Toxinor
Wide Spectrum Mycotoxin Binder

Technical Department

NOREL Animal Nutrition

NOREL ANIMAL NUTRITION

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INTRODUCTION

Mycotoxins are products of a secondary metabolism of fungi and can often be toxic for the animals that consume them. Mycotoxins can accumulate during the transport and storage of cultivated cereals whenever there are favourable conditions for their production. Intoxication by mycotoxins is called mycotoxicosis and the symptoms include allergic reactions, poor reproduction, and loss of appetite, suppression of the immune system, falling production parameters and even death. It is clear that the presence of mycotoxins in animal feeds can produce large economic losses.

CONDITIONS AND ENVIRONMENT THAT FAVOUR THE PRODUCTION OF MYCOTOXINS

Although certain conditions permit the growth of mycotoxin producing fungi, mycotoxin contamination there does necessarily present and it is always advisable to determine their presence if there is any suspicion of contamination.

Not all fungi have the capacity to produce mycotoxins and the ones that do generate them when they have insufficient nutrients, that enable them to compete with the bacteria and other fungi for those nutrients, producing secondary metabolites which that have a toxic capacity. There are many factors that intervene in fungal proliferation and the contamination of crops with mycotoxins; the main factors are:

- Soil type
- Susceptibility of the crop
- Maturity of the grain when harvested
- Temperature and moisture
- Damage to the crop: mechanical or that by insect and/or birds
- Type of storage.

Inadequate management of the crop, one example of this that stands out would be too much moisture when stored in open air, can give rise to the production of mycotoxins. The most common mycotoxin – producing fungi are: *Aspergillus*, *Alternaria*, *Fusarium* and *Claviceps*.

Among the various types of human and animal feeds that can be contaminated by mycotoxins are: maze, sorghum, barley, wheat, other cereals, cotton seed and its derivatives, chestnuts, peanuts and vegetables, etc.

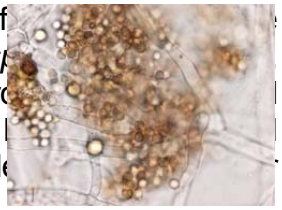
It is calculated that approximately 25% of world agricultural harvests have considerable mycotoxin contamination although this percentage rises in hot and tropical countries (e.g. 41% of samples analysed in Brazil were contaminated – this was from the period between 1986 y 2000).

When fungi produce mycotoxins they can remain in the environment even after the microorganism that produced them has disappeared or been eliminated. This is due to the fact that most mycotoxins show a very high resistance to heat or chemical and biological degradation; also they are highly soluble if in aqueous or highly absorbent mediums.

TYPES OF MYCOTOXINS RELEVANT TO ANIMAL PRODUCTION

Over 300 types of mycotoxins are known and they vary in origin, structure and toxic characteristics. The known mycotoxins are those from fungal metabolism and those that appear from structural changes to naturally occurring mycotoxins within the animal after digestion. This last group are not present in vegetable samples but only in meat products and other animal derivatives. Within the groups of mycotoxins that have a more significant effect on animal health and economic aspects are the following:

AFLATOXINS



Aflatoxins constitute the best known and most studied group of essentially produced by certain strains of *Aspergillus flavus*, *Asp* *Aspergillus nomius* and *Aspergillus niger*. They are generally pro damp environments and can be detected in cereals and cereal meals, manioc, silages, forages, nuts spices, milk and milk de human foods. There are 4 important groups of aflatoxins:

- Aflatoxin B_1
- Aflatoxin B_2
- Aflatoxin G_1
- Aflatoxin G_2

Also there are those types of aflatoxins produced from the naturally occurring ones by the metabolism of the animal:

- Aflatoxin M_1
- Aflatoxin M_2

They affect every animal species but the most relevant in economical terms are the young, which appear more susceptible. Aflatoxin M1 is a metabolic of aflatoxin B1 and can be of high importance in cattle because it can accumulate in milk and milk derivatives.

ZEARALENONE

Produced mainly by *Fusarium roseum* but it can be synthesised by other types of *Fusarium*, like *F. culmorum* and *F. graminearum*. It is found in maize and other cereals and their by-products (hay and silages), in conditions of high moisture. The toxin mimics the effects of oestrogen because it produces estrogenic syndrome that can gravely affect the animal's reproductive system.

OCHRATOXINS

Mainly produced whilst the food or feed are in storage by *Penicillium* and *Aspergillus* (especially *P. viridicatum* and *A. achraceus*). Particularly affects cereals and vegetables that have had an inefficient drying process. Some of the major toxins in this group are the highly toxic ochratoxin A, and ochratoxin B. Monogastrics are more affected by these than ruminants because the latter have a certain protection from the action of the rumen.

TRICHOTHECENES

This is a family of about 150 different mycotoxins that are structurally similar. They are produced by a variety of strains from the genus *Fusarium*. Among the more well known toxins in this group are:

-T-2 Toxin
- Deoxynivalenol or vomitoxin

The principal syndrome that these cause is gastroenteritis, which can affect digestive, nervous and circulation systems as well as the skin.

T-2 Toxin

Produced by *Fusarium tricinctum* and *F. roseum*. It has been found in pre-harvested maize and feeds containing maize. It is a toxin of the A group of trichothenes, very cytotoxic, causing lesions in the gastrointestinal mucosa with haemorrhages and inflammation. It inhibits the protein synthesis and affects the maturing of haematopoietic cells leading to leucopoenia and immune suppression. Infected animals are highly sensitive to secondary infections.

Deoxynivalenol o vomitoxin

Produced by *Fusarium graminearum* – mainly found in wheat and barley but also in maize. It accumulates in the growing cereal infected by the fungi especially in wet and cool climates. The same as other trichothecenos, it causes immune-depression, which heightens the risk of infection by pathogens in the infected animal. As the name suggests the animals reject the feed with frequent vomiting.

FUMONISINS

Group of toxins most recently discovered in South Africa. Produced by *Fusarium moniliforme* and *F. proliferatum* in hot and temperate climates that affects maize especially; there are at least 10 mycotoxins that form the A and B group of fuminosins – equines and birds are most affected.

MYCOTOXICOSES

Intoxicated animals can have a variety of symptoms due to the injurious effects of the mycotoxins. These symptoms are often confused with the other harmful agents but there are standard ways of recognising mycotoxin intoxication.

- Similar symptoms exist in different animals or groups on the same farm/ feedlot without there appearing to be signs that there has been any contact or transmission between them.
- The symptoms do not respond to antibiotic treatment.
- The symptoms are seasonal or associated with certain batches of feed or crops.
- Appears in the raw materials or feeds that have fungal contamination.

BOVINE CATTLE

The heath problems are mainly from the aflatoxins, trichothecenes and zearalenone groups.

- **AFLATOXICOSIS:** Produces effects such as low feed intake, diarrhoea, acute mastitis, lowering of milk production, respiratory problems, hair loss, liver damage (high blood alkaline phosphatase), rumen dysfunction because of poor cellulose digestion and inefficient proteolysis and biosynthesis of the VFA. Traces of aflatoxins (specifically AFB1 and AFM1) are secreted into the milk. Young animals are far more susceptible than adults.

- **TRICHOTHECENOS:** The effects are less severe than in other animals because active rumination allows a detoxification but in cattle farmed for milk production vomitoxin can cause a reduction in feed intake, a lowering of milk yield, higher somatic cell count and reproduction problems. The T2 toxin produces a loss of appetite, curtailed growth, gastroenteritis, intestinal haemorrhages, poor milk production and suppression of the immune system.

- **ZEARALENONE:** Produces estrogenic response, low reproduction levels and abortions; also lack of appetite, poor milk production, vaginitis and the swelling of mammary glands in heifers.

PORCINE

Very sensitive to micotoxicosis, especially aflatoxins, trichothecenes and zearalenones.

- **AFLATOXINS:** Produce very serious effects in suckling piglets, pigs in the growing and finishing stages and breeding sows. It has detrimental effects on feed consumption, food conversion and weight gains. It can cause hepatitis, nephritis and systemic haemorrhages. The intoxication can be transmitted from dam to the young via the uterus affecting their immune system.

- **TRICHOTHENES:** Vomitoxin is the toxin responsible for 'damp- grain intoxication', whose symptoms are refusal of the food due to poor palatability, poor weight gains, more sensitivity to infections, digestive upsets that include vomiting and diarrhoea, reproductive immaturity of gilts and a high litter mortality rate. In addition, piglets can suffer intestinal inflammation and acute diarrhoeas. T2 Toxin can produce ovary and uterus lesions and infertility even when present in tiny amounts.

- **ZEARALENONE**: This causes heavy economic losses due to estrogenic-syndrome. Pigs are most susceptible to this toxin, especially females. Clinical signs begin with poor FCR, changes in animal behaviour and changes in the size of organs. In females the mammary glands become inflamed, vaginal oedemas occur, prolapses to the anus and vagina, ovary and uterus atrophy, and reduction in body size plus high probability of abortion or sterility. In males there is also the swelling of mammary glands, testicular atrophy, prepuce oedema and low sperm quality.

- **OCHRATOXINS:** The effects that ochratoxin A produces are: low feed conversion, general weakness and poor growth plus high water intake and high metabolic production of nitrogen residues i.e. urea and ureic acid due to renal failure (in pigs this will implicate the appearance wet beds). Also liver damage is possible and lower immunity against viruses and bacteria. Fertility problems and defects are produced and as the toxin can pass through the placenta barrier teratogenic defects could occur. The meat of affected animals continues to be infected even after slaughter, as the toxin can exist in the carcass for long periods of time due to its capacity to bond with blood serum proteins. For this reason destroying the carcasses is advisable before they can be consumed.

- **FUMONISINS:** Fuminosin B1 in pigs, although they are less affected than other monogastrics, causes lung oedemas, hydrothorax plus heart and respiratory problems.

BIRDS

The avian species is highly sensitive and susceptible to mycotoxins, a sensitivity made all the stronger with stressful production practises. The effect of the toxins vary according to age, type of bird and nutritional management in that the production phases of higher sensitivity (first days of life, changes in diet, handling etc) can give massive intoxication levels from relatively small doses of mycotoxins.

- **AFLATOXINS:** Produce high economic losses in broiler, layer, duck and turkey production. Continued consumption of low levels of toxin cause elevated death rates just as much as high toxin levels. Symptoms include fatty liver and kidney failure, bone and foot problems and a higher sensitivity to coccidiosis and other infections (especially salmonellosis), and a decline in the effect of commercial vaccines. Also, low haematopoietic production associated with haemorrhages and blotches, low pigmentation of the carcass and pale looking eggs. Causes a lower number of birds reaching slaughter specifications and a drop in egg production both in terms of quality and quantity. In the growing phase there is a higher death rate and the actual rate of growth is diminished.

- **TRICHOTHECENES:** Vomitoxin is associated with low feed consumption in layers and broilers. It causes acute haemorrhaging, increases the formation of urinary calculi, neural toxicity and irritation of the upper gastrointestinal tract. T-2 Toxin is one of the most pernicious for birds. It can cause beak and intestinal lesions, lower feed consumption, weight loss, lack of plumage and sudden drops in egg production and the eggs that are produced are much more fragile. Finally you can observe weight loss and death. In turkey production there will be poor growth, beak lesions and immune-suppression.

- **OCRATOXINS:** Toxicities with ochratoxins produce higher death rates, lower growth rates and refusal of feed. In broiler production ochratoxin A produces apathy, hunching - up of birds, diarrhoeas, neural abnormalities. It affects layers and egg quality greatly, lowering the quality of the shell and increasing the number of 'bloody' eggs.

- **FUMONISINS:** Fuminosin B1 produces loss of bodyweight, diarrhoeas, hepatitic necrosis and lower FCR.

PREVENTION OF MICOTOXICOSIS

There is a system of prevention and control of fungi that begins with the harvest and handling of crops that are to be used in the production of animal feed (a HACCP system is recommended from a point before harvest up to the manufacture of concentrates). This system involves treatment of the feeds and examination of the finished products and animals that consume them.

In the farming industry the application of certain 'rules' is recommended with the aim of avoiding intoxification by mycotoxins in production animals:

- ✓ **Provide non-contaminated feeds (which includes control of suppliers).**
- ✓ **Conserve raw materials and concentrates with a water content of between 9 and 12%, that will give water activity levels of Aw < 0,60.**
- ✓ **Maintain a routine of cleanness wherever possible and hygiene in the feed factory and on the farm.**
- ✓ **Fumigate against insects, mites, rodents, bacteria and fungus.**
- ✓ **In periodical routine treatment of the entire installation use mixes of wide spectrum mould inhibitors active against yeasts, rusts and mildews.**
- ✓ **Have a ventilation/airing system using dry, cold air.**
- ✓ **Use mycotoxin absorbents.**

MYCOTOXIN ABSORBENTS – TOXIN BINDERS

Nowadays there are a variety of products available on the market for animal feed with a 'toxin binder' capacity, **and the risk of mycotoxins in the animal organism is reduced or avoided**. For practical purposes, these products minimize the risk of mycotoxicosis that could be derived from the use of contaminated feeds.

The active substances in these products are distinctly different. Their functions are described as follows:

Phylosilicates, tectosilicates and diatomea sands

Phylosilicates are commonly named "clays", which are broadly defined as mineral components with a diameter less than 2 μm.

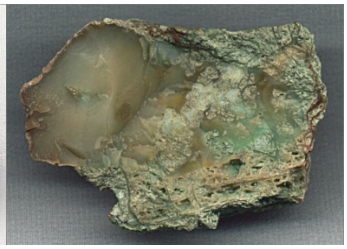
The most common used clays for animal feeding are smectite, kaolin, talc, sepiolite and atapulgite. The latter are classified according to structure and mineral composition. They normally show laminate structure, except sepiolite and atapulgite, which are pseudo-laminate or tubular.

There are non-clay based silicates, such as zeolite (tectosilicates), diatomea sand (from organic origin), perlite and vermiculite (from volcanic origin), which are used as toxin binders.

Indirectly, such molecules are able to bind the toxins' reactive polar groups, therefore avoiding their diffusion into the medium. The anti-aflatoxin effect has been proven the combined by their capacity to bind β-cetolactone or α-bislactone groups contained in the aflatoxin molecule. Equally, they can bind other mycotoxins depending on their chemical structure. There are several hydroscopic clays, which reduce the available water and delay the growth of the alfatoxin-productive fungi.


Kaolin


Talc


Smectite

- **POLYSACCHARIDES**

  They are glucomannanes components obtained from the structural wall of yeasts. Their surface is very reactive against active mycotoxin groups and improves the animal's immune system. Natural compositions present a huge capacity for resistance to digestive degradation; therefore bonded mycotoxins are not reabsorbed inside the animal.

- **ENZYMES**

  Oxidases, catalases, lactonases and sterases can all potentially reduce mycotoxins to inactive forms. Unfortunately there is only a small amount of scientific literature to prove their efficiency.

- **OTHER ADSORBENTS**

  There are certain distinct absorbents capable complexing molecules with phenol rings, and acid or alkaline toxin complexes such as mycotic toxins, thanks to the reactivity and amphoteric properties of their molecular structure. Some of the latter molecules can be especially effective against toxins of bacterial origin, e.g. botulinus toxin. PVPP is one of the absorbents authorized by the European Pharmaceutical Association for use in humans and effective at low inclusion rates.

All the above components are able to significantly reduce the mycotoxin concentration in feed. Additionally, it is widely recommended to include antioxidants and hepatic protective elements (organic selenium, vitamin E, ascorbic acid, glutathione, methionine and cystine, etc.) in order to minimize the residual toxins' negative and toxic impact.

TOXINOR

TOXINOR is the wide spectrum mycotoxin binder for animal feed manufactured by NOREL. It has a high specific surface value to increase the absorption of mycotoxins.

PROPERTIES

- ✓ **TOXINOR** is active against aflatoxins, trichothecenes (vomitoxin and T-2 toxin), zearalenone, ochratoxins and fumonisins.
- ✓ Reduces the impact of mycotoxicosis in contaminated feed of production animals, guaranteeing their optimum growth and productivity.
- ✓ Regulates the speed of intestinal transit, improving feed digestibility, reducing excreted nitrogen compounds and increasing the carcass yield**.**
- ✓ **TOXINOR** is effective at low concentrations so avoiding any reduction of the nutritional components of the ration.
- ✓ Guarantees a longer shelf life of feeds.
- ✓ It is stable and active at various different levels of pH and temperature.

APPLICATION RATE

Prevention: 1 Kg/Mt
High contamination: up to 5 Kg/Mt.

SPECIES

Recommended for: porcine, avian and rumiants.

In Pigs:

- Reduces the incidence of hepatitis, nephritis and haemorrhaging produced by aflatoxins.
- Prevents diarrhoeas and intestinal upsets caused by trichothenes.
- Prevents estrogenic syndrome that can appear when zearalenones is present in the feed.
- Protects against nephropathies and teratogenic effects of ochratoxins.

In Poultry:

- Reduces the incidence of fatty liver, renal failure, osseous alterations, haemorrhaging and immune deficiency caused by aflatoxins.
- Prevents intestinal irritations and neuro-toxicity from trichothecenes.

- Prevents apathy, shivers and hunching-up caused by ochratoxins.
- Reduces the risk of diarrhoeas and hepatic necrosis due to fumonisins.

In Rumiants:

- Prevents acute mastitis, the presence of M_1 toxin in milk, rumen dysfunction, respiratory and liver problems and hide /hair alterations caused by aflatoxins.
- Prevents increases in somatic cells, immune-suppression and digestive traumas produced by trichothecenes.
- Annuls the estrogenic response from the ingestion zearalenones.

TOXINOR

MYCOTOXIN BINDER WITH WIDE SPECTRUM OF ACTION FOR ANIMAL FEEDING

DESCRIPTION

Mycotoxin binder made of inorganic minerals to avoid mycotoxicosis and extending and preserving feed life.

USE

Use is exclusively reserved for animal feeding manufacture.

COMPOSITION

Kieselgur, bentonite-montmorillonite minerals and carrier.

INDICATIONS

Mycotoxicosis treatment and prevention in productive animals.
Active part against *aflatoxin, trichothecenes* (T2 toxin and vomitoxin), *zearalenone, ochratoxin and fumonisins.*

USE AND DOSAGE

Supplying directly by mixing in animal feed or overall diary ration .
Maximum dosage: 2% feed
Recommended dosage: 0.1 to 0.5% feed (1 to 5 Kg per feed ton.).

DOSIFICACIÓN

Dosis máxima..... 2% del pienso
Dosis recomendada ..... de 0,1 a 0,5% del pienso
(1 a 5 Kg. por tonelada de pienso)

PACKAGING

25 Kg. Bags

STABILITY

1 year from manufacturing date.

STORAGE

Once the container is opened, the product should be kept in a dry and fresh place.

TRIALS

In Vitro EVALUATION OF A COMMERCIAL MYCOTOXIN BINDER: EFFICIENCY OF TOXINOR ® AGAINST: ZEARALENONE, AFLATOXIN B1, AFLATOXIN B2, AFLATOXIN G1, AFLATOXIN G2, AFLATOXIN M1, OCHRATOXIN, DEOXYNIVALENOL (DON), T-2 TOXIN Y FUMONYSINE B1.

Biological Science Faculty; Microbiology Department III. Complutense - University of Madrid.

Essay:

Mycotoxin adsorbent is prepared at 5% in 0.1 M sodium phosphate buffer at 4.5 and 7 pH. With a final volume of 10 ml, 2 ppm mycotoxins are added. After 1 hour and 37 AC agitation, the sample is centrifuged and the separation is collected and frozen.

The absorbent alone and free mycotoxin samples are considered as control groups:

	Quantity	Hydrated with	Stock	Added	Final concentration	
Aflatoxin B1	5 mg	3 ml	1.66 mg/ml	12 µl	2 ppm	Non soluble
Aflatoxin B2	5 mg	3 ml	1.66 mg/ml	12 µl	2 ppm	Non soluble
Aflatoxin G1	10 mg	3 ml	3.33 mg/ml	6 µl	2 ppm	Soluble
Aflatoxin G2	5 mg	3 ml	1.66 mg/ml	12 µl	2 ppm	Almost soluble
Aflatoxin M1	10 µg	1 ml	10 µg/ml	50 µl	0.05 ppm	Soluble
Deoxynivalenol	5 mg	3 ml	1.66 mg/ml	12 µl	2 ppm	Soluble
Fumonisine B1	5 mg	3 ml	1.66 mg/ml	12 µl	2 ppm	Soluble
Ochratoxin	1 mg	1 ml	1 mg/ml	20 µl	2 ppm	Soluble
T-2 toxin	5 mg	3 ml	1.66 mg/ml	12 µl	2 ppm	Almost soluble
Zearalenone	10 mg	3 ml	3.33 mg/ml	6 µl	2 ppm	Non soluble

All separated samples were analysed in the Complutense University of Madrid - checking the micotoxin presence in each.

Sampling characteristics:

The mycotoxin absorbent effect was tested in 10 toxins under two different pH conditions and compared with each control group.
The aflatoxin B1, B2, G1, G2 and ochratoxin determination were made in the Arbitral laboratory, within the department managed by Dr. Agustín Pons and Dr. Belén Patiño Álvarez. Aflatoxin M1, fumonisine B1, DON, T-2 toxin and zearalenone were estimated by Rosmer laboratory (ST. Louis, USA).

Material and methods:

Materials:

For aflatoxin determination, the following instruments were used:

- HPLC Liquid chromatograph (High Liquid Performance) of Perkin-Elmer (LC Series 4).
- Column oven, automatic injector from Agilent Technologies (series 100).
- Fluorescent marker of Perkin-Elmer (LS 4).
- Post-column reactive bomb from Waters S.A. (Reagent Manager).
- Chromatography column: ODS-2 of 250 x4.6 mm with 0.5 µm of particle size Inertsil Sugelabor.
- Immuno-affinity columns of Ochraprep and Aflaprep, from Tecnova S.A. (Rhone Diagnostics).
- All reactive and solvents belong to “reactive quality” and HPLC and Sigma norm.
- Alfa-Q water quality from Milippore.

Methodology:

- Aflatoxin analysis was carried out by HPLC inverted phase, post column, iodine derived column and fluorescence detection. Mycotoxin are previously obtained from the samples with the immuno-affinity columns. Detection limit is 50 µg · L^{-1} (ppt) for aflatoxin B1 and 1 µg · L^{-1} (ppb) for the rest of aflatoxins (B2, G1, G2).

- Deoxynivalenol, T-2, Fumonysine B1, Aflatoxin M1 and Zearalenone analysis is made by HPLC in Romer laboratories (ST. Louis, USA). Detection limits are 0.1 ppm for DON, 50 ppb for T-2, 0.1 ppm for Fumomisine B1, 0.05 for aflatoxin M1 and 35 µg · L^{-1} (ppb) for the rest.

- Ochratoxin A (OTA) analysis was made by HPLC inverted phase and fluorescence detection, previous extraction of immuno-affinity columns. Detection limit is 6 µg · L^{-1} (0,006 ppb).

Results:

The residual mycotoxin level for the absorbent at two different pHs and compared with the control groups are described as follows:

Conclusion Table

TOXINOR ABSORBENT LEVEL at 0.50% inclusion rate and 2ppm micotoxin concentration.

% TOXIN ELIMINATION BY TOXINOR

	pH 4.0	pH 7.0
AFLATOXIN B1	**99,86**	**99,64**
AFLATOXIN B2	**99,96**	**99,80**
AFLATOXIN G1	**100,00**	**100,00**
AFLATOXIN G2	**99,87**	**99,74**
AFLATOXIN M1	**100,00**	**100,00**
OCHRATOXIN A	**93,25**	**95,69**
ZEARALENONE	**100,00**	**100,00**
FUMONYSINE 1	**100,00**	**69,30**
VOMITOXINE	**0,00**	**46,00**
T-2 TOXIN	**90,10**	**92,61**

DETERMINATION BY: COMPLUTENSE UNIVERSITY OF MADRID
ARBITRATION LAB AT MINISTRY OF AGRICULTURE

Conclusions:

- TOXINOR absorbency capacity was excellent against all aflatoxins groups, achieving levels close to 100% and without significant differences according to pH value.
- TOXINOR is capable of absorbing 100% of fumonisine B1 at pH 4, however at pH 7, it drops to 70%.
- T-2 toxin adsorbent capacity is 92.6% at pH 7 and 90% at pH 4.
- With Ochratoxin, it is important to emphasise how well “optimum yield absorbency” is reached at pH 7 and also how in general (but in particular for ochratoxin A) “optimum mycotoxin extraction of the sample ” is achieved at the same pH.
- The results for Zearalenone can be classified as excellent, with the lowest values possible within the detection range.
- The poorest results were observed for Deoxynivalenol for both pHs, with 44% adsorbent capacity at pH 7 and zero at pH 4.

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