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# What Do We Feed to Food Production Animals? A Review of Animal Feed Ingredients and Their Potential Impacts on Human Health

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Abbreviations:

AAFCO	Association of American Feed Control Officials
AsIII	arsenite
AsV	arsenate
BSE	Bovine spongiform encephalopathy
CDC	Centers for Disease Control and Prevention
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
GAO	United States General Accounting Office
IARC	International Agency for Research on Cancer
NRA	National Renderers Association, Inc.
PCBs	polychlorobiphenyls

PCDDs	polychlorodibenzo- <i>p</i> -dioxins
PCDFs	polychlorodibenzofurans
PrP <sup>Sc</sup>	protease-resistant protein
SRMs	specified risk materials
TSEs	transmissible spongiform encephalopathies
TEQs	toxic equivalents
USDA	United States Department of Agriculture
vCJD	variant Creutzfeldt-Jakob disease
WHO	World Health Organization

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## **Abstract**

**Objective:** Animal feeding practices in the U.S. have changed considerably over the past century. As large-scale, concentrated production methods have become the predominant model for animal husbandry, animal feeds have been modified to include ingredients ranging from rendered animals and animal waste to antibiotics and organoarsenicals. This article reviews current U.S. animal feeding practices and etiologic agents that have been detected in animal feed. Evidence that current feeding practices may lead to adverse human health impacts is also evaluated. **Data Sources:** Published veterinary and human health literature regarding animal feeding practices, etiologic agents present in feed and human health effects was reviewed along with proceedings from animal feed workshops. **Data Extraction:** Data were extracted from peer-reviewed articles and books identified using PubMed, Agricola, USDA, FDA, and CDC databases. **Data Synthesis:** Findings emphasize that current animal feeding practices can result in the presence of bacteria, antibiotic-resistant bacteria, prions, arsenicals and dioxins in feed and animal-based food products. Despite a range of potential human health impacts that could ensue, there are significant data gaps that prevent comprehensive assessments of human health risks associated with animal feed. Limited data are collected at the federal or state level concerning the amounts of specific ingredients used in animal feed, and there are insufficient surveillance systems to monitor etiologic agents “from farm to fork.” **Conclusions:** Increased funding for integrated veterinary and human health surveillance systems, and increased collaboration among feed professionals, animal producers and veterinary and public health officials is necessary to effectively address these issues.

## **Introduction**

Animal-based food products derived from cattle, swine, sheep, poultry and farmed fish constitute a significant portion of the current U.S. diet. In 2003, the U.S. per capita consumption of total meats (including beef, pork, veal, lamb, poultry, fish and shellfish) was 90.5 kg per year [U.S. Department of Agriculture (USDA) 2005a]. Data from animal production researchers demonstrate that the quality of these products is directly related to animal feeding practices (Capucille et al. 2004; Gatlin et al. 2003; Zaghini et al. 2005). Therefore, given the high consumption of animal-based food products in the U.S., the ingredients used in animal feed are fundamentally important in terms of both the quality of the resulting food products and the potential human health impacts associated with the animal-based food production chain.

In the early 1900s, animals produced for food in the U.S. were raised on small family farms where cows predominantly grazed on pasture, and young chickens were primarily fed a corn-based diet (Erf 1907). However, in the past 60 years, farms and animal feed formulations have undergone significant changes. Small family owned and operated farms have been replaced almost entirely by a system of large-scale operations where individual farmers contract with vertically integrated corporations. High rates of food production have been achieved through these systems where the scale of operations requires the high throughput generation of animals for processing. Animals are raised in confinement and fed defined feeds that are formulated to increase growth rates and feed conversion efficiencies. These present day animal feeds contain mixtures of plant-based products, as well as other ingredients ranging from rendered animals and animal waste to antibiotics and organoarsenicals. The inclusion of these ingredients in animal feeds can result in the presence of a range of biological, chemical and other etiologic agents in feed that can affect the quality and safety of animal-based food products and pose potential risks to human health.

Since December 2003, when the first U.S. case of bovine spongiform encephalopathy (BSE) was identified in a dairy cow in Washington State, there has been increased attention from veterinary and public health professionals regarding the quality and safety of U.S. animal feed, as well as the safety of subsequent animal-based food products. Yet, the focus of such attention is often limited to one particular facet of animal feed and its associated animal or human health effect (i.e. the impact of rendered animals in feed formulations on the risk of BSE, or the impact of bacterial contamination of animal feed on human bacterial illnesses). However, if one is to begin to understand the broad range of potential human health impacts associated with current animal feeding practices, it is necessary to examine the full spectrum of feeding practices and assess their potential human health implications collectively.

This article reviews U.S. animal feed production practices, animal feed ingredients and biological, chemical and other etiologic agents that have been detected in animal feed. In addition, evidence that current feeding practices may be associated with adverse human health impacts is evaluated, and the data gaps that prevent comprehensive assessments of human health risks associated with animal feed are addressed.

## **U.S. Animal Feed Production**

The U.S. animal feed industry is the largest producer of animal feed in the world (Gill 2004). In 2004, over 120 million tons of primary animal feed, including mixes of feed grains, mill by-products, animal proteins and microingredient formulations (ie. vitamins, minerals and antibiotics) were produced in the U.S. (Gill 2004). In the same year, the U.S. exported nearly \$4 billion worth of animal feed ingredients (International Trade Centre 2004).

The structure of the U.S. animal feed industry is complex with a multitude of industries and individual producers contributing to the production, mixing, and distribution of feed ingredients and complete feed products. However, there are a few firms that play principal roles in the manufacture of U.S. feeds, including feed mills, rendering plants and protein blenders [U.S. General Accounting Office (GAO) 2000]. Feed mills combine plant and animal based feed ingredients in order to produce mixes designed for specific animal species (U.S. GAO 2000). Rendering plants transform slaughter by-products and animals that are unsuitable for human consumption into animal feed products using grinding, cooking and pressing processes [U.S. GAO 2000: National Renderers Association, Inc. (NRA) 2005a]. Protein blenders mix processed plant and animal based protein ingredients from many sources into animal feeds (U.S. GAO 2000). Once animal feed ingredients are mixed, an estimated 17,500 U.S. animal feed dealers distribute the final feed products to individual feeding operations (Feedstuffs 2005).

## **Animal Feed Ingredients and Feeding Practices**

Animal feed ingredients that constitute complete feed products are derived from a multitude of raw materials of plant and animal origin, as well as pharmaceutical and industrial sources. While specific feed ingredients vary depending upon the animal (ie. poultry, swine, cattle), Table 1 provides an overview of feed ingredients that are legally permitted and used in U.S. animal feed. Readers interested in more specific information about feed ingredients listed in Table 1 are encouraged to refer to the Official Publication of the Association of American Feed Control Officials, Inc. (AAFCO) that is published annually (AAFCO 2004) and Lefferts et al. (2006). The present review focuses on feed ingredients listed in Table 1 that raise specific concerns for public health, including rendered animal products, animal waste, plant- and animal-based fats, antibiotics and metals.

### *Rendered animal products*

In 2003, the U.S. rendering industry produced over 8 million metric tons of rendered animal products, including meat and bone meal, poultry by-product meal, blood meal and feather meal (NRA 2005b). Most of these products were incorporated into animal feed. However, data concerning the specific amounts of rendered animal protein that are used in animal feed are difficult to obtain because the information is neither routinely collected at the federal or state level nor reported by the rendering industry. The latest available data, collected by the USDA in 1984, estimated that over 4 million metric tons of rendered animal products were used as animal feed ingredients (USDA 1988). Oftentimes these ingredients are listed on animal feed labels as “animal protein products.” Thus, it is difficult to discern precisely which animal protein products are included in a particular animal feed product (Lefferts et al. 2006).

### *Animal waste*

Another major animal protein-based feed ingredient is animal waste, including dried ruminant waste, dried poultry litter and dried swine waste (AAFCO 2004; Haapapuro et al. 1997). As with rendered animal products, there are no national data on the total amounts of animal waste included in animal feeds, although some states have collected limited data concerning this practice. In 2003, it was estimated that approximately one million tons of poultry litter were produced annually in Florida and an estimated 350,000 tons of this litter were available for use in feed (Dubberly 2003). Yet, information concerning the precise amount of this “available” poultry litter that was actually incorporated into Florida animal feed was unavailable.

Recycling animal waste into animal feed has been practiced for over 40 years as a means of cutting feed costs. However, the U.S. Food and Drug Administration (FDA) does not officially endorse the use of animal waste in feed and has issued statements voicing the agency’s concern about the presence of pathogens and drug residues in animal waste, particularly poultry litter (FDA 1998). In line with these concerns, AAFCO, an organization that develops guidelines for the safe use of animal feeds, advises that processed animal waste should not contain pathogenic microorganisms, pesticide residues and drug residues that could harm animals or eventually be detected in animal-based food products intended for human consumption (AAFCO 2004). Nonetheless, these guidelines are not adequately enforced at the federal or state level.

### *Plant- and Animal-based Fats*

In addition to animal protein-based ingredients, fats originating from both plant and animal sources are included in animal feed (Table 1) and may contain contaminants, such as dioxins and polychlorobiphenyls (PCBs), which are harmful to human health. In 1988, the USDA (1988) reported that approximately 1.3 million metric tons of fats were used in the production of U.S.

primary animal feed. Unfortunately, as with many other animal feed ingredients, we were not able to obtain recent data. Yet, since as much as 8% of feed could be comprised of fats alone (Schmidt 2004), the quality (ie. contaminant levels) of both plant and animal fats used in animal feed could be important factors in the ultimate safety of animal-based food products.

### *Antibiotics*

The use of antibiotics in animal feed is also a public health concern. Antibiotics are administered at non-therapeutic levels in feed and water in order to promote growth and improve feed efficiency. This practice has been shown to select for antibiotic resistance in both commensal and pathogenic bacteria in: 1) the animals themselves (Aarestrup et al. 2000; Bager et al. 1997; Gorbach 2001; Wegener 2003); 2) subsequent animal-based food products (Hayes et al. 2003; White et al. 2001); and 3) water, air and soil samples collected around large-scale animal feeding operations (Chapin et al. 2005; Chee-Sanford et al. 2001; Gibbs et al. 2006; Jensen et al. 2002).

While the use of non-therapeutic levels of antibiotics in animal feed is approved and regulated by the FDA (FDA 2004), there is no U.S. data collection system regarding the specific types and amounts of antibiotics that are used for this purpose. In response to this significant data gap, several estimates of non-therapeutic antibiotic usage have been published based on USDA livestock production data and FDA antibiotic usage regulations. For example, Mellon et al. (2001) estimated that as much as 60-80% of antibiotics produced in the U.S. are administered in feed to healthy livestock at non-therapeutic levels. Many of these antibiotics are the same compounds that are administered to humans in clinical settings, and include tetracyclines, macrolides, streptogramins and fluoroquinolones (FDA 2004). Readers interested in additional information regarding the types and amounts of antibiotics used in U.S. livestock are encouraged to refer to AAFCO (2004), FDA (2004) and Mellon et al. (2001).

## *Metals*

Metal compounds are also administered in animal feeds, and the compounds currently added to both swine and poultry feeds that are particularly concerning from a public health perspective are organoarsenicals. The most commonly used organoarsenical, Roxarsone (4-hydroxy-3-nitrobenzenearsenic-acid), is administered to feeds at concentrations ranging from 22.7 g/ton to 45.4 g/ton to promote growth and improve feed efficiency (Chapman and Johnson 2002). When used in combination with ionophores, Roxarsone also act as a co-coccidiostat to control intestinal parasites (Chapman and Johnson 2002). Once roxarsone is ingested by animals, the parent compound can be degraded into inorganic arsenite (AsIII) and inorganic arsenate (AsV) in animal digestive tracts and animal waste (Arai et al. 2003; Stolz et al. 2007). Both AsIII and AsV are classified by the U.S. Environmental Protection Agency (U.S. EPA) as Group A human carcinogens. Many other metallic compounds are also mixed into feeds, including copper, manganese, magnesium and zinc compounds, as well as metal amino acid complexes (AAFCO 2004).

## **Biological, Chemical and Other Etiologic Agents Detected in Animal Feed**

Due to current animal feeding practices, biological, chemical and other etiologic agents have been detected in animal feeds (Table 2) (Hinton 2000; Orriss 1997). These agents include bacterial pathogens, antibiotic-resistant bacteria, prions, metals, mycotoxins, polychlorodibenzo-*p*-dioxins (PCDDs), polychlorodibenzofurans (PCDFs) and PCBs (Crump et al. 2002; Dargatz et al. 2005; Eljarrat et al. 2002; Lasky et al. 2004; Moreno-Lopez 2002).

### *Bacteria*

There is substantial evidence that U.S. animal feeds are often contaminated with important human foodborne bacterial pathogens such as *Salmonella* spp. (Crump et al. 2002; Davis et al. 2003; Krytenburg et al. 1998), and *Escherichia coli*, including *E. coli* O157:H7 (Dargatz et al. 2005; Davis et al. 2003; Lynn et al. 1998; Sargeant et al. 2004). Studies of *Salmonella* spp. indicate that this pathogen can enter animal feeds at several points throughout the feed production process including the primary production of feed ingredients, milling, mixing, and/or storage (Maciorowski et al. 2006). However, it is acknowledged that a main source of *Salmonella* spp. contamination in animal feed is often the specific feed ingredients (originating from both plant and animal sources) that are combined at feed mills (Coma 2003; Davis et al. 2003). Once complete feeds are delivered to animal feeding operations, additional contamination with *Salmonella* spp. can occur if the feeds are disturbed by insects and wild birds or animals that harbor *Salmonella* spp. (Maciorowski et al. 2006).

One of the first reports of the presence of non-typhi serotypes of *Salmonella enterica* in U.S. poultry feed samples was published by Edwards et al. (1948). Since then, researchers have detected *S. enterica* in a variety of feed ingredients and complete feed products; however, the results from these studies have been variable. A study by McChesney et al. (1995) found that 56% of 101

animal protein based feed samples collected from 78 rendering plants, and 36% of 50 vegetable protein based feed samples collected from 46 feed mills were positive for *S. enterica*. In contrast, Krytenburg et al. (1998) detected *S. enterica* in 9.8% of 295 feed samples from commercially prepared cattle feeds present at feedlots in the Northwestern U.S. More recently, Dargatz et al. (2005) detected *Salmonella* spp. in 24% of 175 samples of mixed feed collected from a cattle feedlot in Colorado, and another study identified *Salmonella* spp. in 14% of meat and bone meal samples collected from a poultry feed mill (Hofacre et al. 2001).

*E. coli* also has been detected in animal feeds (Davis et al. 2003; Dargatz et al. 2005; Lynn et al. 1998; Sargeant et al. 2004). In a study by Lynn et al. (1998), 30.1% of 209 samples of cattle feed—collected from 13 dairies, 1 calf research facility and 4 feed mills—were positive for *E. coli*; none of the samples were positive for *E. coli* O157:H7. In contrast, Sargeant et al. (2004) isolated *E. coli* O157:H7 from 14.9% of 504 cattle feed samples collected in the Midwestern, U.S. More recently, Dargatz et al. (2005) recovered *E. coli* from 48.2% of 1,070 cattle feed samples collected in Colorado.

#### *Antibiotic-resistant bacteria*

A limited number of studies also have detected antibiotic-resistant bacteria in animal feeds. Schwalbe et al. (1999) tested poultry feeds and isolated *Enterococcus faecium* that were resistant to vancomycin, gentamicin, streptomycin and ampicillin. In a study of cattle feed ingredients, 38.7% of 514 *E. coli* isolates were resistant to cephalothin, 24.7% were resistant to ampicillin, 16.6% were resistant to cefoxitin, and 12.1% were resistant to amoxicillin/clavulanic acid (Dargatz et al. 2005). Among the 57 *Salmonella* spp. recovered from cattle feed ingredients, 34.5% were resistant to sulfamethoxazole, 15.5% were resistant to cephalothin, 13.8% were resistant to cefoxitin, 12.1% were resistant to ampicillin, 10.3% were resistant to amoxicillin/clavulanic acid and 10.3% were

resistant to ceftiofur (Dargatz et al. 2005). Multiple antibiotic resistant *E. coli* and *Salmonella* spp. were also detected in this study (Dargatz et al. 2005).

In another study, 165 rendered animal protein products originating from poultry, cattle and fish were sampled from a poultry feed mill and tested for antibiotic-resistant bacteria (Hofacre et al. 2001). Eighty-five percent of all feed ingredients sampled contained bacteria resistant to one or more of the following four antibiotics: ampicillin, amoxicillin, clavulanic acid or cephalothin. Poultry meal and bone and meat meal (non-poultry) samples represented the greatest number of feed ingredient samples containing bacteria resistant to five or more antibiotics (Hofacre et al. 2001).

### *Prions*

In addition to bacteria, animal feeds (in particular, cattle feeds) can be contaminated with the infectious agent associated with BSE (Gizzi et al. 2003). BSE, which is commonly referred to as mad cow disease, belongs to a group of progressively degenerative neurological diseases called transmissible spongiform encephalopathies (TSEs) (Deslys and Grassi 2005; Smith 2003). The causative agent of TSEs is believed to be an infectious proteinaceous entity called a prion, which is comprised largely of a protease-resistant misfolded protein (PrP<sup>Sc</sup>). Infectious prions can be present in animal feed as a result of using rendered animal products from diseased animals as feed ingredients. While prions may be present in all body tissues of diseased animals, it is generally acknowledged that prions accumulate in highest concentrations in central nervous system tissues (Smith 2003; U.S. GAO 2002) that are referred to as specified risk materials (SRMs). As defined by the USDA Food Safety Inspection Service, SRMs include the skull, brain, eyes, parts of the vertebral column, spinal cord, trigeminal ganglia and dorsal root ganglia of cattle older than 30 months, as well as the tonsils and distal ileum of all cattle (USDA 2005b). In 1997, the FDA

banned SRMs from use in cattle and other ruminant feed (U.S. GAO 2002). Nonetheless, SRMs were allowed to be incorporated into feeds for non-ruminants (including poultry), and subsequent waste products from non-ruminants are still permitted in ruminant feeds (USDA 2005b).

As of yet, there are no definitive tests for BSE infectivity in live animals (before symptoms appear) (Deslys and Grassi 2005; U.S. GAO 2002). However, a number of rapid screening tests based on ELISA or Western blot analyses have been approved for post-mortem BSE testing in cattle. Currently, the USDA is conducting a national BSE testing program; yet, only high-risk cattle are included in the program and there are no plans to test animal feed samples (that could include animal protein from asymptomatic rendered animals) in this surveillance effort. A variety of tests do exist for the detection of animal tissues (in general) in animal feed, including microscopic analyses, polymerase chain reaction, immunoassay analyses and near infrared spectroscopy (Gizzi et al. 2003); nonetheless, these methods are not robust enough to distinguish between bovine products that are permitted in ruminant feeds (ie. milk and blood) and bovine products that are prohibited from ruminant feeds (Momcilovic and Rasooly 2000; U.S. GAO 2002).

### *Mycotoxins*

Mycotoxins unintentionally appear in animal feed as a result of the inadvertent use of mycotoxin-contaminated feed ingredients such as cereal grains. Mycotoxins are toxic secondary metabolites produced by filamentous fungi (molds) that can invade crops while they are growing in the field and while they are being processed and stored (Bhat and Vasanthi 1999). The mycotoxins of greatest agricultural and public health significance include aflatoxins, ochratoxins, trichothecenes, fumonisins, zearalenone and ergot alkaloids (Cleveland et al. 2003; Hussein and Brasel 2001). The International Agency for Research on Cancer (WHO IARC) has classified aflatoxin as a Group 1 human carcinogen; ochratoxins and fumonisins as Group 2B possible human

carcinogens; and tricothecenes and zearalenone as non-carcinogens (Group 3) (WHO IARC 1993). Tricothecenes are highly toxic to humans and zearalenones are recognized endocrine disruptors (WHO IARC 1993).

Due to these classifications, the FDA has established recommended maximum levels for aflatoxins and fumonisins in animal feed (FDA 2001). For swine, ruminants and poultry, the recommended maximum levels of total fumonisins in complete feeds are 10, 30, and 50  $\mu\text{g/g}$ , respectively (FDA 2001). Nonetheless, while recommended maximum levels exist, it is very difficult to determine the extent of mycotoxin contamination in feedstuffs. Mycotoxins are unevenly distributed in feed, introducing a significant amount of sampling error into sample analyses (Hussein and Brasel 2001). In addition, there is wide geographical and temporal variability in the occurrence of mycotoxins in animal feed that is partially attributed to environmental factors (ie. rainfall, humidity) (Hussein and Brasel 2001).

#### *PCDDs, PCDFs and PCBs*

Other unintentional contaminants of animal feed include dioxins such as PCDDs and PCDFs, and PCBs (Eljarrat et al. 2002). Based on human epidemiological studies, IARC has classified dioxins as known human carcinogens (WHO 1999). The presence of PCDDs, PCDFs and PCBs in the environment is largely attributed to human activities, including the incineration of plastics and industrial processes involving chlorinated compounds. When dioxins and PCBs are released into the environment they can contaminate plant-based animal feeds through a variety of pathways, including the airborne deposition of particles onto plant and soil surfaces (Fries 1995). When these lipophilic compounds are ingested by food production animals, they bioaccumulate in fat tissues, making the use of rendered animal fats and oils in animal feed a significant source of

exposure to dioxins and PCBs among food production animals (Eljarrat et al. 2002; Institute of Medicine 2003).

The most severe example of dioxin- and PCB-contaminated animal feed occurred in Belgium in 1999 (van Larebeke et al. 2001). A fat-melting company inadvertently incorporated mineral oil containing 40-50 kg of PCBs and approximately 1g of dioxins to a mixture of animal-based fats that were subsequently distributed to 10 animal feed producers, resulting in approximately 500 tons of contaminated feed (van Larebeke et al. 2001). The levels of PCBs and dioxins detected in contaminated animal feed were  $1,658.4 \pm 23,584.4$  ng/g of fat and  $2,319.8 \pm 3,851.9$  pg toxic equivalents (TEQ)/g of fat, respectively, and resulted in higher levels of these compounds in animal-based food products such as eggs, poultry and pork (van Larebeke et al. 2001). Beyond this incident, several European studies have described elevated levels of PCDDs and PCDFs in eggs from free-range chickens raised on dioxin-contaminated soils (Schoeters and Hoogenboom 2006). In the United States, a significant episode of dioxin-contaminated feed occurred in 1997 (Hayward et al. 1999). Elevated levels of dioxin were detected in chicken eggs and farm-raised catfish and the source of contamination was traced to ball clay that was used as an anti-caking agent and pelleting aid in poultry feed, bovine pellets and catfish nuggets (Hayward et al. 1999). Once the source of contamination was identified, the FDA issued a statement to producers requesting the elimination of ball clay from feed ingredients (FDA 1997).

Aside from these accidents, there have been little data generated in the U.S. concerning levels of dioxins and PCBs that are typically found in U.S. livestock feed. However, numerous studies have documented higher levels of PCBs and dioxins in farmed salmon versus wild-caught salmon, and these elevated contaminant levels have been attributed to contaminated commercial salmon feed (Easton et al. 2002; Hites et al. 2004). For example, Easton et al. (2002) detected total

PCBs at mean concentrations of 51,216 pg/g and 5,302 pg/g in farmed and wild-caught salmon, respectively, and a mean concentration of 65,535 pg/g in commercial salmon feed.

## **Potential Human Health Impacts Associated with Etiologic Agents Present in Animal Feed**

In order to determine whether the presence of biological, chemical and other etiologic agents in animal feed impacts human health, it is necessary to integrate data from robust veterinary and human health surveillance systems that monitor agents in feed, health effects in animals, contaminants in animal-based food products and illnesses in humans. However, to date, these integrated systems are largely lacking in the U.S. Thus, the current evidence regarding human health risks associated with U.S. animal feed has been obtained mostly from isolated case reports and outbreaks published in the peer-reviewed literature. Some of this evidence is described below and outlined in Table 2; yet, as a result of significant data gaps, it is important to note that this information may represent only a small proportion of potential human health risks associated with animal feed.

### *Bacterial infections*

In a paper by Crump et al. (2002), the authors cited the emergence of *S. enterica* serotype Agona infections in humans in the U.S. as an example of human foodborne bacterial infections that have been definitively traced to contaminated animal feed. *S. enterica* serotype Agona infections are characterized by fever, diarrhea, abdominal cramps, and vomiting, and the illness can be fatal in infants, the elderly and immunocompromised individuals. Prior to 1970, only two cases of *S. enterica* serotype Agona infection had been reported in the U.S. (Crump et al. 2002). However, by 1972, *S. enterica* serotype Agona was among the top ten most frequently isolated *S. enterica* serotypes from human infections (Crump et al. 2002). An epidemiological study identified the source of these *S. enterica* serotype Agona infections as chicken meat that originated from a poultry facility where Peruvian fish meal was used as a feed ingredient (Clark et al. 1973; Crump et al. 2002). A study by Clark et al. (1973) found that the fish meal had been contaminated with *S. enterica* serotype Agona prior to being incorporated into the poultry feed. Crump et al. (2002)

estimated that since the introduction of *S. enterica* serotype Agona in poultry feed in 1968, this serotype has likely caused over 1 million human bacterial illnesses in the U.S.

Besides the *S. enterica* serotype Agona example, there are insufficient data available to understand the extent to which other human bacterial illnesses arising in the U.S. are the result of contaminated animal feed. Outbreaks of human bacterial illness often can be traced to food production animals or facilities; however, due to surveillance inadequacies, it is difficult to determine the initial source of bacterial contamination (ie. animal feed or other factors) within the animal production environment. Moreover, unlike *S. enterica* serotype Agona--which could be traced to poultry feed in 1968 because it was a newly identified serotype--it is much more difficult to understand the associations between more common, widespread serotypes or bacterial species present in animal feed and human illnesses. Nevertheless, with the use of annual U.S. foodborne illness data, estimates concerning the contributions of contaminated animal feed to human bacterial illnesses have been made (Angulo 2004). Based on the assumptions that 1) food production animals are the source of 95% of human non-typhoidal *Salmonella* cases; and 2) 10% of food production animals are infected by *Salmonella* spp. through the ingestion of contaminated animal feed, it has been estimated that approximately 134,000 cases of human non-typhoidal salmonellosis (including 55 deaths and 1,560 hospitalizations) could be attributed to contaminated animal feed each year (Angulo 2004).

#### *Antibiotic-resistant bacterial infections*

Similar to the challenge of determining whether human bacterial illnesses are associated with contaminated animal feed, there are insufficient data available to determine the percentage of antibiotic-resistant human bacterial infections that are attributed to animal feeding practices versus practices and behaviors occurring in human clinical settings. This is largely the result of 1)

insufficient agricultural antibiotic usage data available in the U.S.; 2) insufficient surveillance data concerning the dissemination of antibiotic-resistant isolates from food production animals to humans; 3) insufficient investigations regarding the original sources of resistant infections diagnosed in hospital settings; and 4) under-reporting of community-acquired antibiotic-resistant bacterial infections.

Nonetheless, there is evidence that antibiotic-resistant bacteria can be transmitted from swine and poultry to humans (Aarestrup et al. 2000). Sorensen et al. (2001) reported that after the ingestion of antibiotic-resistant *Enterococcus faecium* originating from contaminated chicken and pork, the resistant bacterium can be isolated from the stool of infected individuals for up to two weeks, indicating that antibiotic-resistant *E. faecium* can survive and multiply in the human gastrointestinal tract. In addition, there is strong temporal evidence suggesting that some domestically-acquired antibiotic-resistant bacterial infections in humans emerged in the U.S. only after the approval of specific human antibiotics for use in animal feed or water. For example, prior to 1985 there were little to no fluoroquinolone-resistant *Campylobacter jejuni* isolated from either poultry or humans in the U.S. (Smith et al. 1999). However, after FDA approved the use of fluoroquinolones in poultry production in 1995, fluoroquinolone-resistant *C. jejuni* were detected in both poultry and human isolates. The Minnesota Department of Health completed an analysis of *C. jejuni* isolates from humans and retail poultry products and found that the proportion of fluoroquinolone-resistant *C. jejuni* isolated from humans increased from 1.3% in 1992 to 10.2 % in 1998 (following the 1995 fluoroquinolone approval) (Smith et al. 1999). In contrast, in Australia, where fluoroquinolones have never been approved for use in animal agriculture, no fluoroquinolone resistance has been detected in *C. jejuni* isolated from domestically-acquired human infections (Unicomb et al. 2003).

### *Variant Creutzfeldt-Jakob disease*

Beyond bacterial infections, a chronic human health risk that has been linked to animal feeding practices is variant Creutzfeldt-Jakob disease (vCJD), a novel human neurodegenerative prion disease that is currently untreatable and fatal (Collinge 1999). vCJD was first described in 1995 in two teenagers in the United Kingdom and was believed to be caused by infection with the causative agent of BSE or mad cow disease (Smith 2003). Molecular strain-typing studies and experimental transmission studies in mice published in 1996 and 1997 confirmed that vCJD is caused by the same prion strain that causes BSE (Collinge 1999).

The primary routes of human exposure to prions remain debatable; however, the most likely route is through the ingestion of beef derived from cattle that were infected when rendered animal proteins from diseased cattle were included in their feed. It is hypothesized that the UK population may have experienced the highest exposures to BSE from 1989-1990, when the incidence of BSE was still increasing in cattle and specific bans on high-risk rendered bovine products were still being implemented (Collinge 1999). From 1995-2002, there were 121 fatalities out of 129 diagnosed cases in the UK (Smith 2003). To date, domestically-acquired human cases of vCJD have not been identified in the U.S. However, since BSE was first identified in the U.S. in 2003, the Centers for Disease Control and Prevention (CDC) have enhanced national surveillance for all types of CJD in the U.S. through the analysis of multiple cause-of-death data derived from death certificates (CDC 2005). Active CJD surveillance is also being implemented through the Emerging Infections Programs established in 4 sites across the U.S. (CDC 2005).

### *Arsenic-related human health risks*

Since inorganic AsIII and AsV are known human carcinogens, there is considerable concern regarding human exposures to these compounds. Chronic arsenic exposures occurring through the

ingestion of contaminated drinking water and dietary sources have resulted in skin cancers, lung cancers, bladder cancers and prostate cancers, as well as hypertensive heart disease and nephritis (WHO 2001). While several research groups have begun to elucidate the effects of arsenic use in animal feed on environmental concentrations of arsenic in areas where animal waste has been land-applied (Bednar et al. 2003; Garbarino et al. 2003; Jackson et al. 2006; Stolz et al. 2007), only one study to date has explored how the presence of arsenic in U.S. meat products could potentially impact the health of consumers (Lasky et al. 2004).

In a study by Lasky et al. (2004), concentrations of total arsenic in poultry samples were determined using data from the USDA Food Safety and Inspection Service, National Residue Program. National chicken consumption data were then used to quantify exposures to total arsenic, inorganic arsenic and organic arsenic resulting from the consumption of poultry meat. The findings of this study indicated that individuals who consume average amounts of poultry (60 grams per day) could ingest 1.38 to 5.24  $\mu\text{g}/\text{day}$  of inorganic arsenic from the ingestion of poultry alone (Lasky et al. 2004), an amount that represents a high proportion of the tolerable daily intake of inorganic arsenic recommended by the Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (2  $\mu\text{g}/\text{kg}/\text{day}$ ). Clearly, additional studies are necessary to further understand the associations between the ingestion of arsenic-contaminated meat and cancer risk.

#### *Mycotoxin-related human health risks*

There are numerous peer-reviewed studies regarding human health effects associated with exposures to mycotoxins. These effects range from carcinogenic and nephrotoxic health effects to dermonecrotic and immunosuppressive health effects (Orriss 1997). While the main route of human exposure to mycotoxins has been identified as the direct ingestion of contaminated cereals and grains (Orriss 1997), there are few and conflicting studies about whether the ingestion of meat,

milk and eggs originating from mycotoxin-exposed food production animals is an additional exposure pathway for mycotoxins among humans.

Researchers from the USDA Division of Epidemiology and Surveillance have articulated that the ingestion of mycotoxin-contaminated animal-based food products could pose a concern to public health (Hollinger and Ekperigin 1999). Several studies have identified elevated levels of aflatoxin M1 and other mycotoxins in cow milk (Ghidini et al 2005; Sorensen and Elbaek 2005). In addition, in a study where pigs were fed 100 mg of fumonisin B1 per day for five to 11 days, mean fumonisin levels in edible muscle tissues were 43 µg/kg (Meyer et al. 2003). While fumonisin levels administered to pigs in this study are significantly higher than levels ingested under normal agricultural conditions, the findings suggest that the consumption of meat from animals inadvertently exposed to elevated levels of fumonisin in feed could be a potential pathway for human exposure to these toxins. Others have found that trace levels of ochratoxin A in pork and poultry samples were likely to pose insignificant risks to consumers (Guillamont et al. 2005; Jorgensen 1998).

#### *PCDD-, PCDF- and PCB-related human health risks*

There are numerous studies indicating that animal-based food products (including fish and dairy products) are the largest dietary contributors to PCDD, PCDF and PCB exposures in the U.S. population (Huwe and Larsen 2005; Schechter et al. 1994). In a study by Schechter et al. (1994), daily dioxin TEQ intakes associated with the ingestion of dairy, meat and fish were estimated by testing samples collected from a grocery store in upstate New York. When combined with 1986 U.S. food consumption rates, these estimates translated to an average daily dioxin TEQ intake ranging from 18 to 192 pg TEQ for an adult weighing 65 kg (Schechter et al. 1994). In another study that analyzed beef, pork and poultry samples collected from 9 cities across the U.S., the estimated daily dietary

intake ranged from 5.3 to 16.0 pg TEQ (Huwe and Larsen 2005). These levels represent a considerable portion of the tolerable daily intake for dioxin (2,3,7,8- tetrachlorodibenzo-para-dioxin) (1 to 4 pg/kg body weight) recommended by WHO (WHO 1999).

Chronic exposures to PCDDs, PCDFs and PCBs can result in adverse health effects ranging from cancers to impairments in the immune system, endocrine system and reproductive organs (WHO 1999). As stated above, animal-based food products are known to be major dietary sources of human exposure to dioxin-like compounds; yet, the specific role that contaminated animal feeds play in this exposure pathway is unclear.

## Conclusions

Food animal production in the U.S. has changed markedly in the past century, and these changes have paralleled major changes in animal feed formulations. While this industrialized system of food animal production may result in increased production efficiencies, some of the changes in animal feeding practices may result in unintended adverse health consequences for consumers of animal-based food products.

Currently, the use of animal feed ingredients including rendered animal products, animal waste, antibiotics, metals and fats, could result in higher levels of bacteria, antibiotic-resistant bacteria, prions, arsenic and dioxin-like compounds in animals and resulting animal-based food products intended for human consumption. Subsequent human health effects among consumers could include increases in bacterial infections (antibiotic-resistant and non-resistant) and increases in the risk of developing chronic (often fatal) diseases such as vCJD.

Nevertheless, despite the wide range of potential human health impacts that could result from animal feeding practices, there are very little data collected at the federal or state level concerning the amounts of specific ingredients that are intentionally included in U.S. animal feed. In addition, almost no biological or chemical testing is conducted on complete U.S. animal feeds; insufficient testing is performed on retail meat products; and human health effects data are not appropriately linked to this information. These surveillance inadequacies make it difficult to conduct rigorous epidemiological studies and risk assessments that could identify the extent to which specific human health risks are ultimately associated with animal feeding practices. For example, as noted above, there are insufficient data to determine whether other human foodborne bacterial illnesses besides those caused by *S. enterica* serotype Agona are associated with animal feeding practices. Likewise, there are insufficient data to determine the percentage of antibiotic-

resistant human bacterial infections that are attributed to the non-therapeutic use of antibiotics in animal feed. Moreover, little research has been conducted to determine whether the use of organoarsenicals in animal feed, which can lead to elevated levels of arsenic in meat products (Lasky et al. 2004), contributes to increases in cancer risk.

In order to address these research gaps, the following principal actions are necessary within the U.S.: 1) implementation of a nationwide reporting system of the specific amounts and types of feed ingredients of concern to public health that are incorporated into animal feed, including antibiotics, arsenicals, rendered animal products, fats and animal waste; 2) funding and development of robust surveillance systems that monitor biological, chemical and other etiologic agents throughout the animal-based food production chain “from farm to fork” to human health outcomes; and 3) increased communication and collaboration among feed professionals, food animal producers and veterinary and public health officials.

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**Table 1:** Animal feed ingredients that are legally used in U.S. animal feeds<sup>a</sup>

<b>Origin</b>	<b>Raw Material</b>	<b>Examples</b>
Plant	Forage	Alfalfa meal and hay, Bermuda coastal grass hay, corn plant, soybean hay
	Grains	Barley, corn (organic and genetically modified), oats, rice, sorghum, wheat
	Plant protein products	Canola meal, cottonseed cakes and meals, peanut meal, safflower meal, soybean (organic and genetically modified) feed and meal
	Processed grain by-products	Distillers products, brewers dried grains, corn gluten, sorghum germ cake and meal, peanut skins, wheat bran
	Fruit and fruit by-products	Dried citrus pulp, apple pomace and pectin pulp
	Molasses	Beet, citrus, starch and cane molasses
	Miscellaneous	Almond hulls and ground shells, buckwheat hulls, legumes and their by-products, other crop by-products
Animal	Rendered animal protein from the slaughter of food production animals and other animals	Meat meal, meat meal tankage, meat and bone meal, poultry meal, animal by-product meal, dried animal blood, blood meal, feather meal, egg shell meal, hydrolyzed whole poultry, hydrolyzed hair, bone marrow, and animal digest from dead, dying, diseased or disabled animals including deer and elk
	Animal waste	Dried ruminant waste, dried swine waste, dried poultry litter, undried processed animal waste products
	Marine by-products	Fish meal, fish residue meal, crab meal, shrimp meal, fish oil, fish liver and glandular meal, fish by-products
	Dairy products	Dried cow milk, casein, whey products, dried cheese
Mixed	Fats and oils	Animal fat, vegetable fat or oil, hydrolyzed fats
	Restaurant food waste	Edible food waste from restaurants, bakeries, cafeterias
	Contaminated/adulterated food	Food adulterated with rodent, roach or bird excreta that has been heat treated to destroy pathogenic organisms
Other	Antibiotics	Tetracyclines, macrolides, fluoroquinolones, streptogramins
	By-products of drug manufacture	Spent mycelium, fermentation products
	Arsenicals	Roxarsone, arsanilic acid

Other metal compounds	Copper compounds, metal amino acid complexes
Non-protein nitrogen	Urea, ammonium chloride, ammonium sulfate,
Minerals	Bone charcoal, calcium carbonate, chalk rock, iron salts, magnesium salts, oyster shell flour
Vitamins	Vitamins A, D, B <sub>12</sub> , E, niacin, betaine
Direct-fed organisms	<i>Aspergillus niger</i> , <i>Bacillus subtilis</i> , <i>Bifidobacterium animalis</i> , <i>Enterococcus faecium</i> , Yeast
Flavors	Aloe vera gel concentrate, ginger capsicum, fennel
Enzymes	Phytase, cellulase, lactase, lipase, pepsin, catalase
Additives Generally Regarded as Safe (GRAS)	Acetic acid, sulfuric acid, aluminum salts, dextrans, glycerin, beeswax, sorbitol, riboflavin
Preservatives	Butylated hydroxyanisole (BHA), sodium bisulfite
Nutraceuticals	Herbal and botanical products
Plastics	Polyethylene roughage replacement

<sup>a</sup>Data adapted from AAFCO 2004.

**Table 2:** Biological, chemical and other etiologic agents detected in animal feed and their potential human health impacts

<b>Etiologic Agent</b>	<b>Examples</b>	<b>Potential Human Health Impacts</b>	<b>References</b>
Bacteria	<i>Salmonella</i> spp., <i>E. coli</i> O157:H7	Bacterial infections <sup>b</sup>	Angulo 2004; Crump et al. 2002; Davis et al. 2003
Antibiotic-resistant bacteria <sup>a</sup>	<i>E. faecium</i> , <i>E. coli</i> , <i>C. jejuni</i>	Antibiotic-resistant bacterial infections <sup>b</sup>	Aarestrup et al. 2000; Dargatz et al. 2005; Schwalbe et al. 1999; Sorensen et al. 2001
Prions	Causative agent of BSE	vCJD <sup>c</sup>	Gizzi et al. 2003; Smith 2003
Arsenicals	Roxarsone, AsIII, AsV	Increased human exposures to inorganic arsenic that may contribute to increases in cancer risk <sup>b</sup>	Chapman and Johnson 2002; Lasky et al. 2004
Mycotoxins	Aflatoxins, ochratoxins, fumonosins, trichothecenes	Increased human exposures to mycotoxins that may contribute to increases in cancer and non-cancer risks <sup>b</sup>	Bhat and Vasanthi 1999; Hussein and Brasel 2001
Dioxins and dioxin-like compounds	PCDDs, PCDFs, PCBs	Increased human exposures to dioxin-like compounds that may contribute to increases in cancer and non-cancer risks <sup>b</sup>	Eljarrat et al. 2002; Fries 1995; Huwe and Larsen 2005

Abbreviations: AsIII, arsenite; AsV, arsenate; BSE, bovine spongiform encephalopathy; vCJD, variant Creutzfeldt-Jakob disease; PCBs, polychlorobiphenyls; PCDDs, polychlorodibenzo-*p*-dioxins; PCDFs, polychlorodibenzofurans

<sup>a</sup> Antibiotic-resistant bacteria initially present in animal feed due to contaminated feed ingredients, and antibiotic-resistant bacteria resulting from the non-therapeutic use of antibiotics in feed

<sup>b</sup> Insufficient data are available to fully understand the magnitude of potential human health impacts associated with contaminated animal feed

<sup>c</sup> Domestically-acquired human cases of vCJD have not been documented in the U.S.