Moniliformin, a *Fusarium* mycotoxin

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Moniliformina, una micotoxina de *Fusarium*

Resumen. La moniliformina (MON), micotoxina producida principalmente por *Fusarium proliferatum* y *F. subglutinans*, es un contaminante natural de maíz y otros cereales con niveles de hasta 530 mg/kg. Es un potente cardiotóxico e inmunosupresor pero no parece ser carcinogénico. Salvo en peces, en el resto de las especies animales la MON, a dosis altas (100-200 mg/kg alimento en aves y cerdos), causa falla cardíaca y muerte súbita. Se ha sugerido su implicación en la cardiopatía "Keshan disease" asociada al consumo de cereales contaminados con mohos y MON en China. La nixtamalización reduce los niveles de MON un 70%, a pesar de ello fue detectada en tortillas de maíz comerciales. La contaminación de alimentos con MON, su co-ocurrencia con aflatoxinas, fumonisinas, ocratoxinas, tricotecenos, zearalenona y sus efectos toxicológicos aditivos con algunas micotoxinas, sugieren que los organismos reguladores, que aún no han establecido límites para MON, incrementarán su vigilancia. Por esta razón, se requerirán estudios adicionales respecto de la toxicidad y del nivel de exposición a esta micotoxina.
Palabras clave: moniliformina, *Fusarium*, maíz.

Abstract. Moniliformin (MON), mycotoxin produced mainly by *Fusarium proliferatum* and *F. subglutinans*, is a natural contaminant of maize and other cereals with levels up to 530 mg/kg. MON is a potent cardiotoxic and immunosuppressive compound, but it does not appear to be carcinogenic. With the exception of fish, MON causes heart failure and acute death at high doses (110-200 mg MON/kg diet in birds and barrows) to many animal species. It has been suggested that MON is involved in a cardiopathy known as Keshan disease occurring in China where maize contaminated with molds and MON is consumed. Nixtamalization reduces MON content up to 70%, in spite of that it has been detected in commercial maize tortillas. No regulations exist for this mycotoxin but the presence of MON in food, its co-occurrence with aflatoxins, fumonisins, ochratoxins, trichothecenes, zearalenone, and its toxicological additive effects with some mycotoxins, show that regulartory bodies might increase surveillance on this area. For that reason, further studies on toxicity and the level of exposure to this mycotoxin will be required.
Key words: moniliformin, *Fusarium*, maize.

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Introduction

Moniliformin (MON) is a *Fusarium* mycotoxin produced mainly by *F. proliferatum* and *F. subglutinans*. Since 1982, when it was first reported as a natural contaminant, MON has been found as a natural contaminant in maize and other cereals in different parts of the world. There is a limited amount of data on the effects of MON on animal species. MON has not received yet much attention because it does not

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appear to be carcinogenic and relatively high amounts appear to be necessary to cause significant toxicological effects. Its stability and fate during processing is also poorly studied so that the extent of consumer exposure is uncertain. The discovery of MON, fungal sources, natural occurrence, toxicity, decontamination strategies, and methods of analysis will be discussed in this paper.

First reports

MON was first reported in 1973 [12] from a corn culture that has been inoculated with *F. proliferatum* isolated from corn kernels in the U.S.A., but that had been misidentified as the closely-related species *F. moniliforme* Sheldon NRRL-5860 (ATCC-26263), thus the name MON. During the studies that drive to the elucidation of the structure of MON, the strain lost the ability to produce the toxin. MON was finally isolated and chemically characterized from *F. nygamai* Burgess & Trimboli NRRL-6022 (ATCC-12763) isolated from millet in Nigeria 43 64. This strain has been reported to produce large amounts of MON [65]. Subsequently, another strain, *F. proliferatum* (Matsushima) Nirenberg NRRL-6322 isolated from raw cotton in North Carolina in the U.S.A. has been used in the production of MON for toxicity studies [6, 43].

The chemical structure of MON, unusual for a natural product, is shown in Figure 1. MON or semisquaric acid are trivial names for 3-hydroxy-3-cyclobutene-1,2-dione. Due to the low pKa value (< 1.7) of the free acid, MON does not occur as such in nature but as a water soluble sodium or potassium salt [65]. Spectroanalytical and physicochemical properties of MON have been published [46, 62, 65]; part of these data has been reviewed by Sydenham *et al*. [67]. The synthesis of the free acid had been reported even before MON was characterized as a mycotoxin [24, 64].

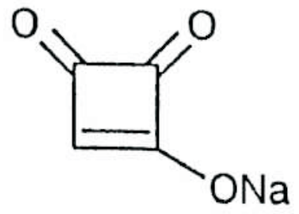

Figure 1.- Chemical structure of monili formin

Fungal sources

MON is produced at least by thirty *Fusarium* species, isolated from different substrates and geographical areas [3, 14, 19, 58], some of which are listed on Table 1 and Table 2. Since F. *proliferatum* and *F. subglutinans* often occur in maize and *F. avenaceum* in wheat, MON can be expected to be present in these crops. This conclusion was already proven to be correct [3, 9, 36]. Although the capacity to synthesize MON is widespread in the genus *Fusarium*, the production of this toxin has been found to be irregular among the *Fusaria*. There exist variations in the percentage of strains that accumulate the toxin among different species as well as in the amounts produced. Culture conditions also cause differences in the amount of MON found. Normally, the mycotoxin-producing ability of *Fusarium* strains is tested on maize kernels but the optimal conditions for toxin production in culture are not known [29]. On rice at 25 ºC for 21 d, MON yields up to 16,000 ppm have been reported for *F. proliferatum* isolated from dairy cattle maize suspected of causing refusal-to-eat syndrome [74]. Differences have been found when the results of the occurrence of specific fungal species such as *F. subglutinans* and the levels of MON found in naturally contaminated samples were compared [42]. Apart from the diverse capabilities of the isolates to produce the toxin, these differences could be due to a different colonization capacity

Table 1. *Fusarium* species producing moniliformin.

Section *Liseola*	*F. anthophilum, F. dlaminii, F. napiforme, F. nygamai, F. proliferatum, F. subglutinans, F. verticillioides*[1]
Section *Arthrosporiella*	*F. concolor, F. semitectum*
Section *Discolor*	*F. culmorum, F. sambucinum*
Section *Elegans*	*F. beomiforme, F. oxysporum, F. redolens*
Section *Gibbosum*	*F. acuminatum, F. equiseti*
Section *Martiella and Ventricosum*	*F. solani*
Section *Roseum*	*F. arthrosporioides, F. avenaceum*
Section *Sporotrichiella*	*F. chlamydosporum, F. sporotrichioides,F. tricinctum*

[1]Formely *F. moniliforme*.

of the host tissues. A same fungal strain can synthesize MON in isolation but also in combination with other mycotoxins such as fumonisins (FB), beauvericin (BEA), enniantins (ENN), fusaproliferin (FP), fusarins, trichothecenes, and zearalenone (ZEA). Besides, a same plant tissue can be colonized by different mycotoxigenic species so that the possibility of the co-occurrence of MON with other mycotoxins exists as is shown in the next section.

Natural occurrence

The natural occurrence of this mycotoxin is well documented. It was first reported in 1982 from moldy maize obtained from Transkei-South Africa at levels of 16-25 ppm [71]. Since then, MON has been informed as a natural contaminant in maize and other cereals (rice, oats, rye, wheat, and triticale) in different parts of the world (Table 3). Recent data suggested that MON could also be found in barley [4]. The concentrations of MON found vary from trace (< 0.05 ppm) to low (< 50 ppm), intermediate (50-200 ppm) or high (> 200 ppm) levels [36]. MON contamination is higher in maize than in other substrates and in visibly infected samples. The maximum level of MON recorded (530 ppm) was detected in *Fusarium*-damaged maize in Poland [8, 10, 36]. Possibly because of being a minor mycotoxin and because of lack of suitable analytical methods until recently, data on the occurrence of MON in food are not readily available. In the Transkei, concentrations up to 12 ppm occurred in maize intended for human consumption [66]. The available data from developed countries show that contamination of foodstuffs is much lower (= 3 ppm) from that of the Transkei and indicate a low level of exposure. Although there exists the possibility for sporadic significant contamination, the Ministry of Agriculture, Fisheries and Food of the U.K. [45] recommended a continued monitoring program to determine any trends in the MON levels. Likewise, as is detailed in Table 3, the co-occurrence of MON with other mycotoxins such as FB, BEA, fusarin C, ZEA, and trichothecenes has been reported. Scudamore *et al*. [60] reported particularly interesting. Their analysis of milled maize products, destined for incorporation into animal feed stuffs in the U.K., showed 60% of samples contaminated with concentrations up to 4.6 ppm of MON. Moreover, in addition to MON, in maize screenings and meal, eleven more *Fusarium* toxins with a total loading of ca 45 ppm were found.

Table 2. Toxicogenic capacity of strains of *Fusarium* isolated from different substrates and countries.

	Source	Mycotoxins[1]	Ref.
Section *Liseola*			
	pre-harvest maize infected with *Fusarium* (Italy)	MON, BEA, FB	[41]
F. proliferatum	maize from corn-growing regions in a survey of corn disease (Canada)	MON, FB, fusarins	[44]
	maize associated with a case of swine pulmonary edema (U.S.A.)	MON, BEA, FB	[56]
	maize dairy cattle feed suspected of causing refusal -to-eat syndrome (U.S.A)	MON, FB[2]	[74]
	rice (different geographies)	MON, FB	[15]
	rice, from fields with *Fusarium* damage, during a harvesting season (U.S.A.)	MON, BEA, FB	[1]
	bananas (different geographies)	MON, FB	[27]
F. subglutinans	pre-harvest maize, visibly damaged by *Fusarium* and highly infected with *F. subglutinans,* from maize fields (Poland)	MON, BEA	[42]
	maize ear rot (Poland)	MON, BEA, FP	[29]
	maize from the main production area during the harvest season (Peru)	MON, BEA	[40]
	maize from small fields (a non major production area) during a crop season (Argentine)	MON, BEA	[72]
	cereals (maize mainly) -[3]	MON, BEA	[28]
		MON, BEA, fusaric acid	[54]
F. verticillioides	maize from the major maize production area (Argentine)	MON, FB	[53]
	maize and sorghum (U.S.A.), bananas (Thailand)	MON, FB	[33]
	rice	MON, BEA	[56]
	bananas (different geographies)	MON, FB	[27]
Fusarium section *Liseola*[3]	maize from grain marketing board centers (Zimbabwe)	MON, FB, ZEA	[50]
Other sections			
F. acuminatum	medicago seeds (South Africa), soil (Denmark, Poland)	MON, ENN	[39]
F. avenaceum	cereals (Norway)	MON, BEA, ENN	[49]
F. sambucinum	soil samples of pasture (New Zealand)	MON, NIV, ZEA	[2]

[1]BEA (beauvericin), ENN (enniantins), FB (fumonisins), FP (fusaproliferin), MON (moniliformin), NIV (nivalenol), ZEA (zearalenone).
[2]This strain also produced a new meatbolite phytotoxic to *Lemna minor.*
[3] Not specified by the authors.

Toxicity

MON can produce plant growth regulating and phytotoxic effects on plant systems [12, 73]. MON also proved to be toxic to several animal species. Among them are cockerels (LD_{50} = 4 mg/kg, oral) [12], ducklings (LD_{50} = 3.68 mg/ kg, oral) [30], rats (LD_{50} = 50 mg/kg and 41.57 mg/kg, oral for males and females respectively) [30], mice (LD_{50} = 24 mg/kg, ip) [6], and mink (LD_{50} 2.2-2.8 mg/kg, ip) [47]. Muscular weakness, respiratory distress, cyanosis, coma, and death are symptoms described in animals [30]. The pathology associated with MON toxicity in most species has primarily involved myocardial changes. Thiel [69] found that exceedingly low

Table 3. Natural occurrence of moniliformin (MON) in different cereals and countries.

Cereal infected	Country	MON (ppm)	Other mycotoxins[1]	Ref.
	Austria	? 20 (21/25)[3]	-[4]	[34]
maize[2]	Italy	200[5] (1/4)	BEA, FB_1	[41]
	Poland	30-530	-	[10]
	Poland	66-530	-	[8]
	Poland	4.2-399 (20/20)	-	[63]
	Poland	17-425[5] (8/14)	BEA	[42]
	Poland	4.2-530 (57/57)	-	[36]
	Poland	0.45-8.53[5] (6/12)	BEA	[28]
	Transkei	16-25 (2/2)	DON, ZEA	[71]
maize	Austria	? 2	-	[18]
crops	Austria	0.22[5] (15% samples)	DON, FB, ZEA	[35]
	Canada	0.06-0.2[5] (2/12)	DON	[59]
	Germany	? 0.65 (25/58)	-	[68]
	South Africa	? 0.39 (2/20)	-	[57]
maize	Switzerland	? 1.34	AFLA, BEA, FB, ZEA	[52]
foods	Transkei	0.35-11.6[6]	FB_1, FB_2, DON, NIV, ZEA	[66]
	Transkei	? 0.17 (2/4)	-	[62]
	U.K.	? 0.25 (33/36)	-	[63]
	U.K.	? 0.14 (21/238)	-	[45]
	U.S.A.	? 0.86 (23/34)	FB_1	[20]
	U.S.A.	? 0.77 (50/100)	FB_1	[20]
	U.S.A.	0.02-0.10[5] (12/14)	-	[7]
maize	U.S.A.	2.82 (1/1[7])	fusarin C	[70]
feeds	U.K.	? 4.60 (41/67)	FB_1, FB_2, DAS,DON, 3-A,DON, 15-ADON, FX,HT-2, MAS,NIV, OA, T-2, ZEA	[60]
maize-	Gambia	? 3.16 (7/9)	-	[63]
others[8]	Kenia	? 0.94 (10/12)	-	[63]
	Malawi	? 0.45 (8/10)	-	[63]
	Netherlands	0.73 (1/1)	-	[63]
	Tanzania	0.38 (1/1)	-	[63]
	Transkei	2.73 (1/1)	-	[63]
	U.K.	0.02-0.52 (31/31)	-	[45]
	Zimbabwe	? 0.16 (6/8)	-	[63]
rice	U.K.	0.07[5] (1/40)	AFLA B_1, OA	[61]
	U.S.A.	+[9] (8/20)	FB_1	[1]
oats	Poland	15.7-38.3 (3/3[2])	-	[63]
rye	Poland	6.1-12.3 (3/3[2])	-	[63]
wheat	Austria	0.88 (ca 45% samples)	DON, ZEA	[5]
wheat	Austria	? 2	-	[18]
	Poland	17.1 (6/6[2])	-	[63]
	Poland	0.42 and 15.9[2]	-	[37]
triticale	Poland	2.6-15.7 (3/3[2])	-	[63]
	Poland	0.25 and 3.5[2]	-	[37]
KSD	China	0.05-1.12[5] (47/104)	-	76
cereals[10]	China	? 0.26	-	[26]
	China	0.07-0.27[5] (8/123)	-	76
	China	? 0.25	-	[26]

[1]AFLA (aflatoxins), AFLA B_1 (aflatoxin B_1), BEA (beauvericin), DAS (diacetoxyscirpenol), DON (deoxynivalenol), 3-ADON (3-acetyl deoxynivalenol), 15-ADON (15-acetyl deoxynivalenol), FB (fumonisins), FB_1 (fumonisin B_1), FB_2 (fumonisin B_2), FX (fusarenon X), HT-2 (toxin HT-2), MAS (monoacetoxyscirpenol), NIV (nivalenol), OA (ochratoxin A), T-2 (toxin T-2), ZEA (zearalenone). [2]Samples with fungal damage. [3]Positive samples over total samples analysed. [4]Other mycotoxins were not analysed or not found. [5]Level, range or average of contamination of positive samples. [6]Healthy or moldy samples with a significant correlation between MON and *F. subglutinans*. [7]Sanple associated with a field outbreak of leukoencephalomalacia in horses. [8]Other maize products. [9]Level of contamination not reported. [10]Cereals implicated in Keshan disease (KSD).

concentrations of MON (< 5 uM) selectively inhibited rat liver mithocondrial pyruvate and á-ketoglutarate oxidations by 50% and suggested that these inhibitory effects could constitute the major molecular mechanism of toxicity. The high metabolic rate of cardiac tissue makes the heart a likely target for the toxic effects of the inhibited energy metabolism.

Investigations on the toxic effects of MON in poultry have been undertaken in recent years. It was observed 70 and 83% mortality in chicks fed 154 and 300 mg MON/kg diet, respectively [25, 32]. Ledoux *et al*. [32] demonstrated that 50 mg MON/kg diet or greater are toxic to broiler chickens with mild to severe cardiomegaly observed in chickens fed 50 to 200 mg MON/kg ration. Engelhardt *et al*. [17] fed turkey, chickens and ducklings, 0, 144, 288 or 576 mg MON/kg diet supplied by culture material and reported 80 to 100% mortality in all treatments, in all three species. Gross lesions included ascites, hydropericardium, and myocardial pallor. Cardiac injury with alterations in cardiac electrical conductance was shown to be the primary cause of mortality of these birds. Feeding low levels of MON to birds has been shown to cause poor growth performance, increased serum piruvate levels, enlarged hearts and cardiac lesions [32]. Harvey *et al*. [23] observed that feeding diets containing 100 mg MON/kg diet also produced renal lesions in growing broiler chicks from 1 to 21 d of age. Li *et al*. [38] demonstrated that dietary MON (75 mg/kg diet) not only suppressed performance but also the immune system. Some researchers ran experiments with: MON and FB, MON and deoxynivalenol (DON), and MON and aflatoxin (AFLA). MON alone and in combination with FB_1 in broiler chicks produced dose-responsive clinical signs, reduced weight gains and mortality [25]. Additive effects were noted when the toxins were given in combination. No toxic synergy was observed when MON and DON were fed simultaneously to growing broiler chicks [23] or turkey poults [48]. Additive or less than additive toxicity was observed in broiler chicks fed 100 mg MON and 3.5 mg AFLA/kg diet [31].

The effects of MON-contaminated diets on growing barrows were also evaluated [21]. Diets of 100 mg or 200 mg/kg feed reduced body weight, body weight gain, and feed consumption. Serum biochemical analytes were also affected. Relative heart weight was increased in the 200 mg MON-treated barrows. The most consistent sign of MON toxicity in barrows appeared to be death induced within 2-5 d by 100-200 mg MON/kg diet. These findings are similar to those observed in poultry. Additive or less than additive toxicity was observed in barrows fed 100 mg MON and 100 mg FB_1/kg diet [22]; clinical disease appears to be due to the toxic expression of FB_1.

Data on the effects of MON on reproduction and the fetus and its mutagenic and carcinogenic potential are negative but extremely limited. In humans a possible link between MON ingestion and Keshan disease, a fatal cardiomyopathy endemic to certain rural areas of China, has been suggested. Although the etiology of this disease is still uncertain and dietary selenium deficiency is also involved, there appears to be a positive correlation between the disease and the ingestion of maize contaminated with molds and MON. Similarities in the ultrastructural changes in the myocardium of rats treated with MON and humans suffering from the disease were reported [11].

Decontamination strategies

Thermal stability

Thermal stability of MON has been studied. From experiments conducted in ground maize and wheat spiked with MON at levels of 1 ppm and heated at 50, 100, and 150ºC for 0.5-2 h moderate decomposition was observed, e.g. 55% remained in corn after 0.5 h at 100ºC [59]. More recently, Pineda *et al*. [55] established that the stability of MON depends on temperature, pH, and time, and that the percentage of reduction was related to an increase in the value of these parameters. MON has been reported to be almost completely destroyed by heating at pH 10 for 1 h at 175ºC. Since the study was done in aqueous solutions (2 ppm), the reduction measured was most likely genuine due to destruction of MON rather than its reaction and binding with the components of the matrix. The mechanism of destruction and whether the heat treatment reduces the toxicity of MON or not still remain to be established.

There is only limited information on MON degradation during processing. From Pineda's results, MON would be expected to be stable in food processes that occur under neutral (baking of maize bread) or acidic (wet milling of maize) conditions and unstable in food processes that occur under basic conditions. In effect, Caputo *et al*. [7] found that alkaline cooking of maize decreased MON levels by about 70% when producing tortillas. These are promising results because the same procedure partially destroys ZEA, DON, and AFLA. But, although maize tortillas manufacture reduces significantly MON content in finished products, it is still possible to detect it in commercially available products (Table 3).

Chemical methods

As has been shown for other mycotoxins such as AFLA, DON, ZEA, and OA ozonization is efficacious in detoxifying MON 13. The IR and NMR spectra of MON showed that after ozone treatment the double bond disappeared and the 4-C ring structure opened. Apparently the H in MON is the key factor for its toxicity [77].

Chlorinated lime, heating, activated carbon, ozone, microwave, and UV were also tested in their ability to reduce MON content in water [78]. In view of these results, the most effective procedure is chlorinated lime. To detoxify 1 mg of MON in water, 1.5 mg of effective chlorine in chlorinated lime are needed. Water wash, fumigation with a gaseous desinfectant (mainly Cl_2), radiation with -rays, and spray treatments with 5% H_2O_2, 5% NH_3 or 10% $NaClO_3$ were evaluated on maize grains. Out of these, oxigenated water showed to be the most effective method to achieve MON detoxification. Both methods, chlorinated lime and oxigenated water, are easy to use, inexpensive and free from secondary pollution.

Biological control

Degradation of MON through the utilization of a bacterial microorganism was studied [16]. The three microorganisms involved, *Ochrobactrum anthropi* isolated from moldy maize, can grow on MON as a sole source of carbon and degrade it partially or totally in the process. Cultures of *O. anthropi* were successfully tested in the field in mature plants inoculated with MON-producing *Fusarium* spp. and in post-harvest cracked maize spiked with the toxin. A broad application in crop agriculture and in the improvement of food grain quality could be visualized but whether the procedure works in naturally contaminated maize, the nature of the degradation products and if any MON detoxification is achieved remains to be determined.

Another different approach, in the area of controlling mycotoxicoses in animals, is that of Wu 75 who investigated the effect of Poultry Aid Plus (PAP) in poultry when supplementing drinking water. PAP is a *Lactobacillus acidophilus* fermentation liquid formula intended for water application to reduce digestive stress in poultry. The formula was tested against a *F. proliferatum* strain that produces MON and FB. The diet with 2% CM reduced weight gain by 23%; this reduction was preventable by PAP. The diet with 4% CM, that provided 144 ppm of MON and 11 ppm of FB in the diet, caused cumulative mortality of 87.5%, which was reduced by PAP to 50%. The protective effect of PAP on toxicity of *F. proliferatum*-contaminated feed was apparent in reducing mortality and improving weight gain. Neither the actual mechanism of action of PAP is known nor the economics of using PAP were addressed by the author. Nonetheless, taking into account the longer survival time of toxin-exposed and PAP-treated chicks achieved in the experiments, the use of

this product might be an economic benefit when feeds are contaminated by *F. proliferatum* mycotoxins because the poultry producers would have more time to identify the causes of the problem and develop strategies to solve them.

Method of analysis

Very few methods have been developed for determining MON in agricultural products. The ionic nature of MON makes its extraction and recovery from biological material difficult so that, until recently, robust methods suitable for reliable surveillance have not been available. Thin layer chromatography (TLC), gas chromatography (GC), and high-performance liquid chromatography (HPLC) have been described for the analysis of MON. TLC with colorimetric detection has been used, in general, for MON detection in fungal cultures. Ion-pair reversed-phase or ion-exchange HPLC with a final UV detection are generally chosen for routine analysis. A procedure with ca 98% recovery, good reproducibility and a limit of determination in corn of 0.025 ppm 51, that has lately been adapted to the analysis of MON in maize tortillas 7, was recently described.

Conclusions

Today, the available information does not allow us to establish the economic and sanitary implications of the contamination of foods and feeds with MON. The following facts: (i) infestation of cereals by species of *Fusarium* that produced MON, (ii) contamination by MON in foods and feeds, (iii) co-occurrence of MON with other mycotoxins (AFLA, FB, ochratoxins, trichothecenes, and ZEA), (iv) oral toxicity in various animal species and acute death due to cardiac failure in birds and pigs, and (v) additive toxicological effects between MON and some mycotoxins, suggest that the international regulatory bodies and food safety authorities that have not established limits for MON in foods and feeds yet, will increase their surveillance in these matters. For this reason and in view of an appropriate risk assessment, it will be necessary more information on (i) eating habits, (ii) the effect of processing in foods and feeds, (iii) natural occurrence, and (iv) chronic toxicity of MON.

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