistent diarrhoea be noted in the end stages of the disease although most sheep that die of Johne's disease (JD) have normal faecal pellets. In a study of 50 sheep with clinical JD, most were emaciated; half had normal faecal pellets; 30% had soft-formed faeces; and 20% had severe diarrhoea (Stehman, 1996; Smith, 1998; Begg and Whittington, 2010; Windsor, 2015).

The disease in camels may have a more rapid course than in cattle, with death occurring after 4–6 weeks' illness. In Bactrian camels, the disease was most severe in 3–5-year-old animals. Clinical disease has occurred in 12–24-month-old alpacas as well as in adults, with signs of diarrhoea, weight loss and hypoproteinaemia. As with other species, necropsy showed emaciation, thickened intestines and enlarged mesenteric lymph nodes (Mackintosh and Griffin, 2010).

The pathogenesis of MAP infection in cervids is different from that in other ruminant species. Deer appear to be highly susceptible to MAP infection and show clinical evidence of disease and severe pathology at an earlier age than other ruminants. Clinical disease has been reported in fawns and yearlings of white-tailed deer, sika and fallow deer, red deer and North American elk. In spite of this, only a small proportion of deer exposed to MAP develop clinical disease (Mackintosh and Griffin, 2010). MAP infection in deer causes long standing infection and minimal mortality (Mackintosh et al., 2004). In farmed deer, two clinical syndromes of JD have been recognised: sporadic cases occurring in mixed-age class with yearly incidence of 1–3%, usually low morbidity (< 1%) and high mortality (∼ 100%); and outbreaks involving young deer (8–15 months of age) up to 20% of a group with a clinical progression to emaciation and death in few weeks. However the prevalence of subclinical MAP infection is not known in farmed deer, but up to 10% of apparently healthy deer from infected farms had macroscopic evidence of infection at slaughter thus is highly probable that the prevalence is much higher and many subclinical infected deer do not report any macroscopic evidence of infection (Mackintosh et al., 2004).

Mortality

Parameter 3 – Case-fatality rate

There is scarcity of valid estimates on the true mortality rate due to the long latent infection period, the absence of sensitive tests and hence our inability to estimate the true prevalence of infection (and therefore the denominator of mortality and other rates). A study conducted on 12 sheep farms in New South Wales, Australia identified the disease mortality rate in 2003 as 8% (Windsor, 2015). Most affected goats, if not culled, go into stage four and develop advanced clinical disease, leading to death (Djønne, 2010). The disease in camels may have a more rapid course than in cattle, with death occurring after 4–6 weeks' illness (Djønne, 2010; Mackintosh and Griffin, 2010).

3.1.1.3. Article 7(a)(iii) The zoonotic character of the disease

Presence

Parameter 1 – Report of zoonotic human cases (anywhere)

The human implications of paratuberculosis depend on the resolution of the question on whether MAP is involved in the aetiology of CD. Existing results are consistent with two possibilities: (i) MAP infection could be the cause of Crohn's in patients who are selectively exposed to this organism or genetically susceptible or (ii) MAP, which is a relatively common dietary organism, may selectively colonise the ulcerated mucosa of CD patients but it does not initiate or perpetuate intestinal inflammation (Naser et al., 2004).

Initially, similarities were noted between chronic idiopathic granulomatous ileocolitis (i.e. the clinical syndrome now called CD) and mycobacterial infections (Crohn et al., 1932). Interest on MAP as a possible cause for Crohn's revived with the culture of MAP from patients with CD (Chiodini et al., 1984b) and intensified after the detection of IS900, the MAP-specific DNA insertion sequence, in relatively high numbers of patients with CD relative to patients with ulcerative colitis and normal controls (Sanderson et al., 1992). Ever since, many studies have been carried out to assess the potential role of MAP in the aetiology of CD. Higher probability of MAP has been reported in patients with CD. However, MAP has also been reported from non-inflammatory bowel disease controls (Mendoza et al., 2010) while others have been unable to detect MAP in the blood of Crohn's patients (Parrish et al., 2009). Effective treatment of Crohn's patients with antimycobacterial drugs has been reported in some studies (Borody et al., 2007), while others cannot find an effect in randomised clinical trials with similar antimicrobials (Selby et al., 2007).

A systematic review and meta-analysis of 28 case–control studies comparing MAP in patients with CD with individuals free of inflammatory bowel disease or patients with ulcerative colitis found a specific association of MAP with CD (Feller et al., 2007). Another meta-analysis of studies using nucleic acid-based techniques to detect MAP in patients with CD confirmed that MAP was detected more frequently from patients with CD compared to those with ulcerative colitis (Abubakar et al., 2008). Both studies concluded that though association between MAP and CD is established, further studies are required to determine its pathogenic role. In consistence with these, a recent meta-analysis (Waddell et al., 2015) appraised the available research (128 papers) on the zoonotic potential of MAP and confirmed a significant positive association for CD (odds ratio range 4.3–8.4). The latter authors also concluded that knowledge gaps exist and therefore current evidence is not sufficient to establish a causal path.

MAP has also been related to an increasing number of diseases: Blau syndrome (Dow and Ellingson, 2010), type 1 diabetes (Sechi et al., 2008; Rosu et al., 2009; Cossu et al., 2011a), Hashimoto thyroiditis (Sisto et al., 2010; Pinna et al., 2014) and multiple sclerosis (Cossu et al., 2011b; Sechi and Dow, 2015). However, in these cases, the so far circumstantial isolation of MAP does not add to the zoonotic potential of MAP. It rather supports the hypotheses that these diseases favour survival and opportunistic growth of MAP in the human gut.

Although a causal link between MAP and CD has not yet been proven concerns are being expressed and, for example, the UK Food Standards Agency has appealed for strategies to further minimise human exposure to MAP (Rubery, 2001), in addition the finding of Viable MAP in powdered infant formula (Botsaris et al., 2016) is worrying.

3.1.1.4. Article 7(a)(iv) The resistance to treatments, including antimicrobial resistance

Parameter 1 – Resistant strain to any treatment even at laboratory level

Antibiotic treatment is not practiced in MAP-infected animals because it is not cost effective. It could be an option, as a means to forestall progression of infection, for selected animals of high genetic value, exceptional production or sport and pet animals.

Susceptibility testing of MAP to 11 antimicrobial drugs *in vitro* revealed that the organism is most susceptible to macrolides, while first-line antituberculosis (ethambutol and isoniazid) or antileprosy drugs (dapsone and clofazimine) are not effective with the exception of the rifampicin family (Krishnan et al., 2009). Gallium nitrate also has *in vitro* activity against MAP isolates (Fecteau et al., 2011). However, *in vitro* drug susceptibility often fails to predict the *in vivo* efficacy of treatments (Griffith, 2007). Drugs that have been used to treat MAP infections are isoniazid, clofazimine (St Jean, 1996) and the most promising appears to be monensin (Brumbaugh et al., 2000).

3.1.1.5. Article 7(a)(v) The persistence of the disease in an animal population or the environment

Animal population

Within infected herds/flocks, animals are exposed to and acquire MAP infection early in their life. Young animals are more susceptible to infection and susceptibility decreases with age (Kostoulas et al., 2010). For example, calves are more susceptible in the first year of their life (Mortier et al., 2015). The majority of infected animals in a herd will be in the early infection stages and the proportion of animals that can be detected by diagnostic tests seriously underestimate the prevalence of infection in the herd (i.e. the 'tip of the iceberg' (Whitlock and Buergelt, 1996)). The disease is more insidious in small ruminant flocks/herds, than in bovine herds with the incubation period being usually at least 1 year. Faecal shedding usually precedes clinical signs with the age of onset of faecal shedding and clinical disease varying with the dose, age at infection, and herd management factors. The typical range for clinical disease is 2–7 years of age; however, in some heavily infected goat and deer herds clinical infection and faecal shedding occur as early as 1 year of age. However, regardless the host species the true morbidity and mortality rates are rarely reported because the exact duration of the latent infection period, the infectious period and the time that MAP can persist in healthy carriers have not been quantified.

Environment

Parameter 4 – Length of survival (dpi) of the agent and/or detection of DNA in selected matrices (soil, water, air) from the environment (scenarios: high and low T)

Sparse information exists on the survival of MAP in the environment but it is clear that MAP can survive in the environment for a long time as it has been shown in studies investigating its survival and the levels of contamination in and around ruminant farms (Waddell et al., 2016). Protected from sunlight – MAP like all mycobacteria is sensitive to ultraviolet light (sunlight) – it survived for up to 55 weeks in a dry fully shaded environment. Water and sediment behind dams prolongs survival times while dry soil, changes in ambient temperature, pH < 7.0, high ammonia levels and low iron contents shortens its survival (Whittington et al., 2004, 2005). If vegetation is removed and shading is limited, then survival is reduced to a few weeks (Eppleston et al., 2014). Water reservoirs may play significant role in MAP infection on farms (Singh et al., 2013). Animals raised in rich organic soil pose a higher probability of acquiring the infection from the environment probably due to the adsorption of MAP to clay content (Dhand et al., 2009).

3.1.1.6. Article 7(a)(vi) The routes and speed of transmission of the disease between animals, and, when relevant, between animals and humans

Routes of transmission

Parameter 1 – Types of routes of transmission from animal to animal (horizontal, vertical)

The primary route of transmission is the faecal–oral route (Sweeney, 1996). Faecal contamination of the udder or the calving environment is a main risk factor for neonatal infection (Collins et al., 1994). MAP can be also excreted in milk/colostrum (Streeter et al., 1995) and shedding depends on the severity of MAP infection and lactation stage with higher risk observed in early than mid or late lactation (Stabel, 2008). *In utero* transmission can also occur and the risk increases with infection stage (Whittington and Windsor, 2009). MAP can also be excreted in semen but data on transmission via semen are sparse (Ayele et al., 2004). Transmission is considered to occur primarily from cows to calves, which are considered most susceptible. Calf-to-calf transmission has been described (van Roermund et al., 2007), and cow-to-cow transmission may take place but remains mainly undetected because delayed exposure results in lower incidence of detectable cases (Espejo et al., 2013). *In utero* infections occur in cattle (Sweeney et al., 1992; Whittington and Windsor, 2009) and have been reported in goats as well (Stehman, 1996). A study by Van Kooten et al. (2006) showed that 90% of clinically affected deer had an infected fetus.

Cross-species transmission exists with different strains of MAP showing preference to different hosts: type I or S strains are predominantly isolated from sheep and less commonly from deer and cattle, type II or C strains have a broad host range but frequently infect cattle, goats and deer and less commonly sheep. Finally, type III strains represent an intermediate type and are predominantly

isolated from sheep and goats (Stevenson, 2015). Cross species transmission between wild and domestic ruminants has also been indicated (Fritsch et al., 2012).

<u>Parameter 2 – Types of routes of transmission between animals and humans (direct, indirect, including food-borne)</u>

If MAP is transmitted to humans, the transmission may occur via ineffectively pasteurised milk (O'Reilly et al., 2004), beef (Alonso-Hearn et al., 2009) or water (Pickup et al., 2005, 2006; Beumer et al., 2010; Rhodes et al., 2014). The overall prevalence in beef is deemed to be low (Okura et al., 2010), but reduction due to cooking has not been extensively studied. One study estimated that long cooking times are required for more than two $\log_{10}$ bacterial reductions (Hammer et al., 2013). The concentrations in milk are most often considered to be within reach of pasteurisation. However, experimental studies indicate that if large numbers of MAP are present in milk the organism may not be completely inactivated through pasteurisation and viable MAP has been found in retail pasteurised milk (Carvalho et al., 2012). A systematic review of the contamination of food products concluded that pasteurised milk is not always MAP free, and it cannot be ruled out that meat and meat products contain MAP (Eltholth et al., 2009). Survival of MAP has also been documented in yoghurt after artificial inoculation of pasteurised milk (Van Brandt et al., 2011). If MAP is confirmed as a zoonotic pathogen, further studies are required to better characterise the routes of transmission to humans.

Speed of transmission

Due to the poor sensitivity of the tests during the long latent period, there is a scarcity of studies aiming to quantify the within herd dynamics of MAP infection. van Roermund et al. (2007) reported transmission rates of 2.7 [1.1, 6.6] new calf infections per infectious cow, and 0.9 [0.1, 3.2] new infections per infectious calf. However, their experimental setting did not mimic a modern dairy farm and results cannot be directly extrapolated to other conditions.

3.1.1.7. Article 7(a)(vii) The absence or presence and distribution of the disease in the Union, and, where the disease is not present in the Union, the risk of its introduction into the Union

Presence and distribution

<u>Parameter 2 – Type of epidemiological occurrence (sporadic, epidemic, endemic) at MS level</u>

The presence of MAP infection has been reported in most Member States (MS). Specifically, MAP has been reported in Austria (Dreier et al., 2006), Belgium (Boelaert et al., 2000), Bulgaria (Kuiumdzhiev, 1950), Croatia (Cvetnic et al., 2012), Cyprus (Liapi et al., 2011), the Czech Republic (Pavlík et al., 1994), Denmark (Nielsen and Toft, 2014), Estonia (Nielsen and Toft, 2009) Finland (Kulkas, 2007), France (Marce et al., 2011), Germany (Donat et al., 2016), Greece (Angelidou et al., 2014), Hungary (Ronal et al., 2015), Ireland (Kennedy et al., 2016), Italy (Cenci-Goga et al., 2010), Lithuania (Nielsen and Toft, 2009), Luxembourg (Fernandez-Silva et al., 2012), the Netherlands (Muskens et al., 2003), Poland (Szteyn and Wiszniewska-Laszczych, 2012), Portugal (Mendes et al., 2004), Slovakia (Mucha et al., 2009), Slovenia (Ocepek et al., 2002), Spain (Dieguez et al., 2009), Sweden (Frossling et al., 2013) and the UK (Woodbine et al., 2009). No data exist for Latvia, Malta and Romania. Reports among the MS are not comparable due to the variation in the type of studies and in the diagnostics used for MAP detection (see Section 3.1.1.2).

Nielsen and Toft (2009) summarised the prevalence of paratuberculosis for dairy cattle, sheep and goats in Europe (Nielsen and Toft, 2009). The true within-herd prevalence in cattle may be 20% and was at least 3–5% in several member states. Herd-level prevalence was probably $\geq$ 50%. Valid prevalence estimates are scarce for sheep or goats. An extensive study in Cyprus estimated that there was at least one infected sheep in 60.8% (95% CI: 42.3; 78.8%) and at least one infected goat in 48.6% (30.4; 68.5%) of the flocks. Within infected flocks, the true prevalence of MAP infection was estimated at 24.6% (16.3; 33.3%) and 23.1% (15.5; 33.6%) in sheep and goats, respectively (Liapi et al., 2011). A study on the seroprevalence of MAP in central Italy revealed that 73.7% of the sheep flocks had at least one seropositive animal and the mean seroprevalence was 6.29% (Anna Rita et al., 2011). A flock-level prevalence of 63% and a mean within-flock prevalence of 6.6% was found in French goats (Mercier et al., 2010).

There are not sufficient data to prove disease freedom or near-zero prevalence in any member state. Some countries such as Sweden may have a low prevalence in cattle, but claims to support

disease freedom (Frossling et al., 2013) are not based on sampling and testing schemes designed and carried out to prove disease freedom.

3.1.1.8. Article 7(a)(viii) The existence of diagnostic and disease control tools

Control tools

Parameter 2 – Existence of control tools

Tests for paratuberculosis can be divided in those that detect the organism and those that assess the host response to MAP infection. An extensive description of these is in Section 3.1.4.1, and Tables 6, 7 and 8 below. Available diagnostic tests are of imperfect sensitivity and specificity (although the latter is often close to 100%). The sensitivity of most of the tests is poor at the early infection stages and increases with disease progression (Nielsen and Toft, 2008). Nonetheless, such tests can and have been used for disease control. Currently, available control strategies include management interventions to improve calf hygiene, test and cull strategies and vaccination (Al-Mamun et al., 2016). The first two of them require long and dedicated efforts from the dairy producers (Groenendaal et al., 2015) and if combined exhibit a synergistic effect. An extensive description of available control tools is provided in Section 3.1.4 below.

3.1.2. Article 7(b) The impact of diseases

3.1.2.1. Article 7(b)(i) The impact of the disease on agricultural and aquaculture production and other parts of the economy

The level of presence of the disease in the Union

Parameter 1 – Number of MSs where the disease is present

Paratuberculosis is present in most of the member states. The reporting of the prevalence studies that have been carried out is poor leading to estimates that are not comparable (Nielsen and Toft, 2009). An extensive list of the prevalence estimates, either apparent or true is given in Tables 2–5 and is discussed in detail in Section 3.1.1.2 Parameter 1. Additional information on the presence of MAP in the MSs is reported in Section 3.1.1.7.

The loss of production due to the disease

Parameter 2 – Proportion of production losses (%) by epidemic/endemic situation

Paratuberculosis has major consequences in the subclinically infected and, especially, the clinically affected animals, leading to decreased and suboptimal productive life due to reduced milk yield (Lombard, 2011), body weight and slaughter value (Hutchinson, 1996), fertility (Johnson-Ifearulundu et al., 2000; Kostoulas et al., 2006a; Marce et al., 2009) and, thus, increased rate of premature voluntary culling. In many species, lowered age of onset linked with increased prevalence and the loss of young animals increases the overall cost of paratuberculosis (Smith, 1998). When considering the cost of MAP infection, it is important to point out that typical 'losses' are in the form of potential or unrealised revenue which are easier for producers with high prevalence herds selling cattle with actual disease to see than for producers with low prevalence herds or culling animals for reasons not being attributed to the presence of paratuberculosis. MAP-infected cattle have been shown to be at twice the risk of being culled compared with uninfected herd mates even when producers were not aware of their infection status (Lombard, 2011).

In two MAP-affected dairy herds (a total of 1048 cows), faecal culture positive cows produced $276 less in milk income per lactation than cows that were faecal culture negative and were 3.0 (1.6–5.8) times more likely to be culled than faecal culture negative cows (Raizman et al., 2007). A recent meta-analysis (McAloon et al., 2016) of studies on the impact of MAP on milk productivity provided a pooled estimate of 5.9% reduction in the milk yield associated with faecal culture or polymerase chain reaction (PCR) positivity. Interestingly, milk production can initially be higher in infected animals before it slowly decreases (Nielsen et al., 2009) and cows have been found to produce more milk before their first positive test when compared to their negative herd mates (Smith et al., 2016). Nielsen et al. (2009) found that MAP associated milk-losses depended on the ELISA profile of dairy cattle as defined through repeated testing and proposed that repetitive testing schemes, combined with milking records, can be a useful management tool for the early identification of animals that experience or are likely to experience milk loss, in the near future (Nielsen et al., 2009).

The stage of MAP infection influences the impact on body weight and slaughter value. Kudahl and Nielsen (2009) directly assessed the slaughter value paid to the farmers for carcases with different combinations of test result and anatomopathological information. They estimated that the slaughter weight was reduced by 5–15% depending on the stage of infection. Lower quality further reduced carcass value: cows with MAP antibodies and MAP detected in faeces had a reduction of 17% in slaughter value. If they also had enteritis and oedema, the slaughter value was reduced by another 31% (i.e. an almost 50% reduction in the slaughter value). Benedictus et al. (1987) estimated the lost value at slaughter to 25–30% in animals with clinical disease. Raizman et al. (2009) recorded total losses of $441 in two dairies (1,048 cows) in culled culture-positive compared to cultured-negative cows with most of this loss being associated with premature culling and reduced beef value.

In the European Union (EU) (the UK), Pritchard et al. (2017) while using ELISA tests in a paratuberculosis control programme, and positive results for MAP in their lifetime as the basis for paratuberculosis infection risk allocation, demonstrated milk yield losses associated with high-risk (HR) cows compared with low-risk (LR) cows in lactations 1, 2 and 3 for mean daily yield of 0.34, 1.05, and 1.61 kg; and accumulated 305-day yields of 103, 316 and 485 kg, respectively. The total loss was 904 kg over the first three lactations. Protein and fat yield losses were likewise significant, but primarily a feature of decreasing milk yield. They observed similar trends for both test-day and lactation-average somatic cell count measures with higher somatic cell counts from medium- and high-risk cows compared with LR cows, and differences were in almost all cases significant. Likewise, mastitis incidence was significantly higher in HR cows compared with LR cows in lactations 2 and 3. They noted that they expected their results to be conservative, as some animals that were considered negative could have become positive after the timeframe of the study, particularly if the animal was tested when relatively young and that test positive cows and/or the worst-affected animals would be culled as part of the paratuberculosis control programme. Results from this study indicate that HR cows were associated with detrimental effects on both production and health.

Estimates on the total annual cost per cow vary from 22 USD$ (Ott et al., 1999) to 49 CDN$ (Chi et al., 2002; Tiwari et al., 2008).

Other losses that have not been quantified may occur under the radar. International trade restrictions based on requirements for commodities, such as beef and milk, to originate from animals free of 'Paratuberculosis' occur, but their extent has not yet been described. Similarly, international livestock trade is also subject to trade restrictions which have not been characterised. For example, Japan banned live animal imports from Australia in 2016. However, official trade restrictions on infected herds within Australia has not been found to be helpful in endemically infected areas because of increased economic and social impact on herds classified as infected. These restrictions are now being actively removed from the Australian programme and replaced by transparent risk-based trading supported by an appropriate herd classification system (Geraghty et al., 2014).

Supporting the expectation that cows infected with MAP have a weakened immune system and therefore are more susceptible to udder infections McNab et al. (1991) and Baptista et al. (2008) have found significant positive associations between SCC and paratuberculosis infection, Dieguez et al. (2008) reported, higher mastitis incidences and Arrazuria et al. (2014) higher culling due to mastitis in MAP affected herds when compared with negative herds (McNab et al., 1991; Baptista et al., 2008; Dieguez et al., 2008; Arrazuria et al., 2014). Also, in animals followed to slaughter, Merkal et al. (1975) observed that culling due to mastitis was greater in animals with subclinical paratuberculosis (22.6%) compared with cows negative for paratuberculosis (3.6%) (Merkal et al., 1975). Other studies have also been reported where paratuberculosis has been associated with reduced lifetime production due to early culling of animals with and without obvious signs (Benedictus et al., 1987; Hutchinson, 1996; Lombard, 2011).

In sheep and goats, progression of *M. avium* subsp. *paratuberculosis* infection to clinical paratuberculosis can result in profound weight loss, premature culling and death, with losses approaching 20% per annum in some sheep flocks in Australia. Negative effects on fertility have additionally been reported in dairy sheep. Evidence from pathological studies on 12 farms in New South Wales, Australia, demonstrated that losses from the disease were significant and could be differentiated from other causes of on-farm mortality. That study identified the disease mortality rate in 2003 on the 12 farms as 8%, resulting in an average reduction in annual income of AU$ 13,715 per farm, due to an average decrease in gross margin of 8.5% per farm (Windsor, 2015). Economic losses of 6.4–8.5% in the gross income margin have been recorded on farms where ovine JD mortality ranged from 6.2% to 7.8% (Bush et al., 2006).

There is limited summary information about the financial impact in the EU. However, if the prevalence of infected animals with infection that will progress to disease is approximately 5% on average, and all infected dairy cattle have an average 10% reduction in the last lactation (irrespective of breed and lactation), and there are 23,400,000 dairy cattle in the EU producing 168,000,000,000 kg milk/year, i.e. 7,200 kg milk per cow per year, then reduced milk production compared to potential is 36 kg milk per cow per year, or 840,000,000 kg milk per year. With an average 33 EUR/100 L of milk, this equals approximately €277M/year. Lost milk yield may account for half of the total costs, which would then be more than €500M for the union per year. This estimate does not include the value of greenhouse gases (GHG). For example, eradication of MAP from Scotland has been estimated to reduce the amount of GHG from agriculture by 1% (reduction of 6,900 kt CO_2 equivalents by 44 $ktCO_2$ equivalents) (Stott et al., 2010). The estimate does not include the impact on other sectors such as beef cattle, sheep and goat farming.

3.1.2.2. Article 7(b)(ii) The impact of the disease on human health

Transmissibility between animals and humans

MAP is not confirmed as a zoonotic agent. However, it equally has not been confirmed that MAP is not a zoonotic agent. Golan et al. (2009) using zenographs of human foetal gut onto SCID mice have demonstrated that MAP actively invades the human gut epithelial goblet cells of the small intestine, inducing severe tissue damage and inflammation. These observations indicate that MAP can specifically colonise the normal human small intestine and can elicit inflammation and severe mucosal damage.

MAP has been extensively investigated as a potential cause of CD in humans.

If confirmed, the most likely routes are consumption of MAP through contaminated milk and beef. An extensive discussion on the potential zoonotic aspects of MAP, as well as the sources of human exposure to MAP is given in Sections 3.1.1.3 Parameter 1 and 3.1.1.6 Parameter 2.

Transmissibility between humans

It is not confirmed that MAP is a zoonotic agent, thus any transmission between humans has therefore not been characterised.

The severity of human forms of the disease

Parameter 5 - Disability-adjusted life year (DALY)

The potential consequences on human health if MAP would be confirmed as the causal agent of CD are explained below.

CD and ulcerative colitis are the two main components of inflammatory bowel disease. It is a relapsing lifelong inflammatory disease that can affect the entire gastrointestinal tract and frequently presents with abdominal pain, fever and clinical signs of bowel obstruction or diarrhoea with passage of blood or mucus, or both. Genetic predisposition to the disease has been confirmed. A series of environmental factors has been implicated in the epidemiology of CD, less women breastfeeding, improved domestic hygiene and sanitation, availability and quality of (hot) tap water, exposure to air pollution, consumption of a western diet and increased tobacco use. The latter has been extensively studied and both active and passive smoking especially if adopted early (even in childhood) significantly increases the risk of developing the disorder (Baumgart and Sandborn, 2012). The highest annual incidence of CD in Europe has been estimated to 12.7 per 100.000 person-years (Molodecky et al., 2012).

Current European consensus reached by European Crohn's and Colitis Organisation (in 2004 and revised in 2008) lists three forms of active disease: mild, moderate and severe (Dignass et al., 2010). There is no single standard for diagnosis, but the forms are often characterised by the course of the disease following different forms of treatment, including steroid therapy. The diagnostic process, however, is long and complex including many steps. Currently, the Montreal Classification scheme is advocated, which summarised recent developments in disease classification and established an integrated clinical, molecular, and serological classification of inflammatory bowel disease (Satsangi et al., 2006).

The availability of effective prevention or medical treatment in humans

<u>Parameter 6 – Availability of medical treatment and their effectiveness (therapeutic effect and any resistance)</u>

The aetiology of CD is not known yet and consequently prevention is a challenge and treatment is mostly palliative. ECCO guidelines for management of CD are given in detail in Dignass et al. (2010), where management is recommended to be course specific.

Dignass et al. (2010) do not mention MAP, but if MAP is a cause in some cases of CD, then antimycobacterial treatment can be of interest. While MAP is generally excluded as a cause by the gastroenterology society, few studies have been conducted to assess the efficacy of antimycobacterials. Borody et al. (2007) reported effective treatment of CD using rifabutin, clofazimine and clarithromycin for a time period from 6 months to 9 years. On the other hand, Selby et al. (2007) conducted a randomised clinical trial with the same drugs (but in different concentrations) for 2 years and had a similar relapse in the CD group as in the placebo group. Still, active research is ongoing on this aspect as some recent publications would indicate (Atreya et al., 2014; Liverani et al., 2014; Naser et al., 2014; Kuenstner et al., 2015; McNees et al., 2015; Abegunde et al., 2016; Singh et al., 2016; Davis et al., 2017).

3.1.2.3. Article 7(b)(iii) The impact of the disease on animal welfare

<u>Parameter 1 – Severity of clinical signs at case level and related level and duration of impairment</u>

Welfare is impaired; in the subclinical phase by reduced immune competence increasing susceptibility to a range of conditions and especially in the late phases of infection (months to years after infection), when constant or intermittent diarrhoea develops accompanied by weight loss. Diarrhoea usually becomes gradually more severe and may lead to emaciation and death. Increased production loss and/or onset of clinical disease leads to premature culling. In GB, cattle sector organisations have identified paratuberculosis as one of the top ten cattle health and welfare issues (CHAWG, 2012).

3.1.2.4. Article 7(b)(iv) The impact of the disease on biodiversity and the environment

Biodiversity

There are no reports of the impact of MAP infection on biodiversity. MAP infection has been reported in endangered species (Table 1). There are no studies on the MAP-associated mortality in these species.

Environment

<u>Parameter 3 – Capacity of the pathogen to persist in the environment and cause mortality in wildlife</u>

MAP is rarely reported outside the farming environment though it has been detected also elsewhere, e.g. drinking water, domestic water tanks, domestic sewage treatment works and domestic showers (Pickup et al., 2005, 2006; Whan et al., 2005; Beumer et al., 2010; Rhodes et al., 2014).

3.1.3. Article 7(c) Its potential to generate a crisis situation and its potential use in bioterrorism

MAP infection has a long latent infection period and consequently is not likely to be used for bioterrorism. Hence its absence from international bioterrorism lists such as the Bioterrorism Agents/Diseases list of the CDC (2017) and the Encyclopaedia of Bioterrorism Defense of Australia Group (Katz and Zilinskas, 2011). Further, it is not included in the Centre for Food Security and Public Health (CFSPH) list of zoonotic pathogens (CFSPH, 2017).

3.1.4. Article 7(d) The feasibility, availability and effectiveness of the following disease prevention and control measures

Successful control of MAP infection has been strongly impeded by the lack of sensitive diagnostic tests that would correctly identify infected animals at the early infection stages, repeated testing schemes, however, can be used to improve the overall discriminatory power of the diagnostic process (Nielsen and Toft, 2007).

Available control strategies include management practices to improve calf hygiene, test-and-cull strategies and vaccination. A combination of the first two effectively reduces the prevalence of MAP infection (Nielsen and Toft, 2011) but it requires long commitment from the dairy farmers. For example, the Danish control programme is based on the early identification and removal of MAP shedders through repeated milk-ELISA testing, which is used to categorise the animals into (i) cows that should be culled before calving or (ii) can be kept but should calve in isolation and (iii) cows in low-risk of shedding MAP. Clearly, repeated testing schemes aim to closely monitor the course of MAP infection and, in this way, increase the diagnostic value of existing tests. On the other hand, vaccination requires less effort and field studies have demonstrated that it effectively reduces faecal shedding (Knust et al., 2013) but restrictions on its use apply mainly due to the fact that vaccination interferes with the testing for of bovine tuberculosis. Hence, the overall benefits of vaccination depend on the level of cross reactivity (Groenendaal et al., 2015). Vaccination has been shown to provide effective disease control in Australia (Windsor et al., 2014) and, while it does not prevent infection or shedding of MAP, it underpins the national control programme for ovine paratuberculosis along with a risk-based trading system. MAP can be effectively controlled by for example risk-based measures to reduce the within-herd spread of MAP (Nielsen and Toft, 2011; Verdugo et al., 2015). Measures to reduce between-herd spread of MAP is still challenging, but can be established if historical test-information at the herd-level is combined with animal-level information (Sergeant et al., 2008; More et al., 2013).

3.1.4.1. Article 7(d)(i) Diagnostic tools and capacities

Availability

Parameter 1 − Officially/internationally recognised diagnostic tool, OIE certified

Available ante-mortem diagnostic tests for paratuberculosis can be divided into those that detect MAP and those that assess the immune response of the host. The first category includes faecal smears, culture and PCR tests. The second category includes antibody response (immunoglobulin G (IgG)) to MAP, delayed type hypersensitivity reaction, lymphocyte proliferation and increased cytokine (interferon gamma (IFN-γ)) production. So far none of the available tests have been certified by the OIE (2015).

The lack of affordable, sensitive, ante-mortem diagnostic tests at the early stages of MAP infection is a major obstacle in the control of paratuberculosis. However, the accuracy of existing tests is improved with testing and/or interpretation of individual tests at the herd-level though, in this case, its usefulness diminishes with lowering within-herd prevalence (Nielsen, 2014).

Feasibility

Parameter 3 − Type of sample matrix to be tested (blood, tissue, etc.)

The sensitivity and specificity of existing, commonly used diagnostic tests for paratuberculosis are given in Tables 6, 7 and 8. However, these estimates are not comparable as they are based on different reference standard methods and were carried out in different populations with likely differences in the distribution of the various infection stages. Sensitivity and specificity estimates are given separately for cattle, sheep and goats because differences exist between species in the immune response (Kostoulas et al., 2006b; Verna et al., 2007), the strain distribution and, hence, the infection stages and the associated test performance.

From a control point of view, prior to the evaluation and subsequent use of diagnostic tests, it is important to establish the target condition (Nielsen and Toft, 2008), which reflects the underlying MAP status being detected (affected, infectious or infected cows or herds). Effectiveness is related to the purpose, and few studies have assessed the effectiveness of diagnostic tests for control and disease prevention. Most studies have been based on simulation models, which suggest that a combination of test-and-cull and test-and-management is a requirement (Groenendaal et al., 2003; Kudahl et al., 2007). A test-and-management, test-and-cull combination has also been effective to reduce the prevalence in a smaller intervention study in the USA (Collins et al., 2010), while a large-scale Danish study also suggested that test-and-cull might be efficient (Nielsen and Toft, 2011). However, in the latter study, the effect of biosecurity measures may have been different than what had been reported by farmers. Nonetheless, it is possible to significantly reduce the prevalence, and also remove infection from individual herds (Verdugo et al., 2015).

Table 6: Sensitivity (Se) and Specificity (Sp) of available diagnostic tests for MAP detection in cattle

Test Category	Diagnostic Test	Products	Se (%)	Sp (%)	Infection stage	Reference
Humoral immune response	Serum ELISA	IDEXX HerdChek Parachek Pourquier Svanova Various	Moderate High	High	Affected	Nielsen and Toft (2008)
			Low Moderate	High Moderate	Infectious	
			Low	High	Infected	
	Milk ELISA	Antel Various	29–61	83–100	Infectious Infected	Nielsen et al. (2002); Klausen et al. (2003); Hendrick et al. (2005)
Cell-mediated immunity	DTH (delayed type hypersensitivity)	Johnin testing	Not determined	High (>90)	Infected	Kalis et al. (2002)
	IFN-γ	CSL algorithm (Bovigam)	13–85	66.1 (63.3–68.8, 95% CI)	Infectious Infected	Kalis et al. (2003); Nielsen and Toft (2008)
		IDEXX algorithm		67.0 (64.1–69.7, 95% CI)		
		New algorithm		93.6 (92.0–95.0, 95% CI)		
Direct	Smears (acid-fast bacilli)	ZN staining (Ziehl-Nielsen)	49.0 (low)	High	Affected	Zimmer et al. (1999)
	Conventional culture	HEYM TREK	Low Moderate	High (~100)	Infected	Whitlock et al. (2000); McKenna et al. (2005)
		HEYM	74 (65–82, 95% CI)	High (~100)	Infectious	Sockett et al. (1992)
		HEYM	70 (56–81, 95% CI)	High (~100)	Affected	Egan et al. (1999)
	Radiometric culture	BACTEC	Moderate	High	Infected affected	Eamens et al. (2008)
	Tissue culture		High	High		McKenna et al. (2005)
	PCR	IMS PCR	Moderate High	High		Fang et al. (2002); Khare et al. (2004)
		Real-time	High	High		
		Nested	High	High		

ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction.

Table 7: Se and Sp of available diagnostic tests for MAP detection in sheep

Test Category	Diagnostic Test	Products	Se (%)	Sp (%)	Infection stage	Reference
Humoral immune response	ELISA	IDEXX Parachek Svanovir	37 (10–80, 95% CI)	97 (93–99, 95% CI)	Affected Infectious Infected	Kostoulas et al. (2006b)
	AGID (agar gel immunodiffusion)		24.6 (19.1–30.7, 95% CI) 13.8 (8.8–20.3, 95% CI)	100 (99.7–100.0, 95% CI)	Infected Infected	Sergeant et al. (2003) Gumber et al. (2006)
Cell-mediated immunity	DTH (delayed type hypersensitivity)	Johnin testing	55.6	100.0		Perez et al. (1999)
Direct	Faecal culture		16 (2–48, 95% CI)	97 (95–99, 95% CI)	Infected	Kostoulas et al. (2006b)

ELISA: enzyme-linked immunosorbent assay.

Table 8:   Se and Sp of available diagnostic tests for MAP detection in goats

Test Category	Diagnostic Test	Products	Se (%)	Sp (%)	Infection stage	Reference
Humoral immune response	ELISA	IDEXX Parachek Svanovir	63 (42–93, 95% CI)	95 (90–98, 95% CI)	Affected, Infectious, Infected	Kostoulas et al. (2006b)
	AGID (agar gel immunodiffusion)		39.5 (30.9–48.7, 95% CI)			Gumber et al. (2006)
Cell-mediated immunity	DTH (delayed type hypersensitivity	Johnin testing	Moderate High	High		Tripathi et al. (2006)
Direct	Faecal culture		8 (2–17, 95% CI)	98 (95–100, 95% CI)	Infected	Kostoulas et al. (2006b)
	Tissue PCR		Moderate	High		Tripathi et al. (2006)

ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction.

3.1.4.2. Article 7(d)(ii) Vaccination

Killed whole cell vaccines as well as non-attenuated and attenuated live vaccines have been developed and used against MAP. Subunit vaccines and more recently DNA vaccines have also been developed (Koets et al., 2006; Roupie et al., 2008). MAP vaccines are administered subcutaneously. Commercially available vaccines are outlined in Table 9. Vaccination is rarely used for cattle but is commonly applied in sheep and goats (Windsor, 2015). Restrictions on its use for cattle apply (i.e. it is prohibited in several European countries such as Denmark, Ireland and Spain), mainly due to the fact that it interferes with the testing for of bovine tuberculosis. The overall benefits of vaccination depend on the level of cross reactivity (Groenendaal et al., 2015).

Vaccination against MAP reduces the incidence of clinical disease (Wentink et al., 1994), MAP shedding (Sweeney et al., 2009) and thus the risk of transmission to uninfected herd-mates (Knust et al., 2013). Differences may exist in the efficacy between live and killed vaccines but these cannot be realised due to the variable study designs, vaccination age and indices of vaccine efficacy that have been used. Further, great heterogeneity exists in the benefits of vaccination probably due to differences in the prevalence of MAP infection and in the existing biosecurity measures that were or were not simultaneously applied among published studies (Bastida and Juste, 2011).

Vaccination does not prevent infection and healthy animals remain susceptible to MAP (Larsen and Miller, 1978). Bastida and Juste (2011) recently reviewed the vaccines that have been experimentally developed and/or the ones that are commercially available. They also looked into available studies and affirmed the positive effects of vaccination: reduced microbial contamination risk – through reduced shedding – and delayed production losses.

Contrary to what constitutes common practice in cattle, vaccination has been extensively applied in sheep and is one of the two main tools (with the other being a risk-based trading scheme) of the Australian programme for MAP control in sheep. The Australian experience indicates that vaccination effects are of increased significance in flocks with high prevalence. However, MAP shedding can persist for many years after vaccination commencement (Dhand et al., 2016). Improved hygiene/management factors play a key role in the persistence of paratuberculosis (Windsor, 2013) and are required to reduce transmission.

Table 9: Commercially available vaccines against MAP

Name/Laboratory	Type	Species	Reference
Mycopar	Killed	Cattle Sheep	Uzonna et al. (2003)
Gudair	Killed	Sheep Goats	Singh et al. (2007)
Lio-Johne	Live	Sheep	Bastida and Juste (2011)
Neoparasec	Live	Cattle Sheep Goats	Griffin et al. (2009)
Silirum	Killed	Cattle	Stringer et al. (2013)
Phylaxia	Killed	Cattle	Kormendy (1994)

The availability of the commercial vaccines varies between MS. Gudair has authorisation in Cyprus, Greece, the Netherlands, Spain and the UK for use in sheep and goats but not in cattle (Videnova and Mackay, 2012).

3.1.4.3. Article 7(d)(iii) Medical treatments

Not relevant. Antibiotic treatment is not practiced in MAP-infected animals with the exception of high value animals. A description of available treatments is given in Section 3.1.1.4.

3.1.4.4. Article 7(d)(iv) Biosecurity measures

For herds/regions that are free of MAP infection, biosecurity measures should focus on preventing the introduction of infected species and/or the co-grazing sharing pastures with infected herds. Contact with wildlife species should not be ignored. Particularly contact to rabbits has been described as a factor associated with lack of Paratuberculosis control (Shaughnessy et al., 2013).

Under endemic disease conditions, biosecurity measures should focus on reducing the exposure of susceptible animals to faeces and/or milk of infectious animals. These efforts should be centred to young stock – a practice that requires long commitment from the farmers.

Risk assessment tools initially developed in the USA (Rossiter and Burhans, 1996) exist in a variety of forms, for example, in the Netherlands (Franken, 2005), Denmark (Kudahl et al., 2008) and Ireland (McAloon et al., 2016). These tools may serve primarily to educate farmers. Pillars et al. (2011) reported on a 5-year trial covering January 2003 to December 2007 where a JD control programme was designed specifically for each participating herd based on the results of an initial risk assessment. The risk assessment was repeated annually and the control programme updated as needed. Herd risk assessment scores were used to measure compliance with the control programme and create JD-risk profiles for individual cows raised on the farms. At the end of the 5 years of the cows that were not exposed to the control programme, 20% were classified as infected, while only 7% of cows that were exposed to the control programme were infected. A summary of the available tools to prevent new infections and manage/minimise the impact of existing infections at the animal and/or herd level can be found in Sweeney et al. (2012).

3.1.4.5. Article 7(d)(v) Restrictions on the movement of animals and products

Transmission between herds/flocks occurs primarily via the introduction of infected animals. Therefore, restrictions of animal movements can be efficient in reducing transmission to MAP-free establishments and/or in preventing re-introduction of MAP infection. In the Netherlands, use of milk from herds containing cows with high antibody ELISA values is restricted by some private milk processors, and most herds cull these animals (Weber et al., 2014). Furthermore, some countries (e.g. Austria) have restrictions on cattle, sheep, goats and farmed deer with clinical disease: milk from these animals cannot be used for human consumption and the animals cannot be slaughtered (Khol and Baumgartner, 2012). Nevertheless, the disease is not regulated at EU level and the extent and nature of programmes in Europe, which are not official programmes, is very diverse, as summarised in Nielsen (2009) and Geraghty et al. (2014).

The Australian programme for the control of paratuberculosis initially applied trade restrictions on infected herds within Australia, a strategy that later was found to be unhelpful due to the increased economic and social impact. These restrictions are now being replaced by a transparent risk-based trading supported by a relevant herd classification system (Geraghty et al., 2014). However,

restrictions are difficult to apply without possible definition of a free-status and the lack of reliable tests.

No official document on movement of livestock with MAP infection exists, but a set of guidelines has been proposed through the IAP (2016).

Accordingly, importing farms or regions should focus on preventing a further spread of the agent, if introduced, by limiting the exposure of animals to infectious materials, removing suspicious cases and the appropriate treatment of manure (IAP 2016).

Moreover, a classification of areas into free (surveillance programmes have not shown endemic infection in 10 years or the agent has been eradicated in the area without MAP detection in the following 2 years), eradication (surveillance programmes only identify low herd prevalences or the agent is being eradicated), certification (herds or flocks are voluntarily classified according to their MAP risk; biosecurity measures, testing and surveillance are in place) and other areas is recommended (IAP, 2016).

3.1.4.6. Article 7(d)(vi) Killing of animals

Culling of test-positive and/or animals with clinical disease appear to have a reducing effect on the prevalence in cattle populations if an appropriate test-strategy is carried out, and it is assisted by other measures to reduce transmission. However, killing of animals may not be sufficient if the general contamination of the environment is maintained (Wolf et al., 2016). Combination of improved calf hygiene with test-and-cull strategies has proved to effectively reduce the prevalence of MAP infection (Nielsen and Toft, 2011).

3.1.4.7. Article 7(d)(vii) Disposal of carcasses and other relevant animal by-products

Carcasses containing MAP can be safely destroyed at rendering plants. However, special precautions during the disposal of carcasses and other relevant animal by-products due to MAP infection have not so far been considered because its zoonotic role has not been confirmed.

3.1.5. Article 7(e) The impact of disease prevention and control measures

3.1.5.1. Article 7(e)(i) The direct and indirect costs for the affected sectors and the economy as a whole

Direct and indirect costs depend on the type of the control programme and the epidemiological situation under consideration. The main cost of test-and-cull strategies is the cost of replacing culled animals and the cost of the – usually repeated – testing scheme. Increased labour and equipment purchase costs are associated with control actions aiming at improved management/hygiene. The direct cost of vaccination-based strategies is low but indirect costs lie in the cross reactivity with tuberculosis testing. So far, assessment of existing control strategies has proven beneficial.

For example, the net benefit of farms in the Alberta Johne's Disease Initiative was estimated to be 74 CDN$ per cow over the course of a decade. The benefits were lowered to 19 CDN$ if costly management practices (i.e. the use of pasteurisers) were applied (Wolf et al., 2014). A cost benefit analysis of vaccination against MAP that adjusted for the cross reactivity with tuberculin tests revealed direct economic benefits of 8 US$ per adult animal per year and indirect economic costs due to cross-reactivity of 2 US$. The combination of test-and-cull strategies with improved management hygiene measures seems to be the most efficient strategy. Groenendaal and Galligan (2003) showed that improved calf-hygiene strategies were critically important in every paratuberculosis control programme especially for midsize US dairy farms while test-and-cull strategies alone may not be efficient in reducing the prevalence of paratuberculosis.

These, of course, depend on the prevalence of MAP infection and the hygiene level. A recent analysis that was based on data from farms participating in the Danish Control programme, where the prevalence of paratuberculosis is low (~ 7%), showed that a test-and-cull strategy is on average the most cost-effective to increase the total net revenue on a farm with low hygiene, but not more profitable than no action on a farm with average hygiene (Kirkeby et al., 2016). If the objective is to completely eradicate MAP, the expenses outweigh the benefits of the existing control efforts.

3.1.5.2. Article 7(e)(ii) The societal acceptance of disease prevention and control measures

Disease control measures are likely to be acceptable to society, except that slaughter of test-positive animals may be of concern to some. Further, farmers may be reluctant to devote the

resources required for the implementation of management practices aiming to improve calf hygiene, despite the fact that the combination of such practices with test-and-cull strategies effectively reduces the prevalence of MAP infection (Nielsen and Toft, 2011). In addition, improved calf hygiene normally has beneficial impacts across a range of other conditions affecting calves.

3.1.5.3. Article 7(e)(iii) The welfare of affected subpopulations of kept and wild animals

Parameter 1 – Welfare impact of control measures on domestic animals

Animal welfare can be affected if offspring is isolated from their dam at birth.

Parameter 2 – Wildlife depopulation as control measure

Wildlife depopulation has not so far been considered as a control measure for MAP.

3.1.5.4. Article 7(e)(iv) The environment and biodiversity

No impact on the environment and biodiversity has been identified, but if wildlife is implicated in transmission and if regulation of wildlife is deemed needed, then a systematic assessment of the biodiversity would be required.

MAP is resistant to common disinfectants. Phenolic and cresylic disinfectants are among the most efficient (Collins, 2003). In a recent study, the application of peracetic acid led to the total elimination of MAP (Kralik et al., 2014). The latter authors also demonstrated that repeated application of disinfection procedures are more effective compared to single increases in the concentration or time of exposure to the disinfectants. There are no reports on the potential impact of residuals in the environmental compartments (soil, water, feed, manure) as a result of MAP-specific disinfection procedures.

There are no reports on mortality in wildlife species due to control measures.

3.2.   Assessment according to Article 5 criteria

This section presents the results of the expert judgement on the criteria of Article 5 of the AHL about paratuberculosis (Table 10). The expert judgement was based on Individual and Collective Behavioural Aggregation (ICBA) approach described in detail in the opinion on the methodology (EFSA AHAW Panel, 2017). Experts have been provided with information of the disease fact-sheet mapped into Article 5 criteria (see supporting information, Annex A), based on that the experts indicate their Y/N or 'na' judgement on each criterion of Article 5, and the reasoning supporting their judgement.

The minimum number of judges in the judgement was 10. The expert judgement was conducted as described in the methodological opinion (EFSA AHAW Panel, 2017). For details on the interpretation of the questions, see Appendix B of the methodological opinion (EFSA AHAW Panel, 2017).

Table 10:   Outcome of the expert judgement on the Article 5 criteria for paratuberculosis

Criteria to be met by the disease: According to AHL, a disease shall be included in the list referred to in point (b) of paragraph 1 of Article 5 if it has been assessed in accordance with Article 7 and meets all of the following criteria		Final outcome
A(i)	The disease is transmissible	Y
A(ii)	Animal species are either susceptible to the disease or vectors and reservoirs thereof exist in the Union	Y
A(iii)	The disease causes negative effects on animal health or poses a risk to public health due to its zoonotic character	Y
A(iv)	Diagnostic tools are available for the disease	Y
A(v)	Risk-mitigating measures and, where relevant, surveillance of the disease are effective and proportionate to the risks posed by the disease in the Union	Y
At least one criterion to be met by the disease: In addition to the criteria set out above at points A(i)–A(v), the disease needs to fulfil at least one of the following criteria		
B(i)	The disease causes or could cause significant negative effects in the Union on animal health, or poses or could pose a significant risk to public health due to its zoonotic character	NC
B(ii)	The disease agent has developed resistance to treatments and poses a significant danger to public and/or animal health in the Union	N

B(iii)	The disease causes or could cause a significant negative economic impact affecting agriculture or aquaculture production in the Union	Y
B(iv)	The disease has the potential to generate a crisis or the disease agent could be used for the purpose of bioterrorism	NC
B(v)	The disease has or could have a significant negative impact on the environment, including biodiversity, of the Union	N

Colour code: green = consensus (Yes/No); yellow = no consensus (NC); red = not applicable (na), i.e. insufficient evidence or not relevant to judge.

3.2.1. Non-consensus questions

This section displays the assessment related to each criterion of Article 5 where no consensus was achieved in form of tables (Tables 11 and 12). The proportion of Y, N or na answers are reported, followed by the list of different supporting views for each answer.

Table 11: Outcome of the expert judgement related to criterion 5 B(i)

Question		Final outcome	Response		
			Y (%)	N (%)	na (%)
B(i)	The disease causes or could cause significant negative effects in the Union on animal health, or poses or could pose a significant risk to public health due to its zoonotic character	NC	80	20	0

NC: non-consensus; number of judges: 10.

Reasoning supporting the judgement

Supporting Yes:

- If the zoonotic risk of CD is proven, this could cause a significant impact.
- Some individual farms have significant health and/or production problems (e.g. reduced milk yield, infertility) where the overt or underlying cause is infection with MAP.
- MAP may be involved in some, but probably not all, cases of CD.
- In Denmark, impact on animal health or production was experienced by approximately half of dairy farmers.

Supporting No:

- After a review conducted in 2015, no strong evidence was found to confirm the zoonotic role of paratuberculosis as a causal agent of CD.
- According to the evidence shown in the present opinion, in most of the studies the morbidity rate and the apparent animal-level prevalence are low.
- The impact on animal health can be considered currently as low considering the whole cattle sector.

Table 12: Outcome of the expert judgement related to criterion 5 B(iv)

Question		Final outcome	Response		
			Y (%)	N (%)	na (%)
B(iv)	The disease has the potential to generate a crisis or the disease agent could be used for the purpose of bioterrorism	NC	30	70	0

NC: non-consensus; number of judges: 10.

Reasoning supporting the judgement

Supporting Yes:

- There is the potential for a major public health crisis if conclusive evidence were to emerge of the zoonotic potential of paratuberculosis.

Supporting No:

- The zoonotic role of paratuberculosis is not confirmed thus the potential to generate the crisis is remote.
- MAP is not listed under pathogens with bioterrorism potential.

3.2.2. Outcome of the assessment of paratuberculosis according to criteria of Article 5(3) of the AHL on its eligibility to be listed

As from the legal text of the AHL, a disease is considered eligible to be listed as laid down in Article 5 if it fulfils all criteria of the first set from A(i) to A(v) and at least one of the second set of criteria from B(i) to B(v). According to the assessment methodology (EFSA AHAW Panel, 2017), a criterion is considered fulfilled when the outcome is 'Yes'. According to the results shown in Table 10, paratuberculosis complies with all criteria of the first set and with one criterion of the second set, therefore it is considered to be eligible to be listed as laid down in Article 5 of the AHL.

3.3. Assessment according to Article 9 criteria

This section presents the results of the expert judgement on the criteria of Annex IV referring to categories as in Article 9 of the AHL about paratuberculosis (Tables 13, 14, 15, 16 and 17). The expert judgement was based on ICBA approach described in detail in the opinion on the methodology. Experts have been provided with information of the disease fact-sheet mapped into Article 9 criteria (see supporting information, Annex A), based on that the experts indicate their Y/N or 'na' judgement on each criterion of Article 9, and the reasoning supporting their judgement. The minimum number of judges in the judgement was ten. The expert judgement was conducted as described in the methodological opinion (EFSA AHAW Panel, 2017). For details on the interpretation of the questions, see Appendix B of the methodological opinion (EFSA AHAW Panel, 2017).

Table 13: Outcome of the expert judgement related to the criteria of Section 1 of Annex IV (category A of Article 9) for paratuberculosis

Criteria to be met by the disease: The disease needs to fulfil all of the following criteria		Final outcome
1	The disease is not present in the territory of the Union OR present only in exceptional cases (irregular introductions) OR present in only in a very limited part of the territory of the Union	N
2.1	The disease is highly transmissible	N
2.2	There be possibilities of airborne or waterborne or vector-borne spread	NC
2.3	The disease affects multiple species of kept and wild animals OR single species of kept animals of economic importance	Y
2.4	The disease may result in high morbidity and significant mortality rates	N
At least one criterion to be met by the disease: In addition to the criteria set out above at points 1–2.4, the disease needs to fulfil at least one of the following criteria		
3	The disease has a zoonotic potential with significant consequences on public health, including epidemic or pandemic potential OR possible significant threats to food safety	N
4	The disease has a significant impact on the economy of the Union, causing substantial costs, mainly related to its direct impact on the health and productivity of animals	Y
5(a)	The disease has a significant impact on society, with in particular an impact on labour markets	N
5(b)	The disease has a significant impact on animal welfare, by causing suffering of large numbers of animals	Y
5(c)	The disease has a significant impact on the environment, due to the direct impact of the disease OR due to the measures taken to control it	N
5(d)	The disease has a significant impact on a long-term effect on biodiversity or the protection of endangered species or breeds, including the possible disappearance or long-term damage to those species or breeds	N

Colour code: green = consensus (Yes/No), yellow = no consensus (NC).

Table 14: Outcome of the expert judgement related to the criteria of Section 2 of Annex IV (category B of Article 9) for paratuberculosis

	Criteria to be met by the disease: The disease needs to fulfil all of the following criteria	Final outcome
1	The disease is present in the whole OR part of the Union territory with an endemic character AND (at the same time) several Member States or zones of the Union are free of the disease	N
2.1	The disease is moderately to highly transmissible	Y
2.2	There be possibilities of airborne or waterborne or vector-borne spread	NC
2.3	The disease affects single or multiple species	Y
2.4	The disease may result in high morbidity with in general low mortality	Y
	At least one criterion to be met by the disease: In addition to the criteria set out above at points 1–2.4, the disease needs to fulfil at least one of the following criteria	
3	The disease has a zoonotic potential with significant consequences on public health, including epidemic potential OR possible significant threats to food safety	N
4	The disease has a significant impact on the economy of the Union, causing substantial costs, mainly related to its direct impact on the health and productivity of animals	Y
5(a)	The disease has a significant impact on society, with in particular an impact on labour markets	N
5(b)	The disease has a significant impact on animal welfare, by causing suffering of large numbers of animals	Y
5(c)	The disease has a significant impact on the environment, due to the direct impact of the disease OR due to the measures taken to control it	N
5(d)	The disease has a significant impact on a long-term effect on biodiversity or the protection of endangered species or breeds, including the possible disappearance or long-term damage to those species or breeds	N

Colour code: green = consensus (Yes/No), yellow = no consensus (NC).

Table 15: Outcome of the expert judgement related to the criteria of Section 3 of Annex IV (category C of Article 9) for paratuberculosis

	Criteria to be met by the disease: The disease needs to fulfil all of the following criteria	Final outcome
1	The disease is present in the whole OR part of the Union territory with an endemic character	Y
2.1	The disease is moderately to highly transmissible	Y
2.2	The disease is transmitted mainly by direct or indirect transmission	Y
2.3	The disease affects single or multiple species	Y
2.4	The disease usually does not result in high morbidity and has negligible or no mortality AND often the most observed effect of the disease is production loss	Y
	At least one criterion to be met by the disease: In addition to the criteria set out above at points 1–2.4, the disease needs to fulfil at least one of the following criteria	
3	The disease has a zoonotic potential with significant consequences on public health, or possible significant threats to food safety	NC
4	The disease has a significant impact on the economy of parts of the Union, mainly related to its direct impact on certain types of animal production systems	N
5(a)	The disease has a significant impact on society, with in particular an impact on labour markets	N
5(b)	The disease has a significant impact on animal welfare, by causing suffering of large numbers of animals	Y
5(c)	The disease has a significant impact on the environment, due to the direct impact of the disease OR due to the measures taken to control it	N
5(d)	The disease has a significant impact on a long-term effect on biodiversity or the protection of endangered species or breeds, including the possible disappearance or long-term damage to those species or breeds	N

Colour code: green = consensus (Yes/No), yellow = no consensus (NC).

Table 16: Outcome of the expert judgement related to the criteria of Section 4 of Annex IV (category D of Article 9) for paratuberculosis

	Criteria to be met by the disease: The disease needs to fulfil all of the following criteria	Final outcome
D	The risk posed by the disease in question can be effectively and proportionately mitigated by measures concerning movements of animals and products in order to prevent or limit its occurrence and spread	Y
	The disease fulfils criteria of Sections 1, 2, 3 or 5 of Annex IV of AHL	Y

Colour code: green = consensus (Yes/No).

Table 17: Outcome of the expert judgement related to the criteria of Section 5 of Annex IV (category E of Article 9) for paratuberculosis

	Diseases in category E **need to fulfil criteria of Sections 1, 2 or 3 of Annex IV of AHL** and/or the following:	Final outcome
E	Surveillance of the disease is necessary for reasons relating to animal health, animal welfare, human health, the economy, society or the environment (If a disease fulfils the criteria as in Article 5, thus being eligible to be listed, consequently category E would apply.)	Y

Colour code: green = consensus (Yes/No).

3.3.1. Non-consensus questions

This section displays the assessment related to each criterion of Annex IV referring to the categories of Article 9 of the AHL where no consensus was achieved in form of tables (Tables 18 and 19). The proportion of Y, N or `na′ answers are reported, followed by the list of different supporting views for each answer.

Table 18: Outcome of the expert judgement related to criterion 2.2 of Article 9

		Final outcome	Response		
Question			Y (%)	N (%)	na (%)
2.2	There be possibilities of airborne or waterborne or vector-borne spread	NC	30	70	0

NC: non-consensus; number of judges: 10.

Reasoning supporting the judgement

Supporting Yes:

- MAP survives well in the environment in water, soil and dust. Infection is normally acquired via the oral-faecal route, therefore waterborne transmission is highly likely where faecal contamination of water occurs either directly through defecation into surface waters by infected bovines (Collins et al., 1994) or water becomes a vehicle for MAP via slurry contamination (Pickup et al., 2006). A number of human Crohn's clusters have been linked to possible MAP presence in water (Van Kruiningen et al., 2005; Pierce, 2009).
- Corner et al. (2004) and Eisenberg et al. (2010) have put forward arguments supporting a role for aerosol transmission. Eisenberg et al. (2011) have demonstrated intestinal infection following aerosol challenge of calves with MAP.

Supporting No:

- No airborne/waterborne/vector-borne transmission of paratuberculosis has been described as yet, even though MAP has been detected in rivers and streams.
- Although these possibilities exist, they are not the main routes of transmission.

Table 19: Outcome of the expert judgement related to criterion 2.2 of Article 9

Question		Final outcome	Response		
			Y (%)	N (%)	na (%)
3 (cat.C)	The disease has a zoonotic potential with significant consequences on public health, or possible significant threats to food safety	NC	50	50	0

NC: non-consensus; number of judges: 10.

Reasoning supporting the judgement

Supporting Yes:

- In experimental studies, every species that became infected following exposure, including non-human primates and human fetal gut matured on the backs of mice, have demonstrated symptoms of CD following infection with MAP. Thus it seems implausible that humans are the only species that do not become infected with MAP.
- There are a number of cases where Crohn's symptoms have been resolved in the long term with antimycobacterial drugs.
- MAP has been isolated from human breast milk.
- MAP has been demonstrated in the blood of some patients with CD.
- MAP has survived pasteurisation in some cases.
- Viable MAP has been isolated from beef of cows with clinical disease and following light cooking of hamburger patties.

supporting No:

- Up to now, a causal link has not been proven between MAP infection and CD in humans. Although a significant association has been identified between MAP and CD, knowledge gaps exist. There is currently insufficient evidence to support a causal relationship. For example, there is no significant association between the prevalence of MAP in livestock and the incidence of CD in human populations. Similarly, other micro-organisms have been also associated with CD. It is recognised that not all individuals from which MAP infection has been detected are susceptible to CD.

3.3.2. Outcome of the assessment of criteria in Annex IV for paratuberculosis for the purpose of categorisation as in Article 9 of the AHL

As from the legal text of the AHL, a disease is considered fitting in a certain category (A, B, C, D or E corresponding to point (a) to point (e) of Article 9(1) of the AHL) if it is eligible to be listed for Union intervention as laid down in Article 5(3) and fulfils all criteria of the first set from 1 to 2.4 and at least one of the second set of criteria from 3 to 5(d) as shown in Tables 13–17. According to the assessment methodology (EFSA AHAW Panel, 2017), a criterion is considered fulfilled when the outcome is 'Yes'.

A description of the outcome of the assessment of criteria in Annex IV for paratuberculosis for the purpose of categorisation as in Article 9 of the AHL is presented in Table 20.

Table 20: Outcome of the assessment of criteria in Annex IV for paratuberculosis for the purpose of categorisation as in Article 9 of the AHL

Category	Article 9 criteria										
	1° set of criteria					2° set of criteria					
	1	**2.1**	**2.2**	**2.3**	**2.4**	**3**	**4**	**5a**	**5b**	**5c**	**5d**
	Geographical distribution	Transmissibility	Routes of transmission	Multiple species	Morbidity and mortality	Zoonotic potential	Impact on economy	Impact on society	Impact on animal welfare	Impact on environment	Impact on biodiversity
A	N	N	NC	Y	N	N	Y	N	Y	N	N
B	N	Y	NC	Y	Y	N	Y	N	Y	N	N
C	Y	Y	Y	Y	Y	NC	N	N	Y	N	N
D	Y										
E	Y										

According to the assessment here performed, paratuberculosis complies with the following criteria of the Sections 1–5 of Annex IV of the AHL for the application of the disease prevention and control rules referred to in points (a) to (e) of Article 9(1):

1) To be assigned to category A, a disease needs to comply with all criteria of the first set (1, 2.1–2.4) and according to the assessment paratuberculosis complies with criterion 2.3, but not with criteria 1, 2.1 and 2.4 and the assessment is inconclusive on compliance with criterion 2.2. To be eligible for category A, a disease needs to comply additionally with one of the criteria of the second set (3, 4, 5a–d) and paratuberculosis complies with criteria 4 and 5b, but not with criteria 3, 5a, 5c and 5d.

2) To be assigned to category B, a disease needs to comply with all criteria of the first set (1, 2.1–2.4) and according to the assessment paratuberculosis complies with criteria 2.1, 2.3 and 2.4, but not with criterion 1 and the assessment is inconclusive on compliance with criterion 2.2. To be eligible for category B, a disease needs to comply additionally with one of the criteria of the second set (3, 4, 5a–d) and paratuberculosis complies with criteria 4 and 5b, but not with criteria 3, 5a, 5c and 5d.

3) To be assigned to category C, a disease needs to comply with all criteria of the first set (1, 2.1–2.4) and according to the assessment paratuberculosis complies with all of them. To be eligible for category C, a disease needs to comply additionally with one of the criteria of the second set (3, 4, 5a–d) and paratuberculosis complies with criterion 5b, but not with criteria 4, 5a, 5c and 5d and the assessment is inconclusive on compliance with criterion 3.

4) To be assigned to category D, a disease needs to comply with criteria of Sections 1, 2, 3 or 5 of Annex IV of the AHL and with the specific criterion D of Section 4, with which paratuberculosis complies.

5) To be assigned to category E, a disease needs to comply with criteria of Sections 1, 2 or 3 of Annex IV of the AHL and/or the surveillance of the disease is necessary for reasons relating to animal health, animal welfare, human health, the economy, society or the environment. The latter is applicable if a disease fulfils the criteria as in Article 5, with which paratuberculosis complies.

3.4.   Assessment of Article 8

This section presents the results of the assessment on the criteria of Article 8(3) of the AHL about paratuberculosis. The Article 8(3) criteria are about animal species to be listed, as it reads below:

'3. Animal species or groups of animal species shall be added to this list if they are affected or if they pose a risk for the spread of a specific listed disease because:

a) they are susceptible for a specific listed disease or scientific evidence indicates that such susceptibility is likely; or

b) they are vector species or reservoirs for that disease, or scientific evidence indicates that such role is likely'.

For this reason, the assessment on Article 8 criteria is based on the evidence as extrapolated from the relevant criteria of Article 7, i.e. the ones related to susceptible and reservoir species or routes of transmission, which cover also possible role of biological or mechanical vectors.[1] According to the mapping, as presented in table 5, Section 3.2 of the scientific opinion on the ad hoc methodology (EFSA AHAW Panel, 2017), the main animal species to be listed for paratuberculosis according to the criteria of Article 8(3) of the AHL are as displayed in Table 21.

Table 21: Main animal species to be listed for paratuberculosis according to criteria of Article 8 (*source*: data reported in Section 3.1.1.1)

	Class	Order	Family	Genus/Species
Susceptible	Mammalia	Artiodactyla	Bovidae	*Bos taurus, Ovis aries, Bos indicus, Bison bison, Bubalis bubalis, Bison bison, Capra ibex, Rupicapra rupicapra, Bos grunniens, Oreamnos americanus, Capra hircus, Capra aegagrus hircus, Capra aegagrus ibex, Ovis orientalis, Ovis Canadensis, Ammotragus lervia, Ovis aries cameroon dwarf, Tragelaphus strepsiceros, Saiga tatarica*
			Camelidae	*Lama glama, Camelus bacterianus, Camelus dromedaries, Vicugna pacos, Lama guanicoe*
			Cervidae	*Dama dama, Cervus elaphus, Cervus Canadensis, Odocoileus virginianus clavium, Odocoileus hemionus, Dama dama, Capreolus capreolus, Odocoileus virginianus, Alces alces, Cervus elaphus nannodes, Cervus elaphus nelson, Cervus nippon, Axis axis, Pudu pudu, Rangifer tarandus*
			Suidae	*Sus* spp., *Sus scrofa*
		Perissodactyla	Equidae	*Equus asinus form. dom., Equus mule, Equus ferus caballus*
		Carnivora	Canidae	*Vulpes vulpes, Canis lupus*
			Felidae	*Felis catus*
			Mephitidae	*Mephitis mephitis*
			Mustelidae	*Meles meles, Mustela ermine, Mustela nivalis*
			Ursidae	*Ursus arctos*
			Procyonidae	*Procyon lotor*
		Lagomorpha	Leporidae	*Lepus* spp., *Oryctolagus cuniculus, Sylvilagus floridanus*
		Rodentia	Muridae	*Mus* spp., *Apodemus flavicollis, Apodemus sylvaticus, Rattus norvegicus*
			Cricetidae	*Mesocricetus* spp., *Clethrionomys glareolus, Microtus agrestis, Sigmodon hispidus*
			Caviidae	*Cavia porcellus*

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[1] A vector is a living organism that transmits an infectious agent from an infected animal to a human or another animal. Vectors are frequently arthropods. Biological vectors may carry pathogens that can multiply within their bodies and be delivered to new hosts, usually by biting. In mechanical vectors the pathogens do not multiply within the vector, which usually remains infected for shorter time than in biological vectors.

	Class	Order	Family	Genus/Species
		Eulipotyphla	Soricidae	*Blarina brevicauda*
		Primates	Cercopithecidae	*Mandrillus sphinx, Macaca arctoides, Callithrix jacchus, Macaca mulatta, Sanguinus Oedipus, Varecia variegata*
		Didelphimorphia	Didelphidae	*Didelphis virginiana*
		Cingulata	Dasypodidae	*Dasypus novemcinctus*
	Aves	Galliformes	Phasianidae	*Gallus gallus, Phasianus colchicus*
		Passeriformes	Estrildidae	*Stagonopleura guttata*
			Corvidae	*Corvus corone, Corvus monedula, Corvus frugilegus*
			Passeridae	*Passer domesticus*
			Sturnidae	*Sturnus vulgaris*
		Accipitriformes	Accipitridae	*Buteo buteo*
		Columbiformes	Columbidae	*Columbia livia, Columba palumbus*
		Charadriiformes	Scolopacidae	*Gallinago gallinago*
	Clitellata	Haplotaxida	Lumbricidae	*Lumbricus* spp.
Reservoir	Mammalia	Artiodactyla	Bovidae	Not specified
			Cervidae	Not specified
		Lagomorpha	Leporidae	Not specified
Vectors	None			

4.   Conclusions

TOR 1: *for each of those diseases an assessment, following the criteria laid down in Article 7 of the AHL, on its eligibility of being listed for Union intervention as laid down in Article 5(3) of the AHL;*

- According to the assessment here performed, paratuberculosis complies with all criteria of the first set and with one criterion of the second set and therefore can be considered eligible to be listed for Union intervention as laid down in Article 5(3) of the AHL.

TOR 2a: *for each of the diseases which was found eligible to be listed for Union intervention, an assessment of its compliance with each of the criteria in Annex IV to the AHL for the purpose of categorisation of diseases in accordance with Article 9 of the AHL;*

- According to the assessment here performed, paratuberculosis meets the criteria as in Sections 3, 4 and 5 of Annex IV of the AHL, for the application of the disease prevention and control rules referred to in points (c), (d) and (e) of Article 9(1) of the AHL.

TOR 2b: *for each of the diseases which was found eligible to be listed for Union intervention, a list of animal species that should be considered candidates for listing in accordance with Article 8 of the AHL.*

- According to the assessment here performed, the animal species that can be considered to be listed for paratuberculosis according to Article 8(3) of the AHL are several orders, families and species of mammals and birds as susceptible and some species of the families Bovidae, Cervidae and Leporidae as reservoirs, as reported in Table 21 in Section 3.4 of the present document.

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Abbreviations

AGID	agar gel immunodiffusion
AHAW	EFSA Panel on Animal Health and Welfare
AHL	Animal Health Law
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention
CFSPH	Centre for Food Security and Public Health
DALY	disability-adjusted life year
DTH	delayed type hypersensitivity
ECCO	European Crohn's and Colitis Organisation
ELISA	enzyme-linked immunosorbent assay

GHG	greenhouse gases
HR	high-risk
IAP	International Association for Paratuberculosis
ICBA	Individual and Collective Behavioural Aggregation
IFN-γ	interferon gamma
IgG	immunoglobulin G
IUCN	International Union for Conservation of Nature
JD	Johne's disease
LR	low-risk
MAP	*Mycobacterium avium* subsp. *paratuberculosis*
MS	Member State
OIE	World Organisation for Animal Health
PCR	polymerase chain reaction
ToR	Terms of Reference