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Abstract: Nearly 25% of all crops worldwide are affected by mycotoxins while annual economic costs of mycotoxins to the U.S. agricultural economy is estimated to average \$1.4 billion. Since 1989, the population of dairy cows has significantly dropped while the milk production has remained relatively constant. As a result of higher dry matter intake (DMI), dairy cows these days produce a lot more milk than decades ago. Higher DMI has led to increased intake of mycotoxins and their negative effects in ruminants. Ruminants have a limited capacity to detoxify mycotoxins through the action of the rumen microbiota. Once this ruminal capacity is saturated, any excess mycotoxins consumed will result in negative effects in the animal. Consequently, in ruminants, mycotoxins and their effects have received less attention and it is only recently that increased consideration has been given to their effect on production, health status and reproduction. The rumen has long been considered relatively resistant to mycotoxins because rumen microflora, which contains dense populations of several species of bacteria, protozoa, was assumed to naturally detoxify mycotoxins. However, stressed dairy cows such as those that are sick and/or lactating may have an increased rumen passage rate and therefore may not be able to denature all of the toxins in contaminated feed. The use of mycotoxin deactivators under conditions where mycotoxins are thought to be present even at low levels appears to restore, to a large extent, productivity and profitability.

Key words: ruminants, mycotoxins, dairy cows, mycotoxins deactivators, milk production, dry matter intake, immune system

1. Introduction

The food and feed industry is affected by consumer requirements and national or international legislation. The complexity and globalization of the current food supply system provides additional pressure and food related risks. Therefore, it is of high importance to control microbiological and chemical hazards for ensuring food safety. Nearly 25% of all crops worldwide are affected by mycotoxins [1] while the annual economic costs of mycotoxins to the U.S. agricultural economy are estimated to average \$1.4 billion [2]. This clearly illustrates the impact of mycotoxins on food and feed production, and livestock farming. The associated health risk for human health is obvious. Aflatoxicosis in humans leads to toxic hepatitis with jaundice and, in severe cases, death [3]. Aflatoxin B_1 (AfB₁) has been extensively linked to human primary liver cancer in which it acts synergistically with HBV infection and was classified by the International Agency for Research on Cancer (IARC) as a human carcinogen (Group 1 carcinogen) [50]. Both deoxynivalenol (DON) and zearalenone (ZEN) have been linked to scabby grain toxicoses in the USA, China, Japan, and Australia. Symptoms include nausea, vomiting, and diarrhea. Fumonisin B_1 was associated with an illness outbreak in India with symptoms of acute abdominal pain and diarrhea. Fumonisins also have been implicated in esophageal cancer in China [51].

Mycotoxins are a structurally diverse group of compounds, mostly of small molecular weight, produced mainly by the secondary metabolism of

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some filamentous fungi, or molds, which under suitable temperature and humidity conditions may develop on various foods and feeds, causing serious health risks for humans and animals. Mycotoxins are secondary metabolites that have no biochemical significance in fungal growth and development; however, they vary from simple C4 compounds, e.g., moniliformin, to complex substances such as the phomopsins [4]. To date, more than 400 chemically diverse compounds have been recognized [56] in this group with new ones still being identified. Whilst not all of them have been studied in terms of their effects on animal health and productivity, the known mycotoxins are of increasing interest to animal nutritionists and producers. The ubiquitous presence of mycotoxins and their general effect on animal health and productivity have been repeatedly described [5-7].

Since 1989 the population of dairy cows has significantly dropped, while the milk production remained relatively constant. As a result of higher dry matter intake (DMI), these days dairy cows produce a lot more milk than decades ago. Higher DMI has led to increased intake of mycotoxins and their negative effects in ruminants [55]. In ruminants, mycotoxins can cause inter alia, decreased performance, feed refusal, poor feed conversion, diminished body weight gain, immunosuppression, reproductive disorders and residues in animal food products [8].

In monogastric species, the toxic effects of mycotoxins are often more pronounced and more readily observed. Ruminants have a limited capacity to detoxify mycotoxins through the action of the rumen microbiota. Once this ruminal capacity is saturated any excess mycotoxins consumed will result in negative effects in the animal. Consequently, in ruminants, mycotoxins and their effects have received less attention and it is only recently that increased consideration is given to their effect on production, health status and reproduction [9-11].

This review is intended to contribute to a better understanding of the effects of different mycotoxins in ruminants.

2. Type of Mycotoxins and Their Effects in Dairy Cattle

2.1 Mycotoxins Overview

A recent study investigated the occurrence of mycotoxins in European feed samples and concluded that 82% of the samples were contaminated with indicating mycotoxins, that mycotoxins are omnipresent [57]. In particular, mycotoxins are a danger because they might be produced under appropriate conditions in a wide variety of situations: either on the growing plant, or during harvesting (late harvesting, dry crops, slow storage filling, e.g., silage clamp, soil contamination), or later during storage (wet grain, poor silage packing, inappropriate fermentation of ensiled products) and transportation (poor hygiene, exposure to air/moisture, incorrect storage, temperature) [12]. Generally, the optimal temperature for mycotoxin production by many molds range between 20-30°C (68-86°F). The type of growing mold and toxins produced generally depend on a variety of plants and are influenced by environmental factors such as climatic conditions (temperature, humidity), soil characteristics (pH, composition, water activity, oxygen content, soil fertility), insect damage and possible competitive actions. Competitive actions mean that mycotoxins may also assist in associated growth of other fungi or microbes. Tropical and subtropical areas are more prone to aflatoxins exposure, while fusarium toxins mainly occur in more moderate regions. So called "storage fungi" (fungi that becomes a problem after harvest) including Aspergillus and Penicillium sp., may grow and produce mycotoxins even when moisture content vary between 14-18% and at temperatures that range from 10-50°C (50-122°F). Moreover, colonization of fungi and therefore toxin formation is often promoted by stress factors such as drought, poor fertilization, high crop densities, weed competition, mechanical damage etc., which weaken the plant's natural defense [13].

Many mycotoxigenic fungi can grow and produce their toxic metabolites under similar conditions resulting in co-contamination with mycotoxins in food and feed. In addition, blends of various raw materials in compound feed can increase the risk of feed pollution with several toxins. The complex diet of ruminants consists of forages, concentrates and preserved feeds and can be a source of diverse mycotoxins that contaminate individual feed components. Penicillium molds are commonly found because they are acid tolerant and have a low oxygen requirement [14].

Numerous combinations of mycotoxins may lead to interactive toxic effects. Of the potentially toxic mycotoxins identified so far, aflatoxins, fumonisins (representative: fumonisin B_1 [FB₁]), trichotecenes (representative: deoxynivalenol [DON]), patulin, ochratoxins, ergot alkaloids and zearalenone (ZEN) were referred as being the most prominent in concentrates, while preserved feeds - notably silages - contain predominantly patulin, mycophenolic acid and roquefortines [9]. Mycotoxins that are formed before ensiling are associated with molds that infect a crop during its growth in the field or with the endophytic molds that live as symbionts in, for instance, grasses of cereals (field mycotoxins). Field mycotoxins include trichothecenes, zearalenone, fumonisins, aflatoxins and ergot alkaloids. Development of typical fusarium mycotoxins is strongly influenced by weather conditions. Infection of plants by fusarium can take place via kernels, leaves, the stalk or infected seed. Soil and decaying plant residues in the field are the main source of fusarium spores and conidia [52].

Generally three groups of fungi are recognized as important for the production of mycotoxins with defined effects in livestock especially dairy cattle: Aspergillus, Fusarium and Penicillium. This discussion is limited to these three groups as they are the dominant ones. Table 1 presents the major mycotoxins produced by these three groups.

Contrary to general belief, fresh pasture grasses are not void of mycotoxins but have their own specific group of mycotoxins such as lolitrems, ergovaline, paspalitrems and associated ergot alkaloids and trichothecenes. It is of interest to note that the effects of these mycotoxins in ruminants are often better documented and understood than the classical mycotoxins that occur in concentrate or preserved feedstuffs [47, 53]. This is especially the case for lolitrems and ergovaline occurring on perennial ryegrass and tall fescue respectively.

While all of these mycotoxins have potential negative effects in ruminants, only the mycotoxins belonging to the aflatoxin group are subject to legal limits and thus strict quality control measures These limits and controls are primarily related to the risks to human health, since aflatoxins (aflatoxin B_1 and aflatoxin M_1) are known carcinogens [48]. However, other mycotoxins, notably ochratoxin A (OTA) and FB₁ are suspected of being carcinogenic and are under investigation [6].

Table 2 presents the current Food and Drug Administration (FDA) and European Union (EU) legal limits for aflatoxins and guidelines for maximum levels for other dominant mycotoxins. There is generally good agreement between the two directives but it is important to note that while the FDA is stricter on fumonisins, the EU is stricter on aflatoxin in feeds. However, the EU allows up to 20 ppb of aflatoxin B₁ in individual feedstuffs. The EU also provides guidelines for OTA, ZEN, T-2 toxin and HT-2 toxin.

2.2 Adverse Effects

Mycotoxins may produce adverse effects on key rumen bacteria [6, 10]. However, it is almost impossible to distinguish the origin of the exposure based on the pathology. Changes in health, behavior,

-	-			
Fungal	Mycotoxins			
genera				
Aspergillus	Aflatoxin, ochratoxin, sterigmatocystin,			
	fumitremorgens, fumigaclavines,			
	fumitoxins, cyclopiazonoic acid, gliotoxin			
Fusarium	deoxynivalenol, zearalenone, T-2 toxin,			
	fumonisin, moniliformin, nivalenol,			
	diacetoxyscirpenol, butenolide, neosolaniol,			
	fusaric acid, fusarochromanone,			
	wortmannin, fusarin C, fusaproliferin			
Penicillium	Ochratoxin, PR toxin, patulin, penicillic			
	acid, citrinin, penitrem A, cyclopiazonic			
	acid, roquefortine, isofumigaclavines A and			
	B, mycophenolic acid			
Claviceps	Ergot alkaloids			

 Table 1
 Major toxigenic fungi and mycotoxins in cattle feeds.*

* Table adapted from Ref. [7].

Table 2 FDA and EU legal limits for Aflatoxins and advisory guidelines on safe levels for other Mycotoxins in feeds for dairy cattle [15, 16].

Myctoxin	FDA	EU
Aflatoxin B ₁	20 ppb	5 ppb
Deoxynivaleol	5 ppm	5 ppm
Fumonisins	15 ppm	50 ppm
Ochratoxin A	ND	250 ppb
Zearalenone	ND	500 ppb

ND = Not determined

FDA = Food and Drug Administration; EU = European Union

productivity, and reproductive capacity are general in nature and not characteristic for a particular mycotoxin. For example, even small concentrations of AfB_1 may result in a significant decrease in feed consumption and decreased rumen motility [17], whereas T-2 toxin intake may provoke ulcers of the abomasum and sloughing of rumen papillae [47].

The primary effect may be associated with changes in the feeds caused by the simple presence of mold or rot. Any significant fungal growth in feeds or feedstuffs will generally render the ration less palatable and often dustier. Even low-level contamination can lead to feed refusals or reduced consumption. Whilst this primary effect on general palatability is immediate and probably the most frequent, at continued high levels of mycotoxin intake a secondary systemic effect through modification of the metabolism or general health status of the animal will emerge. Reductions in feed intake following relatively high doses of pure mycotoxins have been demonstrated [6]. Under normal feeding conditions, this requires that mycotoxins are absorbed and act at the tissue level.

2.2.1 Health and Reproductive Effects

Each mycotoxin causes specific effects on the health of the animal leading to characteristic symptoms. Many of the effects on health are based on the changes in the enzymatic and immune system. These changes are sufficiently specific enough to result in a characteristic etiology associated with each group of mycotoxins. Through their effects on the immune system, opportunistic infections can be the result of the simultaneous presence of a group of mycotoxins. Table 3 gives a general overview of the specific symptoms and effects on reproduction associated with overt cases of toxicosis associated with the various groups of mycotoxins.

The effects of mycotoxins depend on the ingested amounts, the number of toxins, duration of exposure to mycotoxins and animal sensitivity. However, the levels at which health or reproductive symptoms occur are not clearly established (and for some mycotoxins not at all) and the values provided are those at which the effects have been observed under mostly experimental conditions. The symptoms listed, possibly in an attenuated form, may be observed at lower levels, notably under practical conditions, when feedstuffs contain more than one fungus or mycotoxin. Likewise, lower concentrations will apply in the case of sensitive animals such as for high-producing cows or calves. While a considerable uncertainty remains regarding the effect of some mycotoxins on reproduction, the effect of aflatoxins, trichothecenes and zearalenone seem to be reasonably well established. The list in Table 3 is not exhaustive and refers to levels of mycotoxin concentrations that have significant health or reproductive effects. These levels are clearly higher than the levels of mycotoxins that cause the initial decreases in DMI and milk production.

Toxin (acute levels)	Acute symptoms	Reproduction effects	Reference
Aflatoxins > 100 ppb > 1500 ppb	Lethargy, ataxia, fat, accumulation liver, kidney, heart Decreased milk production	reduced	[18]
T-2 toxin > 600 ppb	Feed refusal, gastrointestinal lesions, intestinal hemorrhage	Reduced performance, absence of estrus	[19]
Deoxynivalenol > 1 ppm	Reduced appetite	-	[20]
Zearalenone > 400 ppb	Vaginal secretions, vaginitis, enlarged mammary gland	Reproductive failure, infertility, reproductive tract infections	[21]
Fumonisin B ₁ > 200 ppm	Liver lesions, reduced DMI	ND	[22]

Table 3Symptoms of prolonged or acute ingestion of somemycotoxins in cattle.

ND = Not determined, DMI = Dry matter intake

However, the summary in the table does not take synergistic responses into consideration.

2.2.2 Production and Milk Quality Responses to Dietary Mycotoxins

Acute and elevated levels of mycotoxins will depress milk production and lead to changes in milk composition [7, 22]. This appears true for all mycotoxins including those that are not routinely considered a threat to ruminants. However, it is not clear if this is primarily due to changes in DMI or changes in metabolism. A review of the published experiments indicates that relatively low levels of contamination do not always have an immediate effect on milk production or milk composition. The number of experiments specifically designed to evaluate the effect of mycotoxins on milk production and herd productivity are clearly limited. Most of the reports in the literature relate the acute effects of mycotoxins on health or the carry-over effects with potential harmful consequences for human consumption. Table 4 summarizes results from publications where relatively low levels of AfB₁, DON and ZEN were evaluated for their effect on milk production or milk composition.

With the exception of the trials conducted by Keese (2008) [23] there was no significant effect of mycotoxins on DMI, milk production or milk composition. The levels of aflatoxins used in studies [24, 25] are well above the legal or advisory levels

(Table 2) and at the level where liver fat accumulation occurs (Table 3). However, they are below 1600 ppb where milk production appears to be affected.

The DON trials shown in Table 4 used toxin levels that were generally close to the advisory levels for the mycotoxin. However, they did not lead to significant changes in milk production or milk composition even when levels were increased to 12 ppm [26, 27]. On the other hand, in two related experiments using a larger number of cows but similar type of diets, significant changes in DMI, milk production and milk composition were seen [23]. DON levels close to the EU guidelines actually increased DMI and milk production (P < 0.05) but had a significant negative effect on milk fat and milk protein. Also, and in agreement with observations under practical conditions, somatic cell counts (SSC) increased with DON levels [28]. A similar but non-significant response has also been noted [27]. It should be noted that the Keese (2008) [23] study had a longer duration and the experimental diets contained, apart from DON,

Table 4Summary of trials evaluating effects ofmycotoxins on milk production and milk composition.

Ref.	mycotoxin	concentration	DMI, kg/d or % BW	Milk, kg/d	SCC*1000
[24]	AfB ₁	468 ppb	27.8	15.9	110
		905 ppb	27.6	15.4	187
			NS	NS	ND
[25]	AfB ₁	112 ppb-no deactivators		34.19	
		112 ppb - deactivator-1		34.13	
		112 ppb - deactivator-2		33.73	
		112 ppb - deactivator-3		33.43	
				NS	
[26]	DON	0 ppm	16.3	22.8	
		6 ppm	15.9	21.4	
		12 ppm	16.3	21.5	
			NS	NS	
[27]	DON	0 ppm	24.6	33.4	67
		3.5 ppm	24	35.6	107
			NS	NS	NS
[23]	DON	0 ppm	16.9	28	89
		5.3 ppm	19	31	107
		0 ppm	16.85	24.15	96
		4.5 ppm	18	28.45	116
		III III	*	*	NS
[29]	ZEN	0 ppb	2.90% of BW	22.7	
-		250 ppb	2.79% of BW	23.2	
		500 ppb	2.85% of BW	22.9	
			b 100	2.10	

*P < 0.05; NS = P > 0.05

ND = Not determined, BW = body weight,

DON = deoxynivalenol, ZEN = zearalenone,

 $AfB_1 = aflatoxin B_1$,

SCC = somatic cell count

an average of 73 ppb of ZEN (versus approximately 35 ppb in the control diets). However at much higher levels of zearalenone, no difference in DMI or milk production was seen [29], and traces of ZEN in the total mixed ration (TMR) diets used were noted [27].

Not included in the table are the results from a study where it was found that 100 ppm of fumonisins decreased milk production in a herd during the first 70 days of lactation relative to a control that did consume a non-contaminated diet [22]. These levels that were reported to be accompanied by mildly affected livers reduced milk production by an average 6 kg/head/day. The primary cause of this decrease was thought to be due to reduced DMI.

From this limited review, it seems clear that at low levels of mycotoxin contamination immediate changes in DMI and milk production may be small but that a prolonged exposure will affect milk production and composition. This includes the effect on SCC associated with low levels of mycotoxin contamination reflecting the above mentioned effects on immune competency and the greater exposure to infectious threats.

2.2.3 Immune responses

Mycotoxins will provoke changes in immune response. AfB₁, trichothecenes, and OTA, as well as their metabolites are known to have immuno-toxic and/or suppressive properties acting principally on the cellular immune system [30]. Even low-level exposure to mycotoxins may results in immuno-suppression leading to increased incidence of infectious diseases without overt symptoms of mycotoxicosis [31]. In terms of health effects, the most important consequences of mycotoxins in dairy cows will be during the most critical period of the cow's life: the transition period and subsequent early lactation when the immune status is already compromised and the risk of metabolic diseases is increased.

The increased release of corticosteroids together with the immunosuppressive action of mycotoxins will increase the sensitivity of the cow to external infections and opportunistic infections. This in turn will complicate a diagnosis of mycotoxicosis, especially for effects of low levels of mycotoxins which seem to aggravate the immune status. The immune response in cows fed a feed naturally contaminated with fusarium toxins (primarily DON at 3.5 ppm and only traces of ZEN) was reported [27]. At this low level of contamination, there was no effect on milk production or milk composition, but immune parameters were significantly affected (Table 5). Low levels of trichothecene contamination decreased neutrophil phagocytosis reflecting the reduced capacity to mount a non-specific immune response in cows fed the contaminated diet. The simultaneous increase in the primary antibody response (mainly IgG and IgA) without a change in secondary response was considered indicative of a disruption of the intracellular signaling within leukocytes. A more recent study showed that natural, low-doses of ZEN and DON induced an acute autoimmune response in dairy cows [32]. In the same study, high levels of DON and low levels of ZEN were determined in the blood plasma of affected animals.

3. Rumen Fermentation

The rumen has long been considered relatively resistant to mycotoxins because rumen microflora was assumed to naturally detoxify mycotoxins [33]. However, stressed dairy cows such as those that are sick and/or lactating may have an increased rumen passage rate or overwhelmed rumen microflora and therefore not able to denature all of the toxins in contaminated feed [34]. The same is for calves which are more susceptible to mycotoxins as their rumens are not completely developed.

A major factor in the absorption of mycotoxins in ruminants is rumen fermentation. Table 6 provides a summary of the degree of rumen mycotoxin bio-conversion and transfer to milk.

Density).				
Group	Phygocytic	Primary	Secondary	
Group	activity	response	response	
Control	64.0	0.86	1.2	
Contaminated	53.3	1.15	1.3	
SEM	2.7	0.075	0.060	

Table 5Effect of Diets on Neutrophil Phagocytic Activity(%) and on Antibody Response to Ovalbumin (Optical Density).

Table adapted from [27]

SEM = Standard error mean; *P < 0.05

Table 6RumenBioconversionandTransferofMycotoxins from Feed to Milk*

Mycotoxin	Main product	Reduction of	Estimated
	metabolism	biological potency	milk
aflatoxin B ₁	aflatoxicol	minor	0-12.4µg/1
	aflatoxin M ₁ ^a	minor	2.0-6.2%
fumonisin B1	unchanged	unchanged	0-0.05%
ochratoxin A	ochratoxin-α	significant	n.d. ^b
T-2 toxin	various	significant	DON: trace
deoxynivalenol	de-epoxy-	significant	DOM: 4-24%
(and related	DOM-1		
trichothecenes)			
zearalenone	α -zearalenol	none	0.06-0.08%
patulin ^c	unchanged	unchanged	n.d.

*Table adapted from [9]

^a aflatoxin M_1 is not a product of rumen metabolism — originates from hepatic metabolism of aflatoxin B_1

^b n.d. = Not determined

^c patulin is not altered in the rumen but metabolized in the liver DOM-1 = deoxynivalenol metabolite-1

Microbial fermentation is known to modify the concentration and chemical structure of most, if not all, mycotoxins. In some cases, this bio-transformation results in a partial detoxification such as in the case of DON or OTA [11, 23, 26]. More specifically, in the rumen OTA is rapidly converted into the less toxic ochratoxin- α by the rumen microbes (especially protozoa) and only minimal amounts of intact OTA are absorbed. Contrary to this statement, a review concluded that despite the obvious pathological effects, the common view that OTA is degraded completely by an active rumen microbial population under all circumstances does not hold true [35]. At concentrations described to be safe, OTA occurs systemically in significant amounts [36, 37].

DON is thought to be converted almost completely into the less toxic DOM-1 (the de-epoxidized metabolite of DON). However, the effects of DON in the literature are not unanimous. Field reports support an association of DON with poorly performing dairy herds [38, 39] and the feeding of DON-contaminated feedstuffs has been associated with reduced feed intake and milk production as well as changes in milk composition [26]. On the other hand, recent studies have shown that elevated DON concentrations (up to 3500 ppm) did not cause significant adverse health effects. but increased postprandial ammonia concentrations [10,23]. The increase in ammonia concentration could reflect an increased microbial protein breakdown, or alternatively, a reduction in utilization by rumen microbes. Antimicrobial activities of fusarium mycotoxins have been observed [40].

The effects of DON and OTA on the animal cannot be excluded. Clearly high levels of DON or ochratoxins will "saturate" the rumen system and lead to higher amounts of mycotoxins reaching the small intestine and thus blood and liver. Furthermore, fumonisins seem to pass the rumen unaltered and an intake of up to 1.3 g by Jersey cows for about 2 weeks led to decreased feed intake and milk production, and elevated serum enzyme activity of the liver enzyme (aspartate aminotransferase - AST) [41].

Mycotoxins create a cascade of events by destabilizing the rumen environment leading to endotoxin formation and ruminal wall leakage. Toxins with an antibiotic effect can disturb the rumen microbiota to the point that they cannot properly process toxins. The silage mycotoxins may, through their antibiotic effects on rumen flora, result in common pre-harvest mycotoxins such as DON, ZEN and tremorgens becoming a health problem. Mycotoxins can produce a variety of symptoms in dairy cattle that are vague and nonspecific. Mycotoxins absorbed into the systemic circulation will have various effects and can result in an activation of the immune system [42]. Often there are no clinical signs but subclinical production losses that have a serious financial impact on farm profitability [54].

Mycotoxins that are absorbed from the gastrointestinal tract affect primarily the enzyme systems [43]. As in the rumen, the mycotoxins are transformed in the various tissues involved in absorption or metabolism but most notably in the liver While conversion and/or partial and kidney. detoxification occurs in these tissues, mycotoxins will at the same time affect the metabolism and health of these tissues (and thus the entire organism). The effects of various mycotoxins on specific enzyme functions have been determined, but these reports are not exhaustive and considerable uncertainty remains as to the minimal concentrations that result in significant effects.

Table 7 summarizes the effects of a limited number of mycotoxins on liver enzymes activities, metabolic products and events. The majority of the identified changes concern aflatoxins but some effects of ochratoxin are listed, clearly showing that this mycotoxin is capable of altering liver metabolism in cattle. On their own or in conjunction, these events reflect the potential of mycotoxins to cause hepato-cellular traumas and to seriously affect liver metabolism as well as that of other vital organs.

At low subclinical levels the effects of individual mycotoxins may not be noticeable and threshold levels for metabolic changes have not been determined.

Table 7Documented effects of mycotoxins on liverenzymes activities, metabolic products and events.

Mycotoxin	Enzyme	Change	
AfB ₁	Lactate dehydrogenase Aspartate		
	transaminase		
	Pseudo-cholinaesterase		
	Glutamic oxaloacetic		
	transaminase		
	Sorbitol dehydrogenase	Increase	
OTA and T-2 toxin	L-alanine 2 oxoglutarate	merease	
	Alkaline phosphatase		
	L γ-glutamyltransferase		
FB1	Aspertate aminotransferase		
	Alanine aminotrasferase		
Mycotoxin	Metabolic Products or Events	Change	
AfB ₁	Total bilirubin		
	Tri-iodothyronine (T)	Tri-iodothyronine (T) Increase	
	Preno-plasmic lesions		
	Hormone binding capacity for T		
	Albumin		
	Fibrinogen	Decrease	
	Pro-thrombin	Decrease	
	Pseudo-cholinesterase		
	β-lipoproteins		
FB1	Hepatic glutathione	Decrease	
	Ca ²⁻ concentration	Increase	

* Table is adapted from [49]

However, it is likely that effects of individual toxins are additive. This is especially the case for high producing, early lactation dairy cows where the liver is already heavily stressed and the animal is in a reduced immuno-competent stage. Interference with normal liver function will naturally result in an increased risk of metabolic diseases as well as other metabolic changes leading to decreased production and/or detrimental effects on health.

4. The Role and Efficiency of Mycotoxin Deactivators in Dairy Rations

The widespread presence of mycotoxins along with their synergistic negative effects makes the control of these toxins in dairy rations necessary. Under practical conditions, it appears to be virtually impossible to eliminate mycotoxins from dairy diets. Consequently, measures should be put into place to control or minimize their development. However, this is rarely sufficient and dietary treatments should be included to assure the reduced metabolic activity of mycotoxins. For the latter a number of mycotoxin deactivators are available.

In a publication of Stroud (2006) [44], 60 Holstein lactating cows (producing 13.61-54.43 kg milk) were fed AfB₁-contaminated corn grain (800 μ g/kg) for a minimum of 3 days. If recalculated on total mixed ration (TMR) basis, the AfB₁ contamination was 170 ppb (Table 8). In this table, a positive value indicates a reduction in aflatoxin transfer associated with use of the feed additive, while a negative value indicates an increase in aflatoxin transfer associated with use of the feed additive.

Four of the eight additives resulted in significant reductions (P < 0.05) ranging from 34.98-40.39% for milk AfM₁ concentration, 36.36-52.28% for milk AfM₁ secretion, and 34.45- 48.44% for AfM₁ transfer. DMI was significantly reduced (P < 0.001) by the consumption of AfB₁, while milk production was not affected during the same time period. Neither DMI nor milk production were affected by the addition of

 Table 8
 Percent reductions in milk aflatoxin concentration,

 milk aflatoxin excretion and milk aflatoxin transfer due to
 the addition of adsorbent products[#].

Additive (0.5% of DM)	Milk AfM ₁ concentration, %	Milk AfM ₁ excretion, %	AfB ₁ transfer from feed to milk, %
MTB-100 [®]	-7.81	-6.71	-3.60
Ultra Sorb [®]	7.36	7.85	7.59
Mexsil®	6.62	8.00	7.19
Novasil+®	40.39*	42.59*	42.09*
Toxynil [®] Plus	34.98*	36.36*	34.45*
Condition Ade [®]	7.85	13.79	13.23
Astra Ben [®]	48.90*	52.28*	48.44*
Mil White®	46.49*	48.46*	44.55*

[#]Table adapted from [44]

*Values are significantly different from zero (P < 0.05) DM = dry matter; AfM_1 = aflatoxin M_1 ; AfB_1 = aflatoxin B_1

treatment products to the diet when compared to the (P > 0.05). Adsorptive control performance (adsorption capacity, selectivity, etc.) of the feed additives can be very different even if they belong to the same mineralogical group. A Limitation of clay feed additives is that they accumulate in manure and may be contaminated with toxic metals and dioxins which requires rigorous testing before use. Clay-based feed additives may only bind mycotoxins other than aflatoxins to a limited degree [45]. Commercially available products based on the yeast cell wall, even of the same brand, were shown to differ in type and content of mannan-oligosaccharide (MOS) and β-D-glucan, as well as in ash content and mineral composition [46]. Stroud (2006) [44] is in agreement with Fruhauf et al. (2012) [46], who stated that differences in the content and type of mineral clay components account for different binding capabilities of AfB₁. In Stroud's (2006) [44] study, the adsorption rate at increasing amounts of the toxin revealed big differences between "pure" mineral binder feed additives and yeast-cell-wall-based products with mineral components added. Based on these results, it can be concluded that so called "pure" mineral binder feed additives were much more effective in vivo adsorption of AfB₁ than organic binder feed additives based on MOS and β -D-glucans.

Selection and preparation of the components of a deactivator will determine their effectiveness in capturing and eliminating the different mycotoxins.

The difference in technology applied allows for important differences among mycotoxin deactivators. In the case of dairy cattle, they are primarily evaluated on their capacity to reduce aflatoxin excretion in milk (a fairly objective and direct measure of mycotoxin binding). It is thus imperative when choosing a mycotoxin deactivator to not only pay attention to the composition and reactivity of the components of the deactivator components, but to also understand which mycotoxins are targeted. Selecting an effective deactivator will reduce the aflatoxin contamination of milk (and thus reduce the risk of the condemnation) and at the same time reduce the effects of mycotoxins on immunity and organ metabolism. Α broad-spectrum efficient mycotoxin deactivator will reduce the effects of aflatoxins but also of less-polar mycotoxins.

4.1 Economic Evaluation of Mycotoxin Deactivators

Production losses due to mycotoxin contamination are clearly subject to a great number of factors and uncertainties. The losses are hugely variable in time and difficult to estimate. However, the effects of the contamination are often significant and can be long lasting.

The economic impact of mycotoxins is difficult to estimate even after an outbreak of mycotoxicosis. The most important losses are probably those associated with long-term under-performance. Estimates of this can be made on the basis of the information provided above. Thus a simple simulation model was developed that allows for the estimation of production and financial losses due to the long-term sub-clinical impact of mycotoxins in dairy cattle.

The following assumptions were made:

• No change in dry matter intake or loss in milk production volume.

A decrease of 0.4% — point in milk fat and 0.1%
— point in milk protein.

• No penalizing change in SCC, thus assuming almost ideal sanitary conditions of cows.

• An increase in calving interval of 60 days and an increase in inseminations by 10% along with an increase in veterinary cost of 10%.

• Application of an efficient mycotoxin deactivator restores losses by 80%.

Under these assumptions the model predicts that on a herd-basis mycotoxin contamination will cause losses in milk income of approximately 12% and that the addition of an efficient mycotoxin deactivator will restore losses to just 3% under the income level achieved in the absence of mycotoxins. Total farm revenue changed with similar percentages but variable costs or the operation costs increased by 3% in the presence of mycotoxins. The annual return over variable costs decreased from 14.5 to 7.6% due to the presence of mycotoxins.

The cost of the mycotoxin deactivator for a continuous treatment throughout lactation and dry period was estimated at \$ 28/cow. The application of this mycotoxin treatment lead to an improvement in returns over variable cost to 12.3% due to an improvement in revenue of \$ 225/cow. Consequently the return on investment (ROI) of the use of a mycotoxin treatment is approximately 7:1.

The assumptions associated with these simulations are considered to be rather close to the current US operational conditions. The model can be adapted to other economic situations — for instance those applicable to the EU, Middle East or Latin America. However, following a number of simulations. it appears that the economic returns of mycotoxin deactivators under conditions where contamination is suspected will easily be equal or superior to the rather conservative estimates obtained with these analyses.

5. Conclusions

A large number and variety of mycotoxins are present in plant material and especially in stored products. Their effect on animal health and performance has been demonstrated and is now well accepted. This is as much the case for ruminants, especially under stressful conditions (e.g., the transition period for cows), as it is for monogastric animals (e,g., calves). High levels of milk production will increase susceptibility and thus effects of mycotoxins.

While dairy cows appear to be able to cope with some mycotoxins through their rumen microflora, in reality this flora may contribute to the problem by increasing activity of the metabolites and thus the negative effect on animal and human health. The mycotoxin by-product resulting from the rumen, or escaping fermentation, will affect the metabolism and immune status of the cow. Immediate effects of low-level contamination on milk production, milk composition and reproduction are subtle and not always readily recognized. The decrease in production and reproductive efficiency can be reversed through the use of efficient mycotoxin deactivators. A review of such deactivators on the market indicates that there is a substantial difference in the efficiency of mycotoxin deactivators. The use of such deactivators under conditions where mycotoxins are thought to be present, even at low levels, appear to restore to a large extent productivity and profitability.

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