Newsletter

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> EDITORIAL

Scientific literature is replete with information on the effects of individual mycotoxins in various livestock species, but what about different mycotoxin combinations? This question arises from the fact that concentrations of individual mycotoxins associated with poor livestock performance and/or disease symptoms in commercial operations are usually lower than those reported to cause toxic effects in controlled research studies.

In the field, the response of affected animals to exposure to more than one mycotoxin can be the same as the response from each toxin individually (additive), more than the predicted sum of the responses from each individual mycotoxin (synergistic) and, more rarely, less than the predicted response from each toxin individually (antagonistic).

Currently, there is an increased awareness among animal producers regarding co-contamination of feedstuffs with mycotoxins and the responses that may occur in animals consuming such feedstuffs.

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Mycofix® product line

The presence of different mycotoxins in feed may lead to synergistic interactions between multiple mycotoxins. Synergistic effects occur when the combined effects of two mycotoxins are much greater than the individual effects of each toxin alone (example: 2+2 ≥ 5).

Synergistic effects between mycotoxins

Synergistic effects in poultry

Aflatoxin B_1 (AFB_1) and ochratoxin A (OTA) are involved in most of the studies regarding synergistic interactions between mycotoxins in poultry. AFB_1 as a hepatotoxin and OTA as a nephrotoxin were fed simultaneously to broiler chicks and the toxicity was synergistic (4). Besides higher nephrotoxicity when these two mycotoxins were fed in combination, broiler livers contained markedly higher concentrations of OTA upon combined administration with AFB_1 than with OTA alone (11). The feeding of diets containing both aflatoxins (Afla) and OTA to chickens from hatching to 3 weeks of age resulted in significantly greater relative weight of gizzards and kidneys as well as less weight gain compared to either mycotoxin fed singly (6). AFB_1 acts in synergism with T-2 toxin as well. Both mycotoxins affect protein synthesis, but by different mechanisms, which finally leads to synergistic effects between them (5). Body weight gain in 21 days old broilers was reduced by 16 % by aflatoxin (Afla) alone, 11 % by diacetoxyscirpenol (DAS) alone, and 36 % by the combination of Afla and DAS indicating a significant synergistic interaction between them (9). Cyclopiazonic acid (CPA) at 50 mg/kg (ppm) interacted synergistically with Afla at 3.5 mg/kg feed and adversely affected growth of treated birds (13).

The combination of OTA and CPA significantly reduced the levels of serum total protein, albumin, and cholesterol, whereas uric acid, triglycerides, and creatine kinase activity were increased by the combination of OTA and CPA. The effect resulting from the interaction of OTA and CPA in combination was additive (3). Citrinin and penicillic acid were found to potentiate the nephrotoxic and carcinogenic effects of OTA, respectively (14). Fusaric acid (FA) was shown to be mildly toxic to embryos and when a relatively nontoxic concentration of it was combined with graded doses of fumonisin B_1 (FB_1), a synergistic toxic response was obtained (1). Total body weight gains, final body weights and FCR of 3-week old broilers were significantly reduced by a deoxynivalenol (DON) / T-2 toxin combination but were not significantly affected by the toxins singly. The incidence and severity of oral lesions induced by T-2 toxin was increased in the DON/T-2 toxin combination which indicates a synergistic effect between these two mycotoxins (12). Chicks (Columbia x New Hampshire) were given dietary concentrations of purified FB_1 at 274 and 125 mg/kg, and moniliformin (MON) at 154 and 27 mg/kg. FB_1 and MON, both alone and in combination, produced dose-responsive clinical signs, reduced weight gains and increased the mortality in chicks. Finally, additive effects were noted when the toxins were given in combination (7). The increased toxicity in poultry fed the combination of FB_1 (300 mg/kg) and T-2 toxin (5 mg/kg) can best be described as additive, although some parameters not altered by FB_1 or T-2 singly, were significantly affected by their combination (8). The additive effects (reduced BW gains, feed intake and impaired chicken immune function) of co-contamination of OTA and T-2 toxin have been reported (10; 2; 15).

Synergistic effects in pigs

Sows and gilts are highly susceptible to mycotoxins, which greatly affects their health and productivity. In pigs, a great concern is focused on the synergistic interactions between DON and FA (18, 21), DON and FB_1, Afla and OTA and Afla in combination with T-2 (18, 4).

Additional adverse effects were identified by the combinations between T-2 toxin and OTA; DON and MON; T-2 toxin and fumonisins (FUM); FUM and MON; DAS and FUM; Afla and OTA; Afla and T-2 toxin (18, 19). Several studies have been carried out with combinations of mycotoxins and the amplification of toxicity in animals has been confirmed. A study in piglets with concentrations ranging from 10 to 40 mg/kg of FB_1 and 20 to 39 mg/kg of OTA resulted in sudden death of piglets aged between 13 and 18 weeks after several days of contamination. Piglets presented pathological signs of both toxins such as pulmonary edema, kidney and liver lesions, resulting from the combination between OTA and FB_1 (17). Zielonka *et al.* (2009) reported the difficult examination of histopathological lesions caused by DON intoxication because of the common, often synergistic, reaction of this mycotoxin with other toxins, such as zearalenone (ZON).

Results of another experiment performed in weaned piglets with a combined administration of FB_1, DON, T-2 and OTA in quantities normally present in feeds showed suppression of antibody formation only after the combination between OTA and FB_1 or DON, which did not occur when OTA was administered alone (16).

Additionally, a trial was conducted to determine the effect of feeding diets contaminated with DON and FA in swine. In this trial Smith et al., (1997) found out that feeding FA contaminated diets to immature swine increased the toxicity of DON. A synergism was thus confirmed between these two mycotoxins (24). Feeding a diet contaminated with the combination of Afla and FB_1 to growing barrows resulted in significantly reduced final body weight and body weight gain, with a clear higher toxic response when both mycotoxins were acting together (20). Results of a trial to evaluate the effects of FB_1 and Afla on

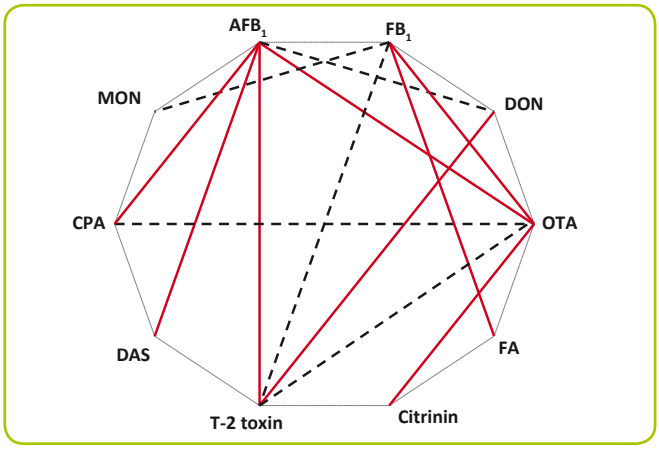

Figure 1. *Synergistic and additive effects of mycotoxins in poultry*
synergistic effect
additive effect

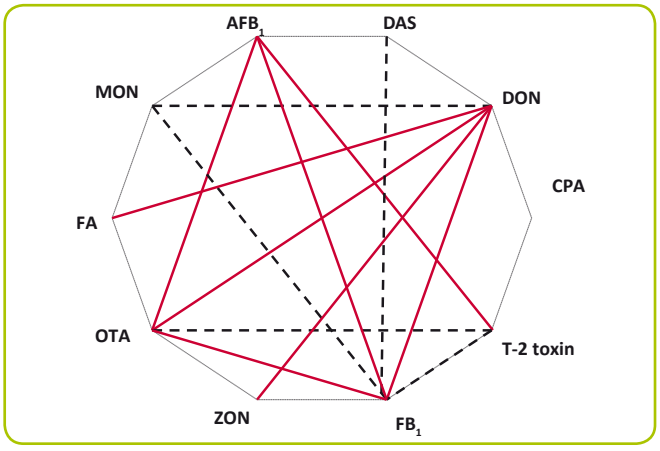

Figure 2. *Synergistic and additive effects of mycotoxins in pigs*
synergistic effect
additive effect

Legend:
AFB_1 – Aflatoxin B_1
FB_1 – Fumonisin B_1
DON – Deoxynivalenol
OTA – Ochratoxin A
ZON – Zearalenone
FA – Fusaric acid
DAS – Diacetoxyscirpenol
CPA – Cyclopiazonic acid
MON – Moniliformin

swine alveolar macrophages confirmed that both FB_1 and Afla are immunomodulatory agents although they exert their effects via different biochemical mechanisms and that respiratory tract exposure to mycotoxins, suppresses not only pulmonary but also systemic host defense systems (23).

Synergistic effects in ruminants

The negative effects of mycotoxins on ruminants are less known than in monogastrics (28, 29). Quite often problems due to subclinical levels of mycotoxins are expressed just as minor increases in "common cow problems", therefore the cumulative and/or synergistic effects of mycotoxins and metabolites are unknown, but likely to aggravate the symptoms observed in the field (26).

Ruminant diets generally include both forages and concentrate, which can increase the probability of multiple mycotoxin contamination (27, 29, 30, 31).

According to D'Mello *et al.* (1999) there are synergistic effects between DAS and Afla in lambs and it is suspected that in dairy cows there are possible additive or synergistic effects on fertility between ZON and T-2 toxin, causing ovarian dysfunction. In general, ruminants are highly exposed to mycotoxins coming from the most variable sources of forage crops, silages and by-products. This leads to a great mixture of mycotoxins with diversified combinations and possible synergism. Further investigation is needed to state reliable conclusions about synergistic effects in ruminants.

Table 1. *Mycotoxin combinations in livestock*

Mycotoxins	Species tested	Effect	References
AFB_1 + OTA	Broilers	synergistic	Huff *et al.*, 1988a
AFB_1 + T-2 toxin	Broilers	synergistic	Huff *et al.*, 1988b
AFB_1 + DAS	Broilers	synergistic	Kubena *et al.*, 1993
AFB_1 + CPA	Broilers	synergistic	Smith *et al.*, 1992
OTA + CPA	Broilers	additive	Gentles *et al.*, 1999
Citrinin + OTA	Broilers	synergistic	Stoev *et al.*, 2002
PCA + OTA	Broilers	synergistic	Stoev *et al.*, 2002
FA+ FB_1	Chicken embryos	synergistic	Bacon *et al.*, 1995
MON + FB_1	Broilers	additive	Javed *et al.*, 1993
T-2 toxin + DON	Broilers	synergistic	Rottinghaus, 1989
T-2 toxin + FB_1	Turkey	additive	Kubena *et al.*, 1995
T-2 toxin + OTA	Broilers	additive	Kubena *et al.*, 1988; Garcia *et al.*, 2003; Wang *et al.*, 2009
AFB_1 + OTA	Pigs	synergistic	D'Mello *et al.*, 1999;Huff *et al.*, 1988a
AFB_1 + FB_1	Growing pigs	synergistic	Harvey *et al.*, 1995; Biing-Hui Liu *et al.*, 2002
AFB_1 + T-2 toxin	Pigs	synergisitic	D'Mello *et al.*, 1999; Schwarzer 2009
DON + FA	Pigs	synergistic	Raymond *et al.*, 2005; D'Mello *et al.*, 1999
MON + FB_1	Pigs	additive	D'Mello *et al.*, 1999; Schwarzer 2009
MON + DON	Pigs	additive	D'Mello *et al.*, 1999; Schwarzer 2009
OTA + DON	Pigs	synergistic	Speijers *et al.*, 2004
OTA + FB_1	Weaned piglets	synergistic	Creppy *et al.*, 2004 ; Speijers *et al.*, 2004
OTA + T-2 toxin	Weaned pigles, piglets	additive	Speijers *et al.*, 2004
DON + ZON	Weaned piglets	synergistic	Zielonka *et al.* 2009
FB_1 + DAS	Pigs	additive	D'Mello *et al.*, 1999; Schwarzer, 2009
FB_1 + DON	Pigs	synergisitc	D'Mello *et al.*, 1999; Huff *et al.*, 1988a; Speijers *et al.*, 2004
FB_1 + T-2 toxin	Pigs	additive	D'Mello *et al.*, 1999; Schwarzer, 2009
DAS + Afla	Pigs	synergistic	D'Mello *et al.*, 1999
ZON + T-2 toxin	Lambs	possible synergism	D'Mello *et al.*, 1999
ZON + T-2 toxin	Dairy cows	possible synergism	D'Mello *et al.*, 1999

Legend: AFB_1 = Aflatoxin B_1; OTA = Ochratoxin A; DAS = Diacetoxyscirpenol; DON = Deoxynivalenol; FB_1 = Fumonisin B_1; CPA = Cyclopiazonic acid; MON = Moniliformin; PCA = Penicillic acid; FA= Fusaric acid; ZON = Zearalenone

CONCLUSION

Why are livestock animals responding to (low) mycotoxin levels which are not supposed to cause any harm if only scientific studies are taken into account? The fact that one fungus is able to produce more than one mycotoxin; that more than one fungus is usually infecting one commodity and that an animal diet is usually a combination of feedstuffs reiterate then importance and occurrence of multiple mycotoxins and their synergistic effects.
All this, in combination with the fact that every year several new mycotoxins are "discovered", tells us that a great deal of attention must be given to this issue. No matter how strong the nutrition and health program are, if livestock farms are not able to keep mycotoxins under control, they will never achieve the greatest genetic potential from the animals or make the greatest profit. Mycotoxin risk management is the key in managing the peak performance of the livestock business.

References available upon request!

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