Naturally Occurring Toxins in Feedstuffs:
Center for Veterinary Medicine Perspective

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ABSTRACT: The objectives of this review are to provide 1) information on the FDA Feed Contaminants Program, 2) the legal history of aflatoxins and their current action levels, 3) a report on the levels of aflatoxins, fumonisins, vomitoxin, ochratoxin A, and zearalenone in domestic and import surveillance samples of feed during fiscal years 1989 through 1992, and 4) information on naturally occurring toxins encountered recently by the Center for Veterinary Medicine. Ten of 644 (1.6%) domestic corn samples and 7 of 106 (6.6%) domestic cottonseed samples contained aflatoxins at levels > 300 ppb. The mean fumonisin level in the 1990 survey of 85 corn screening samples was 12.1 ppm, and the values ranged from 2.6 to 32 ppm. The mean vomitoxin levels in the 1991 survey of 207 winter wheat samples and 206 spring wheat samples was 2.4 and .9 ppm, respectively. Ochratoxin A was not detected in 168 samples. Zearalenone was detected at levels > .15 ppm in only 1 of 161 samples. Cottonseed containing 13,000 ppm gossypol was recently implicated in the deaths of dairy cows. Crambe meal and canola meal are sanctioned for use in feed with certain restrictions, including the levels of glucosinolates. The FDA is continuing its surveillance and will strive to provide guidance on the increasing number of naturally occurring toxins.

Key Words: Aflatoxins, Vomitoxin, Fumonisin, Gossypol, Glucosinolates

Introduction

The U.S. Food and Drug Administration (FDA) is responsible for ensuring the safety of the human and animal food supply. Within the FDA, the Center for Veterinary Medicine (CVM) has the responsibility for ensuring that the animal feed supply is safe and wholesome. The CVM carries out this mission in part through the Feed Contaminants Program (FCP). The FCP (FDA, 1987) provides guidance for the 1) selected inspection of animal feed establishments; 2) collection and analysis of animal feed samples for pesticides, industrial chemicals, heavy metals, mycotoxins, and microbial agents; and 3) investigation into the causes of chemical and biological residues in meat and poultry reported to the FDA through the USDA's Contamination Response System (CRS).

The objectives of this review are to provide 1) information on the FCP; 2) the legal history of aflatoxins and their current action levels; 3) a report on the levels of aflatoxins, fumonisins, vomitoxin, ochratoxin A, and zearalenone in domestic and import surveillance samples of feed during fiscal years (FY) 1989 to 1992 (October 1, 1988 to June 24, 1992); and 4) information on naturally occurring toxins encountered recently by the CVM.

Feed Contaminants Program

The number of samples analyzed and the time spent by the FDA on the FCP during FY 89-92 are provided in Table 1. The FDA analyzed an average of 1,172 animal feed samples annually, of which 1,024 were surveillance samples (i.e., samples collected on an objective basis where there is no inspectional or other evidence of a problem with the product) and 148 were compliance samples (i.e., samples collected on a selective basis as the result of an inspection, complaint, or other evidence that there may be a problem with the product). An average of 373 of the total samples and 320 of the surveillance samples were analyzed annually for mycotoxins. The FDA annually invested an average of 5.3 full-time equivalents (FTE...
Aflatoxins

Legal History and Action Levels

Aflatoxins have been a significant problem since their discovery in the early 1960s. Initially, the FDA set an action level of 30 ppb of aflatoxins in raw or finished products, based on the analytical detection level (Duggan, 1970). In 1969, the FDA revised the action level for aflatoxins to 20 ppb for all foods, including animal feeds, based on the FDA's improved analytical capability and the agency's aim of limiting aflatoxin exposure to the lowest possible level. The FDA later set an action level of .5 ppb of aflatoxin M1 in milk (FDA, 1989a).

During the 1970s and 1980s, data were generated by many researchers to delineate the effects of aflatoxin on several species and classes of animals. There are several recent reviews that provide an excellent background on the scientific aspects of the mechanism of aflatoxin toxicity and on the specific effects on various species (CAST, 1989; Diekman and Green, 1992; Honstead and Dreesen, 1992). From these data, the FDA concluded that levels of aflatoxins > 20 ppb in the feed of certain classes and species of food-producing animals would not result in levels of aflatoxin and(or) its metabolites that would be harmful to the animal or to humans consuming edible animal products.

In 1982, the FDA was asked to consider raising the action level for cottonseed meal because of a continued aflatoxin contamination problem in the southwestern United States. The FDA set the action level for aflatoxin in cottonseed meal at 300 ppb for beef cattle, swine, and poultry (FDA, 1989a). The rationale for this was based, in part, on the fact that cottonseed meal usually makes up a relatively minor part of an animal's diet.

In 1980 and 1983, aflatoxins seemed to be a bigger problem than usual because of drought conditions in the corn belt. During these years, the FDA used regulatory discretion to increase temporarily the aflatoxin action levels in specific instances. This discretion was based on scientific knowledge of the increased tolerance of some animals.

The FDA regulates feed containing aflatoxin under Sec. 402 (a)(1) of the Federal Food Drug and Cosmetic Act (FDA, 1989b), which is the adulteration section. Specifically, aflatoxin is regulated as an added (rather than not added) poisonous and deleterious substance for two reasons. First, the Agency believes that aflatoxin contamination can often be controlled by appropriate storage conditions. Second, as an added substance, the Agency only needs to prove that aflatoxins may render the food injurious to health.

Action levels are those levels above which the Agency has concluded that qualified expert witnesses would testify in a federal court that the toxin may render the food injurious to health. Over the years, action levels have been considered by some to be formal tolerances. Because of the FDA's temporary increase in the action level for aflatoxin in corn, in 1980, a suit was brought against the FDA by the Community Nutrition Institute (CNI), Public Citizen, and two individuals for not using appropriate procedures for establishing action levels (Food Chemical News, 1984). The CNI asserted that the FDA is required to set tolerances for aflatoxin in corn products, whereas the FDA contended that the law authorizes the establishment of tolerances, but does not require it. The District Court for the District of Columbia found in favor of the FDA. However, CNI appealed the case to the D.C. Court of Appeals, and on May 15, 1987, the D.C. Appeals Court held that the FDA action levels are legislative rules rather than a
general statement of policy with the meaning of the law. Legislative rules must be promulgated in accordance with notice and comment procedures. Because the FDA action levels were issued without such procedures, the court found the action levels to be invalid. As a result of the court action, when the FDA encounters an added poisonous or deleterious substance in a food or feed, it can decide to take or not to take regulatory action based on the merits of each individual finding.

When it seemed that the 1988 U.S. corn crop had a potential for higher than normal aflatoxin contamination, the FDA released a document notifying the public that action levels would serve as guidelines rather than as levels binding in the courts (FDA, 1988). In the Federal Register (FR) of May 25, 1989 (Wessel, 1989), the FDA confirmed this policy. The document also stated that the agency believed that enforcement action could be supported in cases involving aflatoxin-contaminated corn shipped in interstate commerce when:

1. Corn containing > 20 ppb aflatoxins was destined for food use by humans, for feed use by immature animals (including immature poultry), dairy animals, or its destination was unknown.
2. Corn containing > 100 ppb aflatoxins was destined for breeding cattle, breeding swine, or poultry.
3. Corn containing > 200 ppb aflatoxins was destined for finishing swine of > 100 pounds (45 kg).
4. Corn containing > 300 ppb aflatoxins was destined for finishing beef cattle.

The FDA believes that enforcement action for milk could be taken under the Interstate Milk Shippers Program when aflatoxin M1 levels are > .5 ppb. This decision was supported by research conducted at the CVM’s Division of Animal Research showing that aflatoxin levels of 20 ppb in lactating dairy cow diets resulted in < .5 ppb of aflatoxin M1 in the milk (Frohish et al., 1986).

A section of the Compliance Policy Guide (CPG) issued by the FDA contains information on measuring aflatoxins (FDA, 1989a). The CPG states that samples (import or domestic) must be analyzed in accordance with applicable methods of the current Official Methods of Analysis of the Association of Official Analytical Chemists (AOAC). The identity of aflatoxin B3 is confirmed by chemical derivative formation and by negative ion chemical ionization mass spectrometry (MS). The MS confirmation is required for all commodities covered by the CPG except corn and corn meal, cottonseed and cottonseed meal, coconut meal, copra, peanut meal, and pumpkin seed.

The May 25, 1989 FR notice (Wessel, 1989) also addressed the practice of blending aflatoxin-contaminated corn with uncontaminated corn as a means of reconditioning. Such blended corn is adulterated within the meaning of section 402(a)(2)(A) of the act, and therefore not allowed. However, for the 1988 corn crop, FDA exercised enforcement discretion in allowing blending to produce a final blended corn that was below one of the aflatoxin action levels for animal feed use, provided that several conditions were met as set forth in the notice.

**Domestic Surveillance**

The FDA has monitored the interstate shipment of feedstuffs for several years, particularly in years when the climatic conditions were favorable for aflatoxin formation. In 1984, the FDA conducted a survey with the objective of looking at the drought-stricken 1983 corn crop intended for interstate shipment. One hundred twenty-two samples were drawn by inspectors from 17 FDA District Offices and analyzed for aflatoxins. Of the samples, 71% had no detectable levels (< 1 ppb), 21% had levels between 1 and 20 ppb, and 8% had levels between 21 and 100 ppb. It was concluded that corn with aflatoxin levels higher than those allowed was not being introduced into interstate commerce.

Table 2 shows the results of the FDA domestic surveillance program for FY 89-92. The individual year data are not shown because no yearly trends were apparent. Even in FY 89, which included the drought year, 1988, 52% of the samples of corn entering interstate shipping channels showed no detectable aflatoxin levels, and only one sample tested > 300 ppb. During the total period for the data presented (FY 89-92), 51% of the corn had no detectable aflatoxins, and only 1.6% of the corn samples were > 300 ppb. For cottonseed products destined for interstate shipment, 45% of the samples had no detectable aflatoxins and 6.6% had levels that were > 300 ppb.

**Import Surveillance**

The FDA has the option of refusing entry of aflatoxin-contaminated feeds, allowing reconditioning under supervision, or ordering the destruction of the contaminated feed. For FY 89–92, 59 import samples were collected. Aflatoxin levels > 20 ppb were detected in only three (5.1%) samples, with only one of those being > 100 ppb. Forty-nine samples had no detectable levels, and seven samples had < 20 ppb aflatoxins.

**Ammoniation**

The states of Arizona, California, and Texas allow aflatoxin-contaminated cottonseed products to be reconditioned by ammoniation, and Texas allows ammoniation of aflatoxin-contaminated corn. The FDA does not allow interstate shipment of ammoniated cottonseed or corn contaminated with aflatoxin because of the lack of evidence of safety of
the ammoniation reaction products. In the FR of February 20, 1990 (Price, 1990), the FDA created a public master file (PMF) and invited the submission of data and information concerning the treatment of animal feeds with ammonia to reduce aflatoxin contamination. The University of Arizona has made submissions in response to the FR notice. The FDA is currently undertaking an assessment of the new data. The PMF is open for the submission of data.

**Fumonisins**

Fumonisins, a family of mycotoxins produced by the molds *Fusarium moniliforme* and *F. proliferatum* (Gelderblom et al., 1988; CAST, 1989; Voss, 1990; Thiel et al., 1991) have recently drawn the concern of the FDA as a contaminant of corn, particularly of corn screenings. Recent publications point out the ubiquitous nature of fumonisins in corn (Nelson et al., 1991) and their detrimental effects in causing equine leukoencephalomalacia (Kellerman et al., 1990) and porcine pulmonary edema (Haschek et al., 1992).

In response to several horse deaths late in 1990, the CVM directed a survey of fumonisin in corn and corn screenings in 1991. The results in Table 3 show that fumonisin was detected in 13 of 99 (13%) shelled corn samples and in all 85 corn screening samples. Fumonisin concentrations in the shelled corn samples ranged from 1.2 to 3.2 ppm. The mean fumonisin concentration in the corn screenings was 12.1 ppm, with a range of 2.6 to 32 ppm and a median of 11.4 ppm.

The National Toxicology Program administrators have designated fumonisin B1 as a priority compound in 1991, and the National Center for Toxicological Research (NCTR) is planning chronic feeding studies with this compound. The CVM and The Center for Food Safety and Applied Nutrition (CFSAN) are providing funding for a contract to produce crude fumonisin toxin for these studies. In addition, the National Animal Disease Center in Ames, IA has ongoing studies in which fumonisin is being fed to horses, cattle, and swine. The results from these research projects may provide data from which no-effect levels for animals can be established.

The CVM has not reviewed any data on the feed-to-tissue or feed-to-milk ratios for fumonisins and has not established action levels for fumonisins in animal feeds. The CVM has reviewed the published literature on fumonisin levels in feed associated with animal health problems (Ross et al., 1991; 1992) and will handle regulatory actions on fumonisin-contaminated feeds on a case-by-case basis. Currently, the CVM recommends not feeding corn screenings to horses and replacing corn in horse diets with oats, barley, or other grains when possible.

**Vomitoxin**

Deoxynivalenol (vomitoxin), one of the trichothecone mycotoxins, was reviewed in a CAST report (1989) and by Beasley and Lambert (1990). Although all major commodity grain crops have been

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**Table 2. Summary of the domestic surveillance of feedstuffs for aflatoxin B1 by the FDA during fiscal years 1989–1992**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Total</th>
<th>ND</th>
<th>1-20</th>
<th>21-100</th>
<th>101-300</th>
<th>&gt; 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn</td>
<td>644</td>
<td>328</td>
<td>224</td>
<td>69</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Mixed diets</td>
<td>111</td>
<td>79</td>
<td>20</td>
<td>8</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Cottonseed b</td>
<td>106</td>
<td>44</td>
<td>36</td>
<td>14</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Grain byproducts</td>
<td>85</td>
<td>41</td>
<td>39</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other grains</td>
<td>47</td>
<td>43</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hay/silage</td>
<td>47</td>
<td>44</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Soybeans c</td>
<td>38</td>
<td>38</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peanuts d</td>
<td>28</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>27</td>
<td>22</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1133</td>
<td>647</td>
<td>337</td>
<td>105</td>
<td>26</td>
<td>18</td>
</tr>
</tbody>
</table>

aND = none detected.
bIncludes 73 cottonseed and 33 cottonseed meal samples.
cIncludes 27 soybean meal and 11 soybean samples.
dIncludes 15 peanut hull, 7 peanut skin, and 6 peanut meal samples.

**Table 3. Summary of the 1990 fumonisin survey**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Total no.</th>
<th>Fumonisin positive a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn grain</td>
<td>99</td>
<td>13</td>
</tr>
<tr>
<td>Corn screenings</td>
<td>85</td>
<td>85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean, ppm</th>
<th>Range, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn grain</td>
<td>2.4</td>
<td>1.2–3.2</td>
</tr>
<tr>
<td>Corn screenings</td>
<td>12.1</td>
<td>2.6–32</td>
</tr>
</tbody>
</table>

aLowest detectable level = .25 ppm.
reported to be contaminated, wheat seems to be the main grain affected in the United States. The FDA's surveillance program for vomitoxin indicated that vomitoxin levels were < 4 ppm in all samples tested except for wheat.

The CVM has updated the 1982 toxicology review of vomitoxin with regard to animal health and has determined that the guidance, issued in 1982, for vomitoxin in animal feeds is appropriate for wheat and other grains. The current guidance for wheat is 4 ppm for animal feed when included at a maximum level of 10% in either swine diets or pet foods, and when included at a maximum level of 50% in other animal diets.

The CVM cooperated with the CFSAN and the USDA's Federal Grain Inspection Service in 1991 in surveying winter and spring wheat for vomitoxin. Vomitoxin was detected in 97.1% (201 of 207) of the winter wheat samples and 58.2% (120 of 206) of the spring wheat samples (Table 4). The vomitoxin levels in the winter wheat samples were > 4 ppm in 18.4% of the samples, whereas only 2.4% of the spring wheat samples were > 4 ppm. The average amount of vomitoxin present in the winter wheat samples varied by state and within areas of the individual states. Only two of the 19 reporting states, both in the midwest, had average vomitoxin levels > 4 ppm. The average spring wheat vomitoxin level (.9 ppm) was substantially less than the average winter wheat vomitoxin level (2.4 ppm).

Table 4. Summary of the 1991 FDA vomitoxin survey

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Total no.</th>
<th>Vomitoxin positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean, ppm</td>
</tr>
<tr>
<td>Winter wheat</td>
<td>207</td>
<td>201</td>
</tr>
<tr>
<td>Spring wheat</td>
<td>206</td>
<td>120</td>
</tr>
</tbody>
</table>

Zearalenone

Zearalenone is a non-steroidal metabolite with estrogenic-like effects that was determined to be the cause of reproductive problems in swine being fed moldy corn (Stob et al., 1962). Zearalenone induces feminization of young pigs at dietary concentrations as low as 1 ppm. Higher concentrations (50 to 100 ppm) can interfere with conception, ovulation, implantation, fetal development, and the viability of newborns (CAST, 1989). The no-observed-adverse-effect level for reproductive effects in pubertal pigs was 60 μg of zearalenone-kg BW⁻¹-d⁻¹ (Kuiper-Goodman et al., 1987).

During FY 89–92, the FDA collected 161 samples for zearalenone analysis (Table 5). One hundred forty-eight samples contained no detectable levels of zearalenone, 12 samples contained between .07 and .15 ppm, and one imported soybean sample contained .45 ppm. The CVM has not established action levels for zearalenone in feeds and will handle regulatory actions on zearalenone-contaminated feeds on a case-by-case basis.

Gossypol

Gossypol is a yellow, polyphenolic pigment found primarily in the glands of cottonseed from the genus *Gossypium*. The gossypol content of cottonseed varies from approximately .002% (20 ppm) to 6.64% (66,400 ppm) and is believed to provide insect resistance to the plant. Cardiac, reproductive, pulmonary, and hepatic lesions have been observed in animals poisoned by gossypol. Nonruminants and immature ruminants (functionally undeveloped rumen) are particularly susceptible to gossypol toxicity (Morgan, 1989). However, there are cases of gossypol toxicity in
mature dairy cows and deaths of cows have been reported (Smalley and Bicknell, 1982; Randel et al., 1992).

A suspected case of gossypol poisoning in a large dairy herd was reported to the CVM in 1992. The finished feed of these dairy cows contained approximately 1,800 ppm of gossypol, and the cottonseed in the diet contained approximately 13,000 ppm of gossypol. The CVM recommended that the liver and kidney from any dairy cow that died be discarded before rendering. The liver contained the highest levels of gossypol (free + bound) in sheep (Morgan, 1990), swine (Sharma et al., 1966), and rainbow trout (Roehm et al., 1967).

Lupine Alkaloids

Lupine seeds are legumes that can be grown in many areas of the world, including regions where soybeans cannot grow. It was estimated that 8,000 ha of lupines were grown in Minnesota and Wisconsin during 1985 and 1986. Lesser acreages were grown in Michigan and Washington (Perez-Escamilla, 1987). Lupines contain less protein than soybean meal does, 33 vs 44%, and are lower in methionine. Some lupines contain quinolizidine and/or piperidine alkaloids that have produced teratogenic effects in cattle (Panter and Keeler, 1990).

The CVM has a working relationship with the Association of American Feed Control Officials (AAFCO). The AAFCO annually revises its Official Publication, which lists recognized feeds and feed additives. The CVM routinely reviews new definitions proposed for inclusion in the publication and makes recommendations on whether to include them, as well as how to word them. Under this arrangement, the CVM has been requested to review a definition for sweet lupine meal.

Sweet lupine meal is obtained from three species, *Lupinus albus* (white), *L. angustifolius* (blue), or *L. luteus* (yellow). Sweet lupine meal is the product resulting from the grinding of the entire plant, from the seeds after mechanical removal of the hulls, or from the flakes after removal of most of the oil by solvent extraction. The newer varieties of these three species reportedly contain < .03% total alkaloids. Currently, the CVM has the definition for sweet lupine meal under review.

Glucosinolates and Erucic Acid

The CVM has previously reviewed data on crambe and canola meal and has sanctioned their use with certain restrictions. Crambe meal was the subject of a food additive petition that was filed by the USDA and approved on June 5, 1981. Crambe meal (heat-toasted) is the seed meal of *Crambe abyssinica* obtained after the removal of oil from the seed and hull. The oil may be removed by prepress solvent extraction or by solvent extraction alone. The resulting seed meal is heat-toasted and shall contain not less than 24% CP, not more than 11% moisture, not more than 4% oil, and not more than 26% crude fiber. It is to be used only in the feed of feedlot cattle, and at a level not to exceed 4.2% of the diet. Further specifications on crambe meal are: glucosinolate calculated as epiprogoitrin, not more than 4%; goitrin, not more than .1%; nitrile, calculated as 1-cyano-2-hydroxy-3-butene, not more than 1.4%. At least 50% of the nitrogen shall be soluble in .5 M sodium chloride. Myrosinase enzyme activity shall be absent (CFR, 1992).

Canola is the name used to identify two plant species, *Brassica napus* and *B. campestris*, that contain low levels of erucic acid and glucosinolates. The CVM reviewed and did not object to the following definition for canola meal on January 18, 1989. Canola meal is a meal obtained from the whole seed of these two species after the removal of most of the oil by a direct solvent or prepress solvent extraction process. The oil from the seed shall contain < 2% of erucic acid. The solid component of the seed shall contain < 30 μmol of any mixture of 3-butenyl glucosinolate, 4-pentenyl glucosinolate, 2-hydroxy-3-butene glucosinolate, and 2-hydroxy-4-pentenyl glucosinolate per gram of air-dry, oil-free solid. Canola meal must contain a minimum of 35% CP, a maximum of 12% crude fiber, and a maximum of 30 μmol of glucosinolates per gram (AAFCO, 1992).

Implications

Toxic levels of many naturally occurring toxins are often produced only under certain environmental conditions. Identification and prevention of these environmental conditions will play an important role in minimizing the adverse effects of these toxins. However, because many of these environmental conditions cannot be controlled, surveillance testing of susceptible commodities will remain of vital importance. To ensure a safe and wholesome feed supply, the Center for Veterinary Medicine is continuing its surveillance testing and will strive to provide guidance on the increasing number of characterized naturally occurring toxins.

Literature Cited


