Current situation and perspective of mycotoxin research in Asia

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Abstract

In conjunction with the international current situation about the regulation for mycotoxins in food, the natural occurrence of trichothecenes (DON and NIV) and aflatoxins in Asia is overviewed. Updated information is very limited, however, being difficult to assess the exposure of Asian populations to the mycotoxins. Comprehensive surveillances are recommended to be conducted nationwide in individual countries using adequate sampling plans and validated methods. Recent advances in molecular genetic approach for identifying *Fusarium graminearum* and *Aspergillus flavus* are also reviewed briefly.

Key words : aflatoxin, deoxynivalenol, nivalenol, exposure,
Fusarium graminearum, *Aspergillus flavus*, Asia

Introduction

Mycotoxins currently considered most significant are aflatoxins (AF), ochratoxin A (OTA), patulin, fumonisins (FM), zearalenone (ZEN) and some trichothecenes including deoxynivalenol (DON) and T-2/HT-2 toxins. The risk assessment of FM, OTA, DON, T-2/HT-2 and AFM₁ was carried out at the 56th JECFA meeting in 2001, and provisional tolerable daily intake values were proposed for FM, OTA, DON and T-2/HT-2¹⁾.

As for worldwide mycotoxin regulations, at least 99 countries have regulations including guidelines for food and/or feed, and the total population in these countries represents approximately 87 % of the world's inhabitants²⁾. Among 47 countries/areas in Asia, 26 countries/areas have regulations for foods and/or feeds in 2003, an increase of 86 percent (12 countries) compared to 1995³⁾. Table 1 shows the current situation of regulations for mycotoxins in food in Asia, in comparison with the situation in 1995. As AF are toxins regulated most strictly and worldwide, all countries/districts with mycotoxin regulations in Asia have at least regulatory limits for AFB₁ or total AF (the sum of aflatoxin B₁, B₂, G₁ and G₂) in food. Total AF and AFB₁ are regulated in 18 and 13 countries, respectively, followed by AFM₁, patulin, OTA, DON and ZEN in 12, 8, 5, 4 and 2 countries, respectively. Only one country has a regulation either FM or T-2.

At the moment, regulatory standards (maximum tolerated levels) set by Codex Alimentarius are 15 µg/kg for total AF in peanuts intended for further processing, and 0.5 µg/kg for AFM₁ in milk, and 50 µg/kg for patulin in apple juice and apple juice ingredients in other beverages. Several regulations have been harmonized between countries belonging to economic communities (EU, MERCOSUR, Australia/New Zealand).

In relation to the international current trend noted above, recent information on the

Table 1. Regulations for mycotoxins in food in Asia. Situation in 2003 compared to 1995

Year	Maximum tolerated levels of mycotoxins ($\mu\text{g/kg}$) in foods							
	2003				1995			
Country/Area	AFB ₁	AFT	AFM ₁	Parulin	OTA	DON	Others	AFB ₁ AFT Others
Armenia	5		0.5	5		700, 1000	T-2/100; ZEN/1000	5, 10, 20 5 15, 20
China	5, 10, 20 (0*)		0.5 (0*)	50, 100		1000		
Cyprus (EU)	2, 5, 8	4, 10, 15	0.05					
Hong Kong SAR	15, 20	15, 20						
India		30						30
Indonesia		20	5		0*		ZEN 0*	
Iran	5, 10 (0.5, 1)	10, 15, 30, 50	0.05	50	5, 10, 20, 50 (1)	1000	ZEN/200, 400; FMB1B2/1000	
Israel	5	15	0.05	50	50			5 15 AFM1/OTA/Parulin
Japan	10			50		1100		10
Jordan	15	30						15 30
Korea	10		0.5	50				
Kuwait		(0.05)						
Malaysia		35						35
Nepal	20							
Oman	10							
Philippines		20						
Saudi Arabia		(0.05)						20
Singapore		5	0.5	50	2.5			0 0
Sri Lanka		30 (1)						30 (1)
Syrian Arab Rep.	5	20 (0.05)	0.2					
Taiwan Prov. (China)		10, 15 (0*)	0.5					50
Thailand		20						20
Turkey (EU cms)	2, 5 (1)	4, 10 (2)	0.05	50	3, 5, 10			
Vietnam		10	0.5					
Total no. of countries	13	18	12	8	5	4		6 10

* Non-detectable.

Values in parentheses are for infant foods.

Abbreviations: AFB₁, aflatoxin B₁; AFT, total aflatoxins; AFM₁, aflatoxin M₁; OTA, ochratoxin A; DON, deoxynivalenol; T-2, T-2 toxin; ZEN, zearalenone; FMB1B2, fumonisin B1 and B2.

All data are cited from FAO Food and Nutrition Papers 64 and 81. See references 2 and 3.

mycotoxin occurrence in Asia is briefly overviewed in this paper. However, updated information is very limited, being difficult to assess the exposure of Asian populations to mycotoxins. Comprehensive surveillances are recommended to be conducted nationwide in individual countries, using adequate sampling plans and validated analytical methods. Furthermore, the co-occurrence of multiple mycotoxins (AF, OTA, various *Fusarium* toxins, etc.) should be taken into account. Several research subjects required are also considered briefly.

Geographical distribution of trichothecene occurrence in Asia

Fusarium head blight (FHB) or scab is a significant fungal disease of wheat, barley and corn imposing a threat to the world's food supply. A major pathogen is the ascomycete *Fusarium graminearum* Swabe (teremorph: *Gibberella zeae* (Schwein.) Petch), and is well-known as one of the most important producer of *Fusarium* mycotoxins such as DON, nivalenol (NIV) and ZEN. Distribution of DON and NIV varies by region in the world⁴. DON is the most widely distributed *Fusarium* mycotoxin and occurs worldwide in cereals of temperate regions. On the other hand, NIV has been found extensively in Japan and Korea and at relatively low levels in cereal samples from Europe, southern Africa and New Zealand, but very rarely found in North and South America.

Table 2 shows the geographical distribution of DON and NIV in wheat, barley and corn in Asia. In Japan, there is a regional difference in the occurrence of DON and NIV in domestic wheat and barley grains⁵⁻⁷. The predominant toxin is DON in the northern areas (Hokkaido and Tohoku) and NIV is in the central area (Honshu), while in the western area (Shikoku and Kyushu) DON is more frequent than NIV. In Korea, a similar pattern to the central Japan was found in barley grains, but in corn samples DON is more important than NIV^{8,9}. In China, DON is known to be the major causative toxin responsible for almost all of the episodes of human red mold intoxication, sometimes with its acetylated derivatives, and NIV being detected in less incidence and level¹⁰⁻¹². In addition, DON is found as a predominant trichothecene in both wheat and corn from high-incidence areas for human esophageal cancer in Henan Province^{13,14} and for Kashin-Beck disease in Shaanxi and Shanxi Provinces¹⁵. NIV has been detected in corn from a southern region of China (Guanxi), the Philippines and Indonesia in far less incidence and level, rarely together with DON¹⁶⁻¹⁸.

Exposure assessment of trichothecenes

Regarding the regulatory or guideline limits of trichothecenes, DON is now regulated in wheat (and/or its flour) and other cereals in 37 countries including four Asian countries; Armenia, China, Iran and Japan². The regulation limit ranges from 300 to 2000 µg/kg, depending on food commodities and food types. Regulation for NIV has not yet been established, but NIV is considered to be given more attention from a regulatory point of perspective, because of its relatively higher toxicity as compared to DON². Recently, a comprehensive project on the exposure of the population to *Fusarium* toxins has been carried out by EU member countries¹⁹. The databases covered altogether 16 *Fusarium* mycotoxins and 44,959 analyses. Wheat and wheat containing products (like bread and pasta) are the predominant source for DON and NIV intake. The average level intakes of DON for entire population as well as for the group adults are low and do not exceed 46.1 % of the tolerable daily intake (TDI) of 1 µg/kg body weight/day. However, for the group of young children the intake might come to the TDI²⁰.

In Japan, 1.1 mg/kg of DON in wheat grain was established as a provisional regulatory

Table 2. Geographical distribution of deoxynivalenol (DON) and nivalenol (NIV) occurrence in wheat, barley and corn in Asia

Country	Region	Commodity	No. sample	DON		NIV		DON ratio %	Ref.
				% Positive	Mean	% Positive	Mean		
Japan	Hokkaido	wheat	101	69%	324	61%	11	97%	5), 7)
	Tohoku	wheat	20	100%	373	95%	106	78%	5), 7)
Korea	Honshu	wheat, barley	70	61%	82	86%	612	12%	5), 7)
	Shikoku/Kyushu	wheat, barley	110	49%	1231	69%	532	70%	5), 7)
	South. prov.	barley	39	90%	153	95%	960	14%	8)
	Central prov.	corn	46	65%	202	35%	27	88%	8)
China	South. prov.	barley	48	58%	119	94%	307	28%	9)
	Central prov.	barley	11	73%	191	82%	296	39%	9)
	Heilongjiang, Jilin	corn	16	25%	187	6%	31	86%	*
	Liangning	corn	25	36%	225	0%	0	100%	*
	Shanxi	corn	15	100%	560	100%	30	95%	15)
Henan	Shanxi	corn	10	100%	152	60%	9	94%	15)
		wheat	10	100%	349	80%	94	79%	15)
		corn	131	60%	205	31%	12	94%	13), 14)
		wheat	86	61%	34	23%	6	85%	13), 14)
Guangxi		wheat	93	90%	1073	1%	6	99%	12)
		corn	20	0%	0	15%	32	0%	16)
		corn	27	0%	0	0%	0	-	17)
Philippines		corn/products	69	0%	0	15%	5	0%	17)
Indonesia		corn	16	13%	4	13%	14	22%	18)
		corn	12	0%	0	0%	0	-	17)

Mean: weighted mean level, µg/kg.

DON ratio %: mean % of DON level to total levels of DON and NIV.

* Yoshizawa, T.: unpublished data.

limit in 2002. According to studies on the exposure assessment of DON, the average level intakes of DON were estimated to be 3.7 % and 8.3 % of the TDI of DON for entire population and children, respectively, based on average levels of DON in domestic and imported wheat grains²¹). The exposure levels estimated from DON in rice were very low; 0.1 % and 0.2 % of TDI for adults and children, respectively²²).

Meky *et al.*²³) established methodology for a candidate biomarker of human exposure to DON and tested this methodology on urine samples from a potentially highly exposed population. Urine samples were collected from female inhabitants of Linxian County, China, a high risk region for esophageal cancer and an area of potentially high DON exposure, and Gejiu, a low risk region in China. The mean levels of DON, following α -glucuronidase treatment, from the suspected high and low exposure regions of China were 37 ng/mL (range 14-94 ng/mL) and 12 ng/mL (range 4-18 ng/mL), respectively. This was estimated to correspond to daily exposures of 1.1-7.4 μ g/kg bw/day and 0.3-1.4 μ g/kg bw/day, respectively.

Aflatoxin occurrence in Asia

AF have been found in a variety of agricultural commodities, but the most pronounced contamination has been encountered in corn, peanuts, cottonseed, dried fruits, tree nuts and spices²⁴). From the point of view of dietary intake, AF in foods used as staples such as rice, wheat and corn are considerable significance. The third joint FAO/WHO/UNEP international conference on mycotoxins (United Nations Environmental Programme) in 1999 made a series of recommendations reflecting a new perspective on the health and economic impact of mycotoxins in staple foods²⁵). Unlike other cereals, however, reports on the actual incidence of mycotoxin in rice are limited, and the data available for rice, especially in Asia, are mostly outdated and there is no comprehensive data set that can serve as basis for assessing exposure of humans to AF due to consumption of these commodities.

Table 3 summaries updated data on AF contamination of rice in Asia^{21, 26-29}). Sales and Yoshizawa²⁶) attempted to apply an immunoaffinity column clean-up method coupled with HPLC (detection limit for AF: 25 ng/kg) to determine an updated profile of AF contamination in rice and its byproducts from the Philippines. The total AF levels in 78 samples of polished and brown rice ranged from <0.025-2.7 μ g/kg (mean of positive samples: 0.37 μ g/kg) and 0.03-8.7 μ g/kg (mean of positive samples: 2.7 μ g/kg), respectively. The incidences (% of positive samples) of AF in polished and brown rice were 94 % and 100 %, respectively. The estimated potential daily intake of AFB₁ from rice is between 0.1 and 7.5 μ g/kg bw/day, the mean of which is 1.0 ng representing 9.1-5.3 times the estimated tolerable daily intake for AFB₁ in Asia which is from 0.11-0.19 μ g/kg bw/day, at a cancer risk level of 10^{-5} . Results of this study are indicative of the potentially high risk of exposure of Filipinos to AF in rice.

Under a multi-centre study conducted by the Indian Council of Medical Research, 1511 samples of parboiled rice were collected from rural and urban areas of 11 states representing different geographical regions of India²⁷). The presence of AFB₁ at levels ≥ 5 μ g/kg was found in 38.5 % of the total number of samples of the parboiled rice. About 17 % of the total samples showed the presence of AFB₁ above the Indian regulatory limit of 30 μ g/kg.

Park *et al.*²⁸) reported that 5/88 (6 %) of food-grade rice samples, collected in Seoul, Korea, were contaminated with AFB₁ with an average of 4.8 μ g/kg. Rice was considered to be the major contributor to the dietary intake of AFB₁, and it was calculated that the probable daily intake of AFB₁ for Koreans exceeds the estimated provisional maximum tolerable daily intakes.

Table 3. Updated data on aflatoxin B₁(AFB₁) contamination of rice in Asia

Commodity	Country	No. samples	Positive (%)	AFB ₁ mean (µg/kg)	Method/LOD (LOQ) (µg/kg)	Ref.
Polished rice, imported	Japan	20	25%	(0.1-0.3)	IAC-HPLC/0.1	29)
Rice, food-grade	Korea	88	6%	4.8	ELISA/1, HPLC/0.6	28)
Brown & polished rice	Philippines	41	100%	0.39	IAC-HPLC/0.025	26)
Rice, imported	Philippines	28	86%	0.08	IAC-HPLC/0.025	26)
Parboiled rice	India	1511	38.5%	>5		27)
			17%	>30		
Rice, domestic	Japan	53	0%	-	IAC-HPLC/0.1	21)

Abbreviations: LOD, limit of detection; LOQ, limit of quantitation; IAC, immunoaffinity column; HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay.

Current taxonomical aspect for *F. graminearum*

Molecular phylogenetic analyses based on eleven nuclear genes at six loci revealed that *F. graminearum* consists of at least nine biogeographically structured lineages^{30, 31)}. Among nine lineages of the species, now named as *F. graminearum*-complex (= *F. graminearum* Group 2) according to the new concept, *F. graminearum* Schwabe s. str. (lineage 7) and *F. asiaticum* O'Donell et al. (lineage 6) are most significant pathogens in wheat, barley and corn in Asia³²⁾. There is a geographical difference in the distribution of these lineages in Asian countries³⁴⁾. For example, *F. asiaticum* is predominant in Chinese wheat, whereas *F. graminearum* is the most predominant followed by *F. boothii* (linkage 3) and *F. asiaticum* in Korean corn. In Japanese wheat and barley, lineage 6 is predominant in western to central regions, while lineage 7 is in northeastern to northern regions. As for trichothecene production of these lineages isolated from Japanese cereals, *F. graminearum* (lineage 7) produced DON, which is subdivided into 3A-DON- (about 70 %) and 15A-DON-producer (about 30 %), and *F. asiaticum* (lineage 6) produced either NIV (about 70 % of isolates) or 3A-DON (about 30 %, 15A-DON producer was below 1 %).³³⁾

Molecular genetic approach for identifying aflatoxigenic fungi

A. flavus and *A. paratiticus* are responsible for the overwhelming proportion of AF found in foodstuffs throughout the world. *A. flavus* produces only B-type AF and sometimes the mycotoxin cyclopiazonic acid (CPA), while *A. paratiticus* produces both B- and G-type AF, but never CPA. Several other *Aspergillus* species are now known to produce AF but they are of little practical importance in foods.

Recent advances in molecular technology have enabled the rapid detection and identification of filamentous fungi. Heteroduplex analysis allows genetic screening of unknown DNA fragments in a sequence-dependent manner^{34,35)}. For identification of *Aspergillus* section *Flavi* species, Kumeda et al.^{36, 37)} developed a new PCR-based method for heteroduplex panel analysis (HPA), which was highly reproducible and proved to be a powerful tool for classifying *Aspergilli* isolates without morphological observation of

phenotypic characteristics. Based on the HPA results, 19 HPA types were identified from a total of 351 examined *Aspergillus* section *Flavi* isolates³⁸⁾. These HPA types includes 6 types (F-1 to F-6 for *A. flavus/A. oryzae*), 2 type (P-1 and P2 for *A. parasiticus*), 5 types (N-1 to N-5 for *A. nomius*). As for *A. flavus/A. oryzae*, type F-1 and F-2 are dominant.

Sales³⁹⁾ applied HPA analysis for identification and differentiation of *Aspergillus* section *Flavi* isolates from different agricultural commodities from the Philippines, indicating eight genotypes with distinct HPA genotypes, with *A. flavus* F-1 and *A. parasiticus* P-1 as the most common genotypes. Furthermore, aside from the previously reported HPA genotypes, five additional *Aspergillus* section *Flavi* genotypes were identified. This strongly indicates a broader diversity of this group in the Southeast Asian region.

Conclusion and recommendation

In general, updated information on mycotoxin contamination in Asia is insufficient, being difficult to assess the exposure of Asian populations to mycotoxins. Comprehensive surveillances are recommended to be conducted nationwide in individual countries, using adequate sampling plans and validated analytical methods. In addition, more emphasis should be placed on total diet and duplicate studies rather than individual foods.

Collaborative and partnership researches between scientists and laboratories in Asian countries should be encouraged to assess the extent of human exposure to mycotoxins in this region. In addition, Asian countries are urged to supply FAO and WHO with all available data on levels of exposure and related effects determined experimentally, clinically, or epidemiologically.

Recent progresses in molecular technology have introduced new concepts in the taxonomy of mycotoxigenic fungi including *F. graminearum*-complex and *Aspergillus* section *Flavi*. Further studies based on molecular genetic approaches are encouraged to elucidate a broader diversity of the fungi in Asian region.

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