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Review Article / Derleme Makale

Genotoxic and Mutagenic Effects of Mycotoxins: A Review

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Abstract: In this article, genotoxic and mutagenic effects of mycotoxins that are produced by various fungus species have been reviewed. A total of 259 mycotoxins were found in the literature. Genotoxic effects of 109 of these were investigated. Among the studied mycotoxins, only actinomycin D, aflatoxin, alternariol, chrysazin (dantron), citrinin, fumonisin, mytomycin C, nivalenol, ochratoxin A, patulin, sterigmatocystin, versicolorin A and B, vomitoxin, and zearalenone have sufficient number of studies that present or prove their genotoxic effects. Additional studies are required in order to determine whether other mycotoxins have any genotoxic effects. The current study provides valuable information regarding studied mycotoxins. Therefore, it may lead researchers for designing future mycotoxin-related studies that have never been studied.

Keywords: Genotoxicity, mutagenicity, secondary metabolites, possible drugs.

Mikotoksinlerin Genotoksik ve Mutajenik Etkileri: Derleme

Öz: Bu makalede, çeşitli mantar türleri tarafından üretilen mikotoksinlerin genotoksik ve mutajenik etkileri derlenmiştir. Literatürde toplam 259 mikotoksin bulundu. Bunların 109'unun genotoksik etkileri daha önce araştırıldı. Bugüne kadar yapılmış olan çalışmalarda, çalışılan mikotoksinler arasında sadece aktinomisin D, aflatoksin, alternaril, chrysazin (dantron), sitrinin, fumonisin, mitomisin C, nivalenol, okratoksin A, patulin, sterigmatosistin, versicolorin A ve B, vomitoksin ve zearalenon genotoksik etki göstermiş veya genotoksik etkileri kanıtlanmıştır. Diğer mikotoksinlerin herhangi bir genotoksik etkisi olup olmadığını belirlemek için ek çalışmalar gereklidir. Bu çalışma, daha önce çalışılan mikotoksinler hakkında önemli bilgiler sunmaktadır. Dolayısıyla bu derleme, araştırmacılara, daha önce hiç çalışılmamış olan mikotoksinlerle ilgili gelecekteki çalışmaları tasarlama konusunda katkı sağlayabilir.

Anahtar kelimeler: Genotoksisite, mutajenisite, ikincil metabolitler, muhtemel ilaçlar.

1. Introduction

The term "mycotoxin" is derived from the combination of two words: Myco- meaning "fungus" and Toxin meaning "naturally produced poison". Mycotoxins are secondary metabolites produced by fungi such as Aspergillus, Penicillium, Fusarium, Alternaria, Claviceps, and many others. They are natural toxins that have low molecular weight with a wide variety of chemical structures. Mycotoxins produce potent and various toxic effects on humans, animals, and plants (Zain, 2011).

Species belonging to Aspergillus and Penicillium produce the most diverse types of mycotoxins. Among these, the most widely known mycotoxins are Aflatoxins. Aflatoxins cause carcinogenicity, teratogenicity, and mutagenicity in animals. The mode of action of Aflatoxin can be listed as inhibition of DNA, RNA, and protein synthesis, reduction in various enzyme activities, depression of glucose metabolism, inhibition of lipid synthesis including phospholipids, free fatty acids, triglycerides, cholesterol and their esters, and inhibition of the coagulation factors (Hussein & Brasel, 2001).

In 1970, some tests were developed to quickly determine whether a chemical substance has any mutagenic and/or carcinogenic effects. Since then, a wide variety of investigation systems have been developed for genotoxicity studies. These are mutagenicity tests that detect gene, chromosome or genomic mutations and indicator tests that show other effects that are induced in parallel to the mutation. Most of the recent genotoxicity studies have been done by using cytogenetic methods (CA: Chromosome Aberration, FISH: Fluorescent *in situ* Hybridization, MN: Micronucleus, and SCE: Sister Chromatid Exchange tests). The cytogenetic methods are capable of determining the structural and numerical chromosome aberrations by using biochemical and electrophoretic methods by detection of DNA damage (adducts, double-strand breaks, cross-linking, alkaline-labile regions, and HGPRT: Hypoxhantine Guanine Phosphoribosyl Transferase gene mutation) (Albertini et al., 2000).

Methods of genotoxicity studies have been continuously evolving. Changes such as large deletions, insertions, inversions, rearrangements, and recombination can be determined at the chromosomal level within the microscopic methods used in routine genotoxicity studies (Noel & Rath, 2006).

Cytogenetic methods known today as short-term genotoxicity tests and used to determine whether a chemical substance is genotoxic are SCE (Tucker et al., 1993), CA (Carrano & Natarajan, 1988; Hagmar et al., 1994) and MN (Fenech, 2002; Heddle et al., 1991). These tests can be performed both *in vitro* in human peripheral lymphocytes and in bone marrow cells of *in vivo* test animals.

Sister chromatid exchange is an exchange in the DNA replication products between the homologous loci of sister chromatids that repair DNA double chain breaks by homologous recombination (Helleday, 2003; Sonoda et al.,

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1999). In humans and animals exposed to substances known to be mutagenic and carcinogenic, it was found out that there is a linear relationship between the increase in the frequency of SCE and the increase in single-gene mutations (Albertini et al., 2000; Carrano & Natarajan, 1988; Perry & Evans, 1975). A similar relationship was found between the increase in SCE and the formation of *in vivo* tumors (Norppa et al., 2006). In contrast to CA, SCE alone is insufficient to determine genotoxic risk. However, in experimental studies, SCE is continued to be used as a suitable indicator method for determining genotoxic effects in humans (Norppa et al., 2006).

Since the development of CA mechanism is similar in different tissues, it is thought that the level of abnormality in lymphocytes is an indicative of the degree of abnormality in cancer-prone tissues and; thus, is indicative of the cancer risk (Albertini et al., 2000; Bonassi et al., 2000; Bonassi, Znaor, Norppa, & Hagmar, 2004; Bonassi et al., 2005). High CA frequency may be an indicator of high cancer risk, regardless of the reason for initiating CA increase because it has been reported that CA formation may also result from incorrect repairment of chain fractures in DNA (Savage, 1993).

MNs are small nuclei parts that can be found out of the nucleus. The MNs are formed on the telophase due to the acentric chromosome or chromatid fractures that occur when nucleoplasmic bridges (NPB) are formed, stretched, and broken during telophase. Micronuclei formation may also result from chromosome (laggard chromosome) malsegregation during anaphase (Surrallés, Xamena, Creus, & Marcos, 1995). In addition, multipolar anaphase and telophase cause MN formation (Topaktas & Rencuzogullari, 2010). The loss of chromosomes that can lead to MN formation or non-disjunction of the chromosomes are among the major events observed in cancer and aging. This is probably the result of distortion in spindle fibers and centromere or condensation of chromosome structure before metaphase (Dellarco, Mavournin, & Tice, 1985). Thus, both the clastogenic and aneugenic effects can be determined by the MN test (Kirsch-Volders, Elhajouji, Cundari, & Van Hummelen, 1997; Norppa & Falck, 2003). In previous studies, the increase in MN frequency in peripheral blood lymphocytes from cancer patients was found to be as much as MN frequency in the cancerous target tissue (Bonassi et al., 2007; Cheng et al., 1996; Duffaud et al., 1997). In addition, Fenech, Holland, Chang, Zeiger, and Bonassi (1999) clearly showed the relationship between MN and cancer in humans.

Recently, molecular geneticists have developed several new, rapid, and reliable methods for measuring genotoxicity (Swaileh, Hussein, & Ezzughayyar, 2008; Zhiyi & Haowen, 2004). One of them is RAPD (Randomly Amplified Polymorphic DNA) technology (Ferrero, Castaño, Gonzalez, Sanz, & Becerril, 1998; Swaileh et al., 2008). RAPD analysis was developed by Williams, Kubelik, Livak, Rafalski, & Tingey (1990). This method is simple, sensitive, and very effective in determining genetic damage (Zhiyi & Haowen, 2004). Also, it gives information about a large number of loci along the genome. The randomly amplified band profiles can be obtained without the need of any information about the target genome or used primers. When electrophoretically observed, changes in band profiles were reported resulted from changes in damage-prone binding sites of genetic material (Becerril, Ferrero, Sanz, & Castaño, 1999; Savva, 2000). In addition to changes in the number of bands, changes in band density have also been associated with genetic changes (Atienzar et al., 2000; De Wolf, Blust, & Backeljau, 2004). This technique is widely used in phylogenetic, taxonomy, ecotoxicology, epidemiological, and genotoxicity studies (Marillia & Scoles, 1996). Additionally, the bacterial reversion test method using *Salmonella typhimurium* LT2 strains known as Ames test is also used as mutagenicity test (Maron & Ames, 1983). Although the above described tests give false positive and false negative results, they are still recommended by some authorities (such as European Food Safety Authority (EFSA) Scientific Committee). In 2011, the EFSA Scientific Committee published an opinion about genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee "Opinion on genotoxicity testing strategies," 2011). As described by the EFSA Scientific Committee, the most commonly used methods for assessing the genotoxic potential of substances are listed as follows together with the relevant Organisation for Economic Co-operation and Development Test Guideline (OECD TG) on the basis of their principal genetic end-point. Bacterial reverse mutation test in *Salmonella typhimurium* and *Escherichia coli* (OECD TG 471) and *in vitro* mammalian cell gene mutation test (OECD TG 476) are used for investigation of point (gene) mutation. *In vitro* mammalian CA test (OECD 473) and *in vitro* mammalian cell MN test (OECD TG 487) are used for investigation of CA. On the other hand, the most commonly used *in vivo* tests can be listed as follows: Mammalian erythrocyte MN test (Test No: 474) and mammalian bone marrow CA test (Test No: 475) are used for investigation of gene mutations, while transgenic rodent somatic and germ cell gene mutation assays (OECD TG 488) are used for CA investigations. Additionally, most common *in vivo* tests used for primary DNA damage investigations are Comet Assay and Unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo* (OECD TG 486) as described by EFSA Scientific Committee (2011).

Currently, mycotoxins are still one of the most important food contaminant compounds. Along with their carcinogenic effects, mycotoxins can cause to mutations in our genetic structure by showing genotoxic effects. Too many types of mycotoxins have been detected so far. Numerous studies have been done on determining their genotoxic effects. Therefore, the aim of this study is to guide researchers in order to design better experiments by bringing all of the previous results together. In this study, both *in vitro* and *in vivo* genotoxic effects of mycotoxins are described in table 1.

2. Materials and Methods

A total of 259 mycotoxins were found as a result of the literature review (Atherton & Betb, 2019; Blanc et al., 1995; Bosio, Siciliano, Gilardi, Gullino, & Garibaldi, 2017; Chagas, Dias, & Pupo, 2013; Escrivá, Font, & Manyes, 2015; Hradil, Hallock, Clardy, Kenfield, & Strobel, 1989; Kokkonen, Ojala, Parikka, & Jestoi, 2010; Limón, Rodríguez-Ortiz, & Avalos, 2010; Lin, Zhang, Wang, Wang, & Chen, 1998; Mikami et al., 1984; Ostry, 2008). Undoubtedly, this number has been increasing day by day and new mycotoxins are being defined. Genotoxic and mutagenic effects of these mycotoxins have been reviewed by checking previous studies.

Genotoxicity or mutagenicity tests can be classified as *in vitro* tests, *in vivo* tests, bacterial tests (Ames test, also among *in vitro* tests), and molecular genotoxicity tests. These tests are also referred to as short-term genotoxicity tests. Previously published articles provided information on the advantages and disadvantages, the methodology, and the conditions to be considered of the *in vitro* testing system (Albertini et al., 2000; Atienzar & Jha, 2006; Kirsch-Volders et al., 1997; Maron & Ames, 1983; Norppa & Falck, 2003; Perry & Evans, 1975). More detailed information can be obtained from articles published in different years by the OECD (OECD 1986, 1997a, b) and EFSA Scientific Committee (EFSA, 2011, 2017).

More than 341 articles on investigation of genotoxic effects of mycotoxins were found by searching "Mycotoxin names and genotoxicity", "Mycotoxin names and mutagenicity", and "Mycotoxin names and comet assay" key words in PubMed. In these studies, genotoxic effects of various mycotoxins in different organisms were investigated using both *in vitro* and *in vivo* cytogenetic methods and molecular genotoxicity methods. In addition, the mutagenicity studies of mycotoxins with the Ames test were also reviewed. The obtained results from examining all previous studies are presented in table-formats (Table 1 and 3).

3. Results

A total of 259 mycotoxins were found in the literature. Genotoxic or mutagenic effects of 109 were investigated (Table 1). No studies have been found on the genotoxic or mutagenic effect of the remaining 150 mycotoxins (Table 2). This result shows that we have no knowledge about the genotoxicity or mutagenicity of 57.91% of all mycotoxins. Additionally, the methods used for cell and tissue types used in genotoxic studies are presented in Table 3.

Table 1. Genotoxic and mutagenic effects of mycotoxins that have been studied.

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Acetoxyscirpenol (mo-, di- and tri- derivatives) Trichothecenes	*Pa. tenuipe* *F. semirectum* *F. equiseti* *A. chevalieri*	*S. typhimurium*	LT2 strains					-	(Wehner et al., 1978a)
		E. coli	PQ37 strains					-	(Krivobok, Olivier, Marzin, Seigle-Murandi, & Steiman, 1987)
		D. melanogaster	Wing SMART				-	-	(Gürbüzel, Uysal, & Kızılet, 2015)
		Mice	Bone marrow	+					(Hassanane, Abdalla, El-Fiky, Amer, & Hamdy, 2000)
		Mice	Germ	+					(Hassanane et al. 2000)
Actinomycin D	*St. parvullus*	*S. typhimurium*	LT2 strains					+,-	(Beljanski et al., 1982; Benedict, Baker, Haroun, Choi, & Ames, 1977)
		E. coli	WP2 UvrA-					-	(Nestmann, Nasim, Haynes, & Kowbel, 1981)
		Euglena gracilis	Body cells				+		(Aoyama, Iwahori, & Miyata, 2003)
		S. cerevisiae	Haploid, diploid					-	(Nestmann et al., 1981)
		N. crassa	Ad-3 mutants					+	(Fisher, Malling, De Serres, & Snyder, 1975)
		Rat and Mice	Hepatocyte					+	(Mori et al., 1984)
		Chicken	DT40				+		(Yamamoto et al., 2011)
		Mice	Lymphoma tk+/-				+	+	(DeMarini, Brock, Doerr, & Moore, 1987; Wangenheim & Bolcsfoldi, 1988)
		Mice	Blastocysts				+		(Fabian et al., 2003)
		Chinese hamster	CHO 5 genetic loci					+	(Gupta & Singh, 1982)
		Chinese hamster	Lung CHL,V79			+	+		(Hashimoto et al., 2010; Olive & Banáth, 1997; Wilson, Harris, & Ferguson, 1984)
		Human	Fibroblast	+	+				(Parkes & Scott, 1982)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
		S. typhimurium	LT2 strains,					+	(Mori et al., 1986; Wehner, Marasas, et al., 1978; Wehner, Thiel, et al., 1978; Wong et al., 1977; Xu, Whong, & Ong, 1984; Yourtee & Kirk-Yourtee, 1986)
		S. typhimurium	SV50 ara					+	(Xu et al., 1984)
		E. coli	PQ37 strains					+	(Auffray & Boutibonnes, 1987; Krivobok et al., 1987; Sakai et al., 1992)
		Rat and Mice	Bone marrow		+	+			(Corcuera et al., 2015; Madle et al., 1986)
		Rat and Mice	Hepatocyte, Liver				+	+	(Corcuera et al., 2015; Mirsalis, Tyson, & Butterworth, 1982; Mori et al., 1984)
		Mice	Embrio					-	(Matthiaschk & Korte, 1986)
		Mice	C3H,FM3A	+?				+	(Umeda, Tsutsui, & Saito, 1977)
Aflatoxins (B1,B2,G1,G2,M1,Q1, Aflatoxicol)	*A. flavus, A. parasiticus*	Human	Lymphocytes			+			(Bayram et al., 2016)
Anthraquinones		Human	A549			+	+		(Jakšić et al., 2012)
		Human	Hepatocytes, Hep2, HepaRG cells			+	+		(Le Hegarat et al., 2010; Liu et al., 2019; Uhl, Helma, & Knasmüller, 2000)
		Human	Colon caco-2 cells				+		(Zhang et al., 2015)
		Human	Umblical cord blood cells				+		(Ghaderi, Allameh, Soleimani, Rastegar, & Ahmadi-Ashtiani, 2011)
		Chinese hamster	Bone marrow		-,+	-			(Madle et al., 1986; Matthiaschk & Korte, 1986)
		Turkey and Chicken	Fetal liver cells				+		(Williams, Deschl, & Williams, 2011)
		Pig	Blastocysts, Liver and blood cells				+		(Miranda et al., 2007; Shin, Guo, Niu, & Cui, 2018)
		Fish	blood, liver, kidney				+		(Abd-Allah, el-Fayoumi, Smith, Heckmann, & O'Neill, 1999)
		Monkey	Kidney Vero				+		(Golli-Bennour et al., 2010)
Agroclavine 1-propyl and 1-pentyl Clavine alkaloids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Glatt, Jung, & Oesch, 1983; Glatt, Pertz, Kasper, & Eich, 1992)
		E. coli	WP2 uvrA					+	(Glatt, Eich, Pertz, Becker, & Oesch, 1987)
1-allylelymoclavine Clavine alkaloids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Glatt et al. 1992)
6-allyl-1-propyl-6-norfestuclavine Clavine alkaloids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Glatt et al. 1992)
Alternariol Mycoestrogens	*Al. altyernata Al. tenuissima Ni. sphaerica*	Human	H-29, HT29				+,-		(Aichinger, Beisl, & Marko, 2017; Tiessen et al., 2013)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Alternariol Mycoestrogens	*Al. altyernata* *Al. tenuissima* *Ni. sphaerica*	Human	KYSE510, Colon cacao-2 cells				+		(Fernández-Blanco, Font, & Ruiz, 2015; Tiessen et al., 2017)
		Chinese hamster	V79				+		(Brugger et al., 2006; Fleck et al., 2016)
		Mice	L5178Y			+			(Brugger et al. 2006)
		Mice	Mcrophage RAW, fibroblast NIH/3T3				+		(Solhaug et al., 2012)
		S. typhimurium	LT2 strains					+,+?	(Schrader et al., 2006, 2001; Scott & Stoltz, 1980)
Altenuene Dibenzopyrone derivatives	*Alternaria* sp.	*S. typhimurium*	LT2 strains					-,+	(Schrader et al. 2006)
Altertoxin Polyketides stemphyperylenol	*Al. tenuissima* *Ni. sphaerica*	Human	HT29				-		(Schwarz et al., 2012)
		Chinese hamster	V79				-,+,+?		(Fleck, Burkhardt, Pfeiffer, & Metzler, 2012; Fleck et al., 2016; Schrader et al., 2006)
		S. typhimurium	LT2 strains					+	(Schrader et al., 2001, 2006)
Asperlin	*A. nidulans*	*S. typhimurium*	LT2 strains					-	(Glatt et al., 1983)
Aurosporin Quinone chemicals	*Ep. floccosum* *Mi. cookei*	*S. typhimurium*	LT2 strains					+?	(Mori, Kawai, Ohbayashi, Kitamura, & Nozawa, 1983)
Austdiol	*A. ustus* *Penicillium* sp.	*S. typhimurium*	LT2 strains					+	(Wehner et al., 1978b)
Austocystins A, D	*A.puniceus* *A.ustus* *Penicillium* sp.	*S. typhimurium*	LT2 strains					+	(Wehner et al., 1978b)
Averufin (dehydroaverufin) Anthraquinones	*A. versicolor* *A. multicolor*	*E. coli*	PQ37 strains					-	(Krivobok et al., 1987)
		S. typhimurium	LT2 strains					+?	(Wong et al., 1977)
		Rat and Mice	Hepatocyte					+	(Mori et al., 1984)
Azaserine***	Natural	Rat and Mice	Hepatocyte				+	+	(Mori et al., 1984; Mirsalis et al. 1982)
		Rat	Pancreas				+		(Shepherd, Tsao, & Duguid, 1990; Zurlo, Roebuck, Rutkowski, Curphey, & Longnecker, 1984)
		Rat	Kidney				-		(Tyson & Mirsalis, 1985)
		Chinese hamster	V79					+	(Schaeffer, Curphey, & Longnecker, 1987)
Baccharin B3,B4,B5***	Natural	*E. coli*	PQ37 strains					-	(Sakai et al., 1992)
Beauvericin Emerging mycotoxins	*B. bassiana* *Fusarium* sp. *Co. coronatus*	Human	Lymphocyte	+	+	+	+		(Celik, Aksoy, & Yilmaz, 2010; Klarić, Darabos, Rozgaj, Kasuba, & Pepeljnjak, 2010)
		Pig	Kidney PK15				+		(Klarić et al., 2010)
Bikaverin Polyketides stemphyperylenol	*Fusarium* sp. *My. jaapii* *V. agaricinum*	Rat	Hepatocyte				-		(Norred, Plattner, Vesonder, Bacon, & Voss, 1992)
17-bromofestuclavine Clavine alkaloids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Yen, Chang, Sheu, & Chiang, 2001;Glatt et al., 1992)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
13-bromo-1-cyclopropylmethylfestuclavine Clavine alkaloids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Glatt et al., 1992)
Candidusin B	*A. candidus*	Human	intestine 407				-		(Yen, Chang, Sheu, & Chiang, 2001)
		Salmonella	LT2 strains					-	(Yen et al., 2001)
Chaetoglobosin B (Penochalasin)	*Ch. globosum* *P. chrysogenum*	Mice	C3H,FM3A	-				-	(Umeda et al., 1977)
Chevalone	*N. siamensis*	Human	Colon HCT116 Liver HepG2 Melanoma A375				-		(Prata-Sena et al., 2016)
Chrysazin (Dantron) Anthraquinones	*Paraconiothyrium* sp.	*E. coli*	PQ37 strains					-	(Sakai et al., 1992)
		S. typhimurium	LT2 strains					+	(Krivobok, Seigle-Murandi, Steiman, Marzin, & Betina, 1992; Tikkanen, Matsushima, & Natori, 1983; Zhang et al., 2011)
		Human	Brain GBM8401				+		(Lu et al., 2010)
		Mice	Balb/c 3T3			+	+		(Zhang et al., 2011)
		Mice	Lymphoma L5178Y			+	+	+	(Müller, Eckert, Lutz, & Stopper, 1996)
		Rat and Mice	Hepatocyte					+	(Mori et al., 1984)
Chrysophanol Anthraquinones	*P. rugulosum* *P. islandicum*	*E. coli*	PQ37 strains					-	(Sakai et al., 1992)
		S. typhimurium	LT2 strains					+	(Liberman et al., 1980; Tikkanen et al., 1983)
		S. typhimurium	TM677,LT2 strains					-	(Stark et al., 1978)
		Human	Lung A549				+		(Ni et al., 2014)
		Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
		Mice	Lymphoma L5178Y			-	-	-	(Mueller et al., 1999)
		Chinese hamster	Ovary	-					(Mengs et al., 2001)
		E. coli	PQ37 strains					-	(Auffray & Boutibonnes, 1987)
Citrinin Benzopyran compounds	*P. expansum* *P. viridicatum* *P. citrinum* *P. camemberti* *A. niveus, A. terreus* *A .oryzae* *A. candidus* *A. carneus* *A. flavipes* *M. ruber* *M. purpureus*	Human	Lymphocyte		-	+		-	(Dönmez-Altuntas, Dumlupinar, Imamoglu, Hamurcu, & Liman, 2007)
		Human	Hep3B		+				(Anninou, Chatzaki, Papachristou, Pitiakoudis, & Simopoulos, 2014)
		Human	Lymphocytes, HEK293		-		-		(Liu et al., 2003)
		Pig	Kidney PK15			+			(Klarić et al., 2012)
		Monkey	Renal				+?		(Bouslimi et al., 2008)
		Mice	Bone marrow	+?					(Bouslimi et al., 2008)
		Rat	F344 and gpt delta	-			-	-	(Kuroda et al., 2013)
		Chinese hamster	Ovary and HEK293	-	-			-	(Flajs & Peraica, 2009; Liu et al., 2003)
		Chinese hamster	V79	+	+				(Thust & Kneist, 1979)
		Mice	Bone marrow	+					(Jeswal, 1996)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Citrinin Benzopyran compounds	*P. expansum* *P. viridicatum* *P. citrinum* *P. camemberti* *A. niveus, A. terreus* *A .oryzae* *A. candidus* *A. carneus* *A. flavipes* *M. ruber* *M. purpureus*	*E. coli*	PQ37 strains					-	(Auffray & Boutibonnes, 1987; Krivobok et al., 1987; Malaveille, Brun, & Bartsch, 1991, 1994; Sakai et al., 1992)
		S. typhimurium	LT2 strains					+,-	(Flajs & Peraica, 2009; Wehner, Thiel, et al., 1978; Würgler, Friederich, & Schlatter, 1991)
6-cyano-1-propyl-6-norfestuclavine Clavine alkaloids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Glatt et al., 1992)
Cyclochlorotine Chlorinated pentapeptide	*P. rugulosum* *P. islandicum*	*S. typhimurium*	TM677, LT2 strains					-	(Stark et al., 1978)
1-cyclopentylfes-tuclavine Clavine alkaloids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Glatt et al., 1992)
Cyclopiazonic acid Ergoline alkaloids	*A. flavus* *A. versicolor* *P. aurantiogriseum* *P. griseofulvum* *P. roqueforti* *P. camembertii* *P. cyclopium* *P commune*	*S. typhimurium*	LT2 strains					-	(Wehner et al., 1978b)
Cyclosporin A Non-ribosomal peptide	T. inflatum	Human	Lymphocytes	-	+	+			(Shah, Prasanth Kumar, Rao, & Pandya, 2018; Yuzawa, Kondo, Fukao, Iwasaki, & Hamaguchi, 1986; Zwanenburg & Cordier, 1994)
		Human	MRC-5			+	+		(Cilião et al., 2015)
		Mice	Bone marrow	-		-			(Matter, Donatsch, Racine, Schmid, & Suter, 1982)
		Chinese hamster	Bone marrow	-		-			(Matter et al., 1982)
Cytochalasin B, E Polyketide-amino acid hybrid	*Phoma* sp. *A. clavatus*	Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
		Human	Lymphocytes	+		-,+			(Fenech & Morley, 1985; Lindholm, Norppa, Hayashi, & Sorsa, 1991)
2,4-dihydroxy-3-methylacetophenon	*N. siamensis*	Human	Colon HCT116 Liver HepG2 Melanoma A375				-		(Prata-Sena et al., 2016)
Duclauxin, Xenoclauxin and desacetylduclauxin	*P. duclauxii*	Rat and Mice	Hepatocyte					-	(Mori et al., 1984; Kawai et al. 1985)
Echinuline Diketopiperazines	*A. amstelodami* *A. chevalieri* *A. herbariorum* *Eu. chevalieri*	Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
Emodin,Archin,Emodol, Frandulic Acid Anthraquinones	*P. rugulosum* *P. islandicum* *A. glaucus* *A. aureus* *A. sclerotiorum* *A. terreus* *A. wentii*	*E. coli*	PQ37 strains					-	(Sakai et al., 1992)
		S. typhimurium	LT2 strains					+,-	(Krivobok et al., 1992; Li et al., 2010; Nesslany et al., 2009; Tikkanen et al., 1983)
		S. typhimurium	TM677,LT2 strains					-	(Stark et al., 1978)
		Human	Lymphocytes, MCF-7, SCC-4, H460 cells			+	+	+	(Brkanac et al. 2015; Li et al., 2013; Li et al., 2010; Chen et al., 2010; Lee et al., 2006)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Emodin,Archin,Emodol, Frandulic Acid Anthraquinones	*P. rugulosum* *P. islandicum* *A. glaucus* *A. aureus* *A. sclerotiorum* *A. terreus* *A. wentii*	Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
		Mice	Lymphoma L5178Y			+	-,+	+	(Müller et al., 1996; Mueller et al. 1999)
		Mice	Liver,Kidney			+	+		(Nesslany et al., 2009)
Enniatin B Emerging mycotoxins	*Fusarium* sp. *Co. coronatus*	Chinese hamster	V79	-		-	-	-	(Föllmann et al., 2009; Behm et al., 2009)
		S. typhimurium	LT2 strains					-	(Föllmann et al., 2009; Behm et al., 2009)
		Human	HeLa	-	+	-	+		(Mamur et al., 2018a)
Festuclavine Clavine alkaloids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Glatt et al., 1992)
Fiscalin A (epi-neofiscalin A, epi-fiscalin A, C)	*N. siamensis*	Human	Colon HCT116 Liver HepG2 Melanoma A375				-		(Prata-Sena et al., 2016)
Flavoglaucin	*A. ruber*	Rat and Mice	Hepatocyte					-	(Mori et al., 1984; Kawai et al., 1983)
Floccosin Quinone chemicals	*Ep. floccosum* *Mi .cookei*	Rat and Mice	Hepatocyte					-	(Mori et al., 1983; 1984)
		S. typhimurium	LT2 strains					+?	(Mori et al., 1983)
Fumagillin	*A. fumigatus*	Mice	Bone marrow	+		+			(Stanimirovic et al., 2007)
		Human	Lymphocytes	+	+	+			(Stevanovic et al., 2008)
Fumitremorgen B Tremorgenic mycotoxins	*A. caespitosus* *A. egyptiacus* *A. fumigatus* *N. fischeri*	*S. typhimurium*	LT2 strains					-	(Wehner et al,. 1978b; Sabater-Vilar et al., 2003)
		Human	Lymphocytes				+		(Sabater-Vilar et al., 2003)
Fumonisin B(1), B(2)yB(3),FB(1),FB(2)yFB(3) Trichothecenes	*F. verticillioides* *F. moniliforme* *F. proliferatum* *F. nygamai* *Al. alternata* *A. niger* *Co. coronatus*	Rats, Mice	Bone marrow			+,-	+		(Theumer et al., 2010; Aranda et al., 2000; Karuna & Rao, 2013)
		Rat	Hepatocyte	+		+	-		(Knasmüller et al., 1997; Norred et al., 1992)
		Rat	Kidney, Astrocytes				+		(Domijan et al., 2007; Domijan et al., 2006; Galvano et al., 2002a)
		Human	Lymphocytes, HepG2 cells, Fibroblasts	+	+	+	+		(Lerda et al.,2005; Domijan et al., 2015; Ehrlich et al., 2002a; Galvano et al., 2002b)
		Allium cepa	Root tip cells	+					(Lerda et al., 2005)
		E. coli	PQ37 strains					-	(Knasmüller et al., 1997)
		S. typhimurium	LT2 strains					-	(Aranda et al., 2000; Knasmüller et al., 1997; Ehrlich et al., 2002a)
Fusarenon X Trichothecenes	*F. graminearum*	Chinese hamster	V79 cells	+?	+?				(Thust et al., 1983; Bony et al., 2007)
		Human	Enterocyte-like Caco-2				+		(Bony et al., 2007)
		Mice	C3H,FM3A	-				-	(Umeda et al., 1977)
Fusaric acid	*F. heterosporium*	Human	Lymphocytes	-	-	-	+		(Mamur at al., 2018b)
		Human	Oesophageal SNO, HepG2				+		(Ghazi et al., 2017; Devnarain et al., 2017)
Fusarin Mycoestrogens	*F. moniliforme*	Rat	Hepatocyte				?		(Norred et al., 1992)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
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Gliotoxin Epipolythiodioxo piperazine	*A. fumigatus* *A. terreus* *A. flavus* *A. niger* *Eu. chevalieri,* *N. pseudofischeri*	*E. coli*	PQ37 strains					-	(Auffray & Boutibonnes, 1987; Nieminen et al., 2002)
		E. coli	WP2, CM871				+		(Nieminen et al., 2002)
		S. typhimurium	LT2 strains					-	(Nieminen et al., 2002)
		Chinese hamster	Ovary		-				(Nieminen et al., 2002)
		Mice	Macrophage RAW264.7					+	(Nieminen et al., 2002)
Griseofulvin	*P. griseofulvum* *P. janczewskii*	*E. coli*	PQ37 strains					-	(Venier et al., 1989)
		S. typhimurium	LT2 strains					-	(Wehner et al., 1978b)
		Mice	Bone marrow		+				(Curry et al., 1984)
		Mice	Lymphoma L5178Y			+			(Oliver et al., 2006)
		Mice	Spermatocyte, Oocyte	+					(Fahmy & Hassan, 1996; Mailhes et al., 1993)
		Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
		D.melanogaster	Wing SMART				+	+	(Inoue, Baba, Awano, & Yoshikawa, 1995)
		Human	Lymphocyte	+	+	+	+		(Frenzilli, Bosco, & Barale, 2000; Migliore & Nieri, 1991; Muehlbauer & Schuler, 2005; Rosefort, Fauth, & Zankl, 2004)
		Vicia faba	Root tip cells	+					(Sandhu & Acedo, 1988)
3-hydroxyterphenyllin	*A. candidus*	Human	intestine 407				-		(Yen et al., 2001)
		Salmonella	LT2 strains					-	(Yen et al., 2001)
Iridoskyrin Anthraquinones	*P. rugulosum* *P. islandicum*	Rat	Hepatocyte					-	(Mori et al., 1988)
		S. typhimurium	TM677,LT2 strains					-	(Stark et al., 1978)
Islandicin Anthraquinones	*P. rugulosum* *P. islandicum*s	*S. typhimurium*	LT2 strains					+	(Liberman et al., 1980; Tikkanen et al., 1983)
		S. typhimurium	TM677,LT2 strains					-	(Stark et al., 1978)
		Rat	Hepatocyte					-	(Mori et al., 1988)
Kojic acid	*A. arachidicola* *A. candidus* *A. minisclerotigenes* *A. oryzae* *Penicillium* sp.	*S. typhimurium*	LT2 strains					+,+?	(Bjeldanes & Chew, 1979; Higa et al., 2007; Nohynek et al., 2004; Shibuya, Murota, Sakamoto, Iwahara, & Ikeno, 1982; Wehner, Thiel, et al., 1978; Wei, Huang, Fernando, & Chung, 1991)
		E. coli	WP2uvrA					+	(Nohynek et al., 2004)
		Rat	Liver, bone marrow			-	-		(Higa et al., 2007; Ogiwara et al., 2015; Suzuki et al., 2005)
		Rat	Lymphocyte			+?,+	-		(Ogiwara et al., 2015; Suzuki et al., 2005)
		Mice	Epiderma, Bone marrow			-	-		(Higa et al., 2007; Nohynek et al., 2004)
		Mice	Lymphoma					-	(Nohynek et al., 2004)
		Mice	Embrio					-	(Shibuya et al., 1982)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Kojic acid	*A. arachidicola* *A. candidus* *A. minisclerotigenes* *A. oryzae* *Penicillium* sp.	Chinese hamster	V79	+?			-	-	(Nohynek et al., 2004; Shibuya et al., 1982)
		Chinese hamster	Lung	-					(Higa et al., 2007)
		Chinese hamster	Ovary	+	+				(Wei et al., 1991)
		Human	Keratinocyte, hepatocyte			-			(Nohynek et al., 2004)
Leucinostatins Peptide mycotoxins	*Pa. lilacinus* *Pa. marquandii*	*A. nidulans*	Fungus cells					-	(Crebelli et al., 1988)
Luteoskyrin Lumiluteoskryin Anthraquinones	*P. islandicum* *P. rugulosum*	*S. typhimurium*	LT2 strain					-	(Wehner et al., 1978b; Stark et al., 1978; Tikkanen et al., 1983)
		S. typhimurium	TM677					+	(Stark et al., 1978)
		E. coli	PQ37 strains					-	(Sakai et al., 1992)
		Mice	C3H,FM3A	-				-	(Umeda et al., 1977)
		Rat and Mice	Hepatocyte					+	(Mori et al., 1984)
Luteosporin Quinone chemicals	*P. chermesinum* *Mi. cookei* *Ep. floccosum*	Rat and Mice	Hepatocyte					+	(Mori et al., 1983; 1984)
Lysergic acid, -diethylamide Clavine alkaloids	*C. purpurea*	Drosophila	Recessive lethal					+	(Browning, 1968)
		Mice and rats	Spermatocytes	+					(Goetz, Srám, & Zudová, 1974)
		Mice	Bone marrow			-			(Van Went, 1978)
		Mice	Dominant lethal					+	(Šrám, Zudová, & Goetz, 1974)
		Human	Lymphocyte	+					(Cohen, Marinello, & Back, 1967; Li & Lin, 1998; Muneer, 1978; Nielsen, Friedrich, Jacobsen, & Tsuboi, 1968)
		Human	Sperm	+					(Estop, Cieply, Vankirk, Munne, & Garver, 1991)
1-methyllysergol methyl ether Clavine alkalaoids	*C. purpurea*	*S. typhimurium*	LT2 strains					+	(Glatt et al., 1992)
Mevinolin (lovastatin) (dihydromevinolin)	*A. terreus*	Chicken	**DT40**				+		(Yamamoto et al., 2011)
		Human	**Colon HT29 cells**				+		(Jafari, Rezaei, Kalantari, & Hashemitabar, 2013)
Mitomycin C	*St. caespitosus*	Human	Lymphocyte	+	+		+		(Frenzilli et al., 2000; Muehlbauer & Schuler, 2005; Rosefort et al., 2004)
		Human, Mice	Lymphocytes				-		(Wang & Qian, 1997)
		Mice	L5178Y, Multiple organs				+		(Miyamae et al., 1997; Sasaki, Nishidate, Izumiyama, Matsusaka, & Tsuda, 1997)
		Mice	Erythroblasts			+			(Cole, Taylor, Cole, & Arlett, 1981)
		Mice	Bone marrow, L929			+			(Salamone et al., 1980, Nito et al., 1988)
		Rat	Lymphocytes				+		(Wang & Qian, 1997)
		Rat	HTC		+				(Dean, Bynum, Kram, & Schneider, 1980)
		Rat and Mice	Hepatocyte					+	(Mori et al., 1984)
		Chinese hamster	**CHO 5 genetic loci**					+	(Gupta & Singh, 1982)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Mitomycin C	*St. caespitosus*	Chinese hamster	**V79**			+			(Krishna, Kropko, & Theiss, 1989)
		Oncorhynchus mykiss	**Gonad RTG-2**	+	+				(Kocan, Landolt, & Sabo, 1982)
		Vicia faba	Ceeds				+		(Koppen & Verschaeve, 1996)
		Euglena gracilis	Body cells				+		(Aoyama et al., 2003)
		S. typhimurium	LT2 strains					+	(Beljanski et al., 1982)
		E. coli	PQ37 strains					+	(Venier et al., 1989)
Moniliformin Emerging mycotoxins	*Fusarium* sp.	*E. coli*	PQ37 strains					-	(Auffray & Boutibonnes, 1987; Knasmüller et al., 1997)
		S. typhimurium	LT2 strains					-	(Wehner et al., 1978a; Knasmüller et al., 1997)
		Rat	Hepatocyte	+		+	-		(Knasmüller et al., 1997; Norred et al., 1992)
		Human	Lymphocyte	+	+	+			(Celik et al., 2009)
Mycophenolic acid Meroterpenids	*Penicillium* sp.	*S. typhimurium*	LT2 strains					-	(Wehner et al., 1978b)
		Mice	C3H,FM3A	+?				+	(Umeda et al., 1977)
Nidurufin	*A. versicolor* *P.* flavidorsum	*S. typhimurium*	LT2 strains					+?	(Mori et al., 1985)
		Rat	Hepatocyte					+?	(Mori et al., 1985)
3-Nitropropionic acid	*A. flavus* *A. oryzae* *A. wentii*	Mice	Blood			+			(Alarcón-Herrera et al., 2017; Norberto et al., 2017)
		Mice	lymphoma tk+/-					+	(Oshiro, Piper, Balwierz, & Soelter, 1991)
		Chinese hamster	CHO/HPGRT			-			(Oshiro et al., 1991)
		Drosophila melanogaster	Wing SMART				+		(Batiste-Alentorn, Xamena, Creus, & Marcos, 1995)
		S. typhimurium	LT2 strains					+,+?	(Oshiro et al., 1991; Hansen, 1984)
Nivalenol, 3- and 15-acetyldeoxy derivatives Trichothecenes	*A. flavus*, *P. aurantiogriseum* *F. nivale* *F. graminearum*	Human	Enterocyte-like Caco-2				+		(Bony et al., 2006; 2007)
		Human	Lymphocyte	+			+		(Yang et al., 2014)
		Human	TK6,HepaRG			+?	-		(Takakura, Nesslany, Fessard, & Le Hegarat, 2014)
		Boar	Lymphocytes	+					(Lusky, Wagner, Stähr, Doberschütz, & Peter, 1991)
		Chinese hamster	Ovary cells				+		(Tsuda et al., 1998)
		Mice	Organs and tissues				±		(Tsuda et al., 1998)
		Mice	Hepatocyte, bone marrow			+	+		(Singh, Banerjee, Chattopadhyay, Borthakur, & Veer, 2015)
		Chinese hamster	V79 cells	+?	+?				(Hsia, Wu, Lu, & Li, 1988; Thust, Kneist, & Hühne, 1983)
		S. typhimurium	LT2 strains					-	(Wehner et al., 1978a; Takakura et al., 2014)
Norsolorinic acid Trichothecenes Anthraquinones	*A. versicolor*	*E. coli*	PQ37 strains					-	(Krivobok et al., 1987)
		S. typhimurium	LT2 strains					+?	(Wong et al., 1977; Mori et al., 1985)
		Rat	Hepatocyte					+?	(Mori et al., 1985)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Ochratoxin A Ochratoxin mycotoxins	*A. ochraceus* *A. alliaceus* *A. auricomus* *A. carbonarius* *A. glaucus* *A. melleus* *A. niger* *A. affinis* *A. albertensis* *A. citricus* *A. fonsecaeus* *A. lanosus* *A. ochraceopetaliformis* *A. ostianus* *A. petrakii* *A. sclerotiorum* *A. sulphureus* *P. verrucosum*	Human	Hep3B, HepG2		+		+		(Anninou et al., 2014; Ehrlich et al., 2002b)
		Human	Lymphocytes		+	+	+,+?		(Domijan, Gajski, Novak Jovanović, Gerić, & Garaj-Vrhovac, 2015; Dönmez-Altuntaş, Hamurcu, Imamoglu, & Liman, 2003; González-Arias et al., 2014; Hennig, Fink-Gremmels, & Leistner, 1991; Klarić et al., 2010; J. Liu et al., 2012)
		Human	Urothelial, Fibroblast, kidney			+	+		(Ali et al., 2011; Degen, Lebrun, Lektarau, & Föllmann, 2005; Dörrenhaus et al., 2000; Lebrun, Golka, Schulze, & Föllmann, 2006; Robbiano, Baroni, Carrozzino, Mereto, & Brambilla, 2004; Russo et al., 2005)
		Human	A549, HK-2, CYP2C9-hOR, CYP3A4-hOR, Neuro-2a,				+		(Arbillaga, Azqueta, Ezpeleta, & López de Cerain, 2007; Bhat et al., 2016; Šegvić Klarić et al., 2015; Simarro Doorten, Nijmeijer, de Nijs-Tjon, & Fink-Gremmels, 2006)
		Monkey	Renal, kidney vero				+?,+		(Bouslimi et al., 2008; Costa et al., 2016; Golli-Bennour et al., 2010)
		Canine	Kidney				+		(Lebrun & Föllmann, 2002)
		Bovine	Lymphocytes	+	+				(Lioi, Santoro, Barbieri, Salzano, & Ursini, 2004)
		Mice	Liver, kidney				+		(Creppy et al., 1985)
		Mice	Bone marrow	+?		-			(Bouslimi et al., 2008; Corcuera et al., 2015)
		Mice	L5178Y tk(+/-)				+,-	+	(Ali et al., 2014; Bendele et al., 1985)
		Mice	C3H,FM3A	-				-	(Umeda et al., 1977)
		Rat and Mice	Hepatocyte, kidney			+	+,-	+	(Bendele et al., 1985; Corcuera et al., 2015; Domijan, Zeljezić, Kopjar, & Peraica, 2006; Mori et al., 1984; Robbiano et al., 2004; Zeljezić, Domijan, & Peraica, 2006)
		Rat	F344 and gpt delta, Liver, kidney				+		(Kamp et al., 2005; Kuroda et al., 2014; Mally et al., 2005)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Ochratoxin A Ochratoxin mycotoxins	*A. ochraceus* *A. alliaceus* *A. auricomus* *A. carbonarius* *A. glaucus* *A. melleus* *A. niger* *A. affinis* *A. albertensis* *A. citricus* *A. fonsecaeus* *A. lanosus* *A. ochraceopetaliformis* *A. ostianus* *A. petrakii* *A. sclerotiorum* *A. sulphureus* *P. verrucosum*	Pig	Kidney PK15, bladder epithelial		+	+	+		(Föllmann, Hillebrand, Creppy, & Bolt, 1995; Föllmann & Lebrun, 2003; Klarić et al., 2010, 2012)
		Chinese hamster	V79, CHO-K1-BH4 bladder epithelial		-	+	+		(Ali et al., 2011; Bendele et al., 1985; Föllmann, Behm, & Degen, 2007)
		Allium cepa	Root tip cells	+					(Lerda, Biagi Bistoni, Pelliccioni, & Litterio, 2010)
		E. coli	PQ37 strains					-,+	(Auffray & Boutibonnes, 1987; Krivobok et al., 1987; Malaveille et al., 1991, 1994; Sakai et al., 1992)
		S. typhimurium	LT2 strains					-,+	(Bendele et al., 1985; Ehrlich et al., 2002b; Hennig et al., 1991; Obrecht-Pflumio, Chassat, Dirheimer, & Marzin, 1999; Wehner, Thiel, et al., 1978b; Würgler, Friederich, & Schlatter, 1991)
Ochratoxin B Ochratoxin mycotoxins	*A. acanthosporus* *A. albertensis* *A. alliaceus* *A. auricomus* *A. carbonarius* *A. ochraceopetaliformis* *A. ochraceus* *A. sclerotiorum* *A. sulphureus* *A. wentii*	Rat	F344,Liver, Kidney				+		(Mally et al., 2005)
		E. coli	PQ37 strains					-	(Malaveille et al., 1991; 1994)
		S. typhimurium	LT2 strains					-	(Würgler et al., 1991)
Ochratoxin alpha Ochratoxin mycotoxins	*Aspergillus* sp.	*E. coli*	PQ37 strains					-	(Malaveille et al., 1991; 1994)
		Pig	Bladder epithelial		+				(Föllmann et al., 1995)
Oosporein Quinone chemicals	Cc. kusanoi.	Canine and Mice	Kidney, Spleen, RAW 264,7 cells,				+		(Ramesha et al., 2015)
Oxalic acid	*A. niger*	Human	Buccal cells				+		(Unlu & Saglar, 2015)
Patulin Benzopyran compound	*P. patulum* *P. expansum* *P. expansum* *Byssochlamy* sp. *A. clavatonanicus* *A. clavatus* *A. longivesica* *A. terreus*	*S. typhimurium*	LT2 strains					-	(Würgler et al., 1991)
		E. coli	PQ37 strains					-	(Auffray and Boutibonnes, 1987; Krivobok et al., 1987; Sakai et al., 1992)
		Chinese hamster	V79, bone marrow, CHO	+	+		+	+	(Alves, Oliveira, Laires, Rodrigues, & Rueff, 2000; Liu et al., 2003; Matthiaschk & Korte, 1986; Schumacher, Metzler, & Lehmann, 2005)
		Mice	Embrio					-	(Matthiaschk and Korte, 1986)
		Mice	Bone marrow	+		+			(Song et al., 2014)
		Mice	Brain, kidney, skin				+		(de Melo et al., 2012; Saxena et al., 2009)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Patulin Benzopyran compound	*P. patulum* *P. expansum* *P. expansum* *Byssochlamy* sp. *A. clavatonanicus* *A. clavatus* *A. longivesica* *A. terreus*	Mice	C3H,FM3A	+				+	(Umeda et al., 1977)
		Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
		Human	Lymphocytes, HEK293		+		+		(Liu et al., 2003)
		Human	Lymphocytes			+			(Alves et al., 2000; Donmez-Altuntas, Gokalp-Yildiz, Bitgen, & Hamurcu, 2013)
		Human	HepG2			+	+		(Zhou, Jiang, Geng, Cao, & Zhong, 2009, 2010)
Paxilline Tremorgenic mycotoxins	*Aspergillus* sp. *Penicillium* sp. *Claviceps sp*	*S. typhimurium*	LT2 strains					-	(Sabater-Vilar, Nijmeijer, & Fink-Gremmels, 2003)
		Human	Lymphocytes				+		(Sabater-Vilar et al., 2003)
Penicillic acid Isopropylidene tetronic acid	*P. roqueforti* *P. camemberti* *Aspergillus* sp.	*S. typhimurium*	LT2 strains					-	(Wehner et al., 1978b)
		E. coli	PQ37 strains					-	(Krivobok et al., 1987; Auffray & Boutibonnes, 1987)
		Mice	C3H,FM3A	+				+	(Umeda et al., 1977)
		Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
Penitrem A Tremorgenic mycotoxins	*P. crustosum*	Human	Lymphocytes				-		(Sabater-Vilar et al., 2003)
		S. typhimurium	LT2 strains					-	(Sabater-Vilar et al., 2003)
Physcion Anthraquinones	*Microsporum* sp. *A. glaucus*	*S. typhimurium*	LT2 strains					+	(Krivobok et al., 1992)
		Mice	Lymphoma L5178Y			-	-	-	(Mueller et al., 1999)
Pibasterol	*P. rugulosum* *P. islandicum*	*S. typhimurium.*	TM677,LT2 strains					-	(Stark et al., 1978)
PR toxins	*P. roqueforti* *P. camemberti*	*E. coli*	PQ37 strains					-	(Auffray & Boutibonnes, 1987; Sakai et al., 1992)
		S. typhimurium	LT2 strains					-	(Moulé, Hermann, & Renault, 1981; Xu et al., 1984)
		S. typhimurium	SV50 ara					+	(Xu et al., 1984)
		Chinese hamster	V79		-				(Moulé et al., 1981)
Radicinin	*Al. alternata*	*S. typhimurium*	LT2 strains					-,+	(Schrader et al., 2001; 2006)
Roquefortine Diketopiperazines	*P. roqueforti* *P. camemberti*	*S. typhimurium*	LT2 strains					-	(Schoch, Lüthy, & Schlatter, 1984)
Roridin A Trichothecenes	*Mr. roridum* *Cylindocarpon* sp.	*E. coli*	PQ37 strains					-	(Sakai et al., 1992)
Rubratoxin B Alpha, beta unsatu-rated lactone	*P. rubrum*	*E. coli*	PQ37 strains					-	(Sakai et al., 1992)
Rubroskyrin Anthraquinones	*P. rugulosum* *P. islandicum*	*S. typhimurium*	TM677s					+	(Stark et al., 1978)
		S. typhimurium	LT2 strains					-	(Stark et al., 1978)
		Rat	Hepatocyte					-	(Mori et al., 1988)
Rugulosin Anthraquinones	*P. rugulosum* *P. islandicum*	*E. coli*	PQ37 strains					-	(Sakai et al., 1992)
		S. typhimurium	LT2 strains					-,+?	(Tikkanen et al., 1983; Stark et al., 1978; Krivobok et al., 1992; Mori et al., 1983)
		S. typhimurium	TM677					+	(Stark et al., 1978)
		Rat and Mice	Hepatocyte					-	(Mori et al., 1983; 1984)
Satratoxin H Trichothecenes	*S. chartarum* *S. atra*	Rat	P12	+		+	-	+	(Nusuetrong et al., 2012)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Secalonic acid D	*A. aculeatus* *A. ochraceus* *A. uvarum* *A. japonicus*	*S. typhimurium*	LT2 strains					-	(Wehner et al., 1978b)
		Mice	Male germ					-	(Reddy, Reddy, Chan, & Hayes, 1980)
		Mice	Bone marrow			+?			(Reddy et al., 1980)
		Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
Simatoxin	*P. rugulosum,* *P. islandicum*	*S. typhimurium*	LT2 strains					-	(Stark et al., 1978)
		S. typhimurium	TM677					+	(Stark et al., 1978)
Skyrin Anthraquinones	*P. rugulosum* *P. islandicum*	*S. typhimurium*	LT2 strains					-	(Tikkanen et al., 1983; Krivobok et al., 1992)
		S. typhimurium	TM677					+	(Stark et al., 1978)
		Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
Sporidesmin Epidithiodioxopi-perazine mycotoxins	*Pi. chartarum*	*S. typhimurium*	LT2 strains					-	(Ferguson et al., 1992)
		Mice	Bone marrow			+?			(Munday, Pearson, & Ferguson, 1993)
		Chinese hamster	AA48	+					(Ferguson et al., 1992)
		Sheep	Lymphocytes		-				(Ferguson et al., 1992)
Stemphyltoxin Perylenequinone metabolites	*Al. alternata* *Al.* cassiae *Se. botryosum*	*S. typhimurium*	LT2 strains					+	(Davis & Stack, 1991)
		Chinese hamster	V79				+		(Fleck et al., 2016)
Stemphyperylenol	*Al. alternata* *Al.* cassiae	*S. typhimurium*	LT2 strains					+	(Davis & Stack, 1991)
Sterigmatin	*A. nidulans* *A. versicolor*	*S. typhimurium*	LT2 strains					-	(Mori et al., 1986)
Sterigmatocystin, (5,6-Dimethoxy-,O-methyl-,5-methoxy-, 5-Methoxydihydros-,Dihydro-, Demethyl-, Demethyldihydro-, O-Acetyls-, Hydroxymethyl-) derivatives Anthraquinones	*A. versicolor* *A. parasiticus* *A. flavus* *A. rambellii* *A. discophorus* *A. multicolor* *A. nidulans* *A. olivicola* *A. ustus* *Emericella nidulans,* *Emericella venezuelensis*	*E. coli*	PQ37 strains					+	(Krivobok et al., 1987; Sakai et al., 1992)
		S. typhimurium	LT2 strains					+,-	(Wehner et al., 1978a; 1978b, 1979; Mori et al., 1986; Wong et al., 1977)
		Human	Hep3B,A549, Liver cells, GES-1		+	+	+		(Anninou et al., 2014; Gao et al., 2015; Jakšić et al., 2012; Zhang et al., 2013)
		Chinese hamster	V79				-		(Fleck et al., 2016)
		Mice	C3H,FM3A	+?				+	(Umeda et al., 1977)
		Mice	Bone marrow		+				(Curry, Reed, Martino, & Kitchin, 1984)
		Rat and Mice	Hepatocyte					+	(Mori et al., 1984)
T-2 toxins Trichothecenes	*F. sporotrichioides* *F. sulphureum*	*S. typhimurium*	LT2 strains					-	(Wehner et al, 1978a; 1978b)
		E. coli	PQ37 strains					-	(Krivobok et al., 1987)
		Chinese hamster	V79 cells	+?	+?	+			(Hsia et al., 1988; Li & Lin, 1998; Thust et al., 1983)
		Chiken	Blood, liver, spleen leukocytes				+		(Frankic, Pajk, Rezar, Levart, & Salobir, 2006; Rezar, Frankič, Narat, Levart, & Salobir, 2007; Sokolovic, Garaj-Vrhovac, Ramic, & Simpraga, 2007)
		Pig	Mononuclear cells				+		(Horvatovich et al., 2013)
		Mice	Leydig cells				+		(Zhang, Yang, Li, & Zhou, 2017)
		Rat	Hepatocyte, esophageal epithelial		+				(Li & Lin, 1988)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
T-2 toxins Trichothecenes	*F. sporotrichioides* *F. sulphureum*	*D. melanogaster*	Wing SMART				-	-	(Gürbüzel et al., 2015)
Tentoxin	*Al. alternata* *Al. tenuis*	*S. typhimurium*	LT2 strains					-	(Schrader et al., 2006, 2001)
Tenuazonic Acid Tetramic acid deri-vatives	*Al. tenuis* *Al. alternata*	*S. typhimurium*	LT2 strains					-	(Parkes & Scott, 1982; Schrader et al., 2006, 2001)
		Human	HT29				-		(Schwarz et al., 2012)
Tryptoquivaline (Iso-,Nor-derivatives)	*A. fumigatus* *A. clavatus* *N. fischeri* *N. siamensis*	Human	Colon HCT116 Liver HepG2 Melanoma A375				-		(Prata-Sena et al., 2016)
Verrucosidin Tremorgenic mycotoxins	*P. aurantiogriseum* *P. melanoconidium*	Human	Lymphocytes				+		(Sabater-Vilar et al., 2003)
	P. polonicum	*S. typhimurium*	Lt2 strains					+	(Sabater-Vilar et al., 2003)
Verruculogen Tremorgenic mycotoxins	*A. egyptiacus* *A. fumigatus* *P. estinogenum* *N. fischeri*	Human	Lymphocytes				-		(Sabater-Vilar et al., 2003)
		S. typhimurium	Lt2 strains					+	(Sabater-Vilar et al., 2003)
Versicolorin A, B (6,8-O-Dimethyl- and 6-deoxy-versicolorin) Anthraquinones	*A. flavus* *A. versicolor* *Penicillium sp*	*E. coli*	PQ37 strains					+	(Krivobok et al., 1987; Sakai et al., 1992)
		S. typhimurium	LT2 strains					+	(Wehner et al., 1978b; Wong et al., 1977; Mori et al., 1985)
		Rat and Mice	Hepatocyte					+	(Mori et al., 1984, 1985, 1988)
		Human	A549			+	+		(Jakšić et al., 2012)
Versiconal (hemiacetal acetate) Anthraquinones	*A. parasiticus* *A. versicolor*	*S. typhimurium.*	LT2 strains					+?	(Wong et al., 1977)
Violaceol (Aspermutarubrol, Ethericin A)	*A. funiculosus* *A. sydowii* *Em. Violacea*	Rat and Mice	Hepatocyte					-	(Mori et al., 1984)
Viomellein Benzopyran compounds	*A. melleus* *A. ochraceus* *Penicillium* sp.	*E. coli*	PQ37 strains					+?	(Auffray & Boutibonnes, 1987)
Viridicatumtoxin	*Aspergillus* sp. *Penicillium* sp.	*S. typhimurium*	LT2 strains					+	(Wehner et al., 1978b)
Vomitoxin (4-deoxynivalenol) Tricothecenes	*F. graminearum*	*E. coli*	PQ37 strains					-	(Knasmüller et al., 1997)
		S. typhimurium	LT2 strains					-	(Wehner et al., 1978a; Knasmüller et al., 1997; Takakura et al., 2014)
		Chinese hamster	V79	+?				-	(Hsia et al., 1988; Rogers & Héroux-Metcalf, 1983)
		Mice	Bone marrow			+			(Singh et al., 2015)
		Rat	Blood, tissue	+			+		(Abdel-Wahhab et al., 2018)
		Rat	Hepatocyte	+		+			(Knasmüller et al., 1997)
		Chicken	Lymphocytes, Spleen leukocytes				+		(Awad et al., 2012; Awad, Ghareeb, Dadak, Hess, & Böhm, 2014; Frankic et al., 2006)
		Boar	Lymphocytes	+					(Lusky et al., 1991)
		Human	Lymphocytes	+					(Yang et al., 2014)
		Human	Caco-2, intestinal				+		(Bony et al.,2006)
		Human	TK6,HepaRG			-	-		(Takakura et al., 2014)
		Human	HT29, HepG2				+		(Bensassi et al., 2009; Zhang et al., 2009)
Wortmannin	*A. janus*	Chinese hamster	V79			+			(Oliveira et al., 2002)

Mycotoxins and mycotoxin group	Fungus produced*	Test materials	Tissue and cells	Abnormalities**					References
				CA	SCE	MN	DF	GM	
Xanthomegnin Quinone chemicals	*A. melleus* *A. ochraceus* *A. sulphureus* *Tr. megninii* *Mi. cookei* *Ep. floccosum*	Rat and Mice	Hepatocyte					+	(Mori et al., 1983, 1984)
		S. typhimurium	LT2 strains					+?	(Mori et al., 1983)
Zearalenone (F2-Toxin) α-, β-zearalenol, Zeranol Mycoestrogens Trichothecenes	*F. graminearum* *F. culmorum* *F. equiseti* *F. crookwellense*	*S. typhimurium*	LT2 strains					-	(Wehner et al., 1978a; Bartholomew and Ryan, 1980)
		E. coli	PQ37 strains					-	(Krivobok et al., 1987; Auffray & Boutibonnes, 1987; Sakai et al., 1992)
		E. coli	C600					+	Ghédira-Chékir et al. 1998
		Chinese hamster	V79, CHO-K1	-	-		-,+	+	(Thust et al., 1983; Hsia et al., 1988; Scheutwinkel et al., 1986; Tatay et al., 2016)
		Boar	Lymphocytes	+					(Lusky et al., 1991)
		Bovine	Lymphocytes	+	+				(Lioi et al., 2004)
		Mice	Bone marrow	+		+			(Ayed, Ayed-Boussema, Ouanes, & Bacha, 2011; Ouanes et al., 2003)
		Mice	Liver, kidney				+		(Pfohl-Leszkowicz et al., 1995)
		Mice	Spermatids			-			(Pylkkänen et al., 1991)
		Mice	L5178Y tk(+/-)					-	(McGregor et al., 1988)
		Rat	Liver, kidney				-		(Pfohl-Leszkowicz et al., 1995)
		Monkey	Kidney vero	+		+	+		(Ayed-Boussema et al., 2007; Abid-Essefi et al., 2003; Ouanes et al., 2003)
		Human	HeLa	+					(Ayed et al., 2011)
		Human	Enterocyte-like Caco-2,DOK, HepG2; HEK293				+		(Abid-Essefi et al., 2003; Gao et al., 2013; Hassen, Ayed-Boussema, Oscoz, Lopez, & Bacha, 2007; Tatay, Espín, García-Fernández, & Ruiz, 2017)
		Zebrafish	Embrios				+		(Muthulakshmi, Maharajan, Habibi, Kadirvelu, & Venkataramana, 2018)

***A:**Aspergillus sp.; **Al:**Alternaria sp.; **B:**Beauveria sp.; **C:**Claviceps sp.; **Ch:**Chaetomium sp.; **Co:**Conidiobolus sp; **Cc:** Cochliobolus sp.; **E:**Eupenicillium sp.; **Em:**Emericella sp.; **Ep:**Epidermophyton sp.; **Eu:**Eurotium sp.; **F:**Fusarium sp.; **M:**Monascus sp.; **Mr:**Myrothecium sp.; **Mi:**Microsporum sp.; **My:**Mycogone sp.; **N:**Neosartorya sp.; **Ni:**Nigrospora sp.; **P:**Penicillium sp; **Pa:**Paecilomyces sp; **Pi:**Pithomyces sp.; **Po:**Podostroma sp.; **S:**Stachybotrys sp; **Se:**Stemphylium sp.; **St:**Streptomyces sp; **T:**Tolypocladium sp.; **Tr:**Trichophyton sp.; **V:**Verticillium sp.

****CA:**Structural and numerical chromosome abnormalities; **SCE:**Sister chromatid exchanges; **MN:**Micronucleus; **DF:**DNA fragmentations, Unsheduled DNA synthesis, Comet assay; **GM:**Gene mutation, Nucleotide substitution, Dominant lethal mutation. **(+):**genotoxic or mutagenic; **(-):**non-genotoxic or non-mutagenic; **(+?):**weakly or moderately genotoxic or mutagenic; **(?):**inconclusive (questionable) results; **(±):** in some tissues of animals are genotoxic or mutagenic and in other tissues are non-genotoxic or non-mutagenic

***** Baccharin, a component of Brazilian propolis, isolated from natural plant Baccharis dracunculifolia DC (Asteraceae). It was evaluated as a mycotoxin.[92,143] Azaserine (9-diazoacetyl-L-serine) is a natural diazoazetyl amino acids (dipeptide). It was evaluated as a mycotoxin (Mori et al. 1984).

Table 2. List of mycotoxins that have not been investigated in terms of genotoxic and mutagenic effects

13-O-Methylviriditin	Dihydrogeodin	Astellolide B	Kotanin
2-hydroxy-3-methyl-1,4-benzoquinone	Dihydroxyaflavinine	Astepyrone metabolite 3, 4, 6	Lolitrem
2-Methyl-1,4-benzoquinone 5,6-epoxide	Dioxopiperazine	Asterric acid	Malformins
2"-oxoasterriquinol D Me ether 1	Dithiosilvatin	Asterriquinone (Demethyl) B1, B3, D, A4,C2	Maltoryzine
3'-hydroxy HT-2 toxin	Ditryptophenoline	Auranthine	Mellein (Ochracin)
3'-Hydroxy T-2 triol	Emestrin	Auroglaucine	Methoxyhydroxyheptadienylbenzyl
3-Furanacetic acid	Emethacin	Austamide	Mevalonate
3-Methylorsellinic acid	Equisetin	Austin (Deacetylaustin)	Monascidin A
Aflatrem	Erdin	Azaphilon	Naphthalic anhydride
Aflavinine	Erythroglaucin	Benzylbismethylthiopiperazinedione	Naphthazarin epoxide
Alanyltryptophan anhydride	Ethanedioc acid	Bianthrone	N-benzoyl-L-phenylalaninol
Alpha-sarcin	Flavipin	b-Resorcylaldehyde-a-14C	Neoechinuline
Alteichin	Flavoglaucin	b-Resorcylic-carboxy-14C	Neosartorin
Alterperylenol	Frequentin	Brevianamide	Neosolaniol
Andibenin C	Fumigaclavine	Butanedioic acid	Nidulin
Andilesin	Fumitoxin	Butenolide	Nidulol
Anditomin	Fusaproliferin	Butyrolactone	Norisotryptoquivaline
Aranotin bisdethiobismethylthioacetyl	Fusarochromanone	Canescin	O-ethylparvulenone
Asparvenone	Geodin 1 (Dihydrogeodin)	Carboxydiphenylbutenoic anhydride	Rubrocristin
Asperfuran	O-Methylasparvenone	Catenarin	Scleramide
Asperfuranone	O-methylparvulenone	Chlorflavonin	Sclerin
Aspergillic acid	Orlandin	Chloromethyresorcyloylhydroxyanisinate	Siderine
Aspermutarubrol	Pachybasin	Chrysogine	Silvaticamide
Asperphenamate	Palitantin	Cichorine	Silvaticol
Asperthecin	Paraherquamide	cis-4-Hydroxymellein	Sphingofungin
Aspertoxin	Paspalicine	Citraconic anhydride	Spinulosin
Aspochalasin A,B,D	Paspaline (Paspalinine)	Cladosporin	Sulochrin
Aspulvinone	Paspalitrem	Gregatin	Sydonic acid
Compactin	Pergillin	Helvolic acid	Sydonol
Crotocin	Phenprocoumon	Hexanoic	Terphenyllin
Cryptoechinuline	Phomopsin	HT-2 toxin	Terreic acid
Cyclopaldic acid	Phthalide (Chromanol)	Hydrazinecarboxamide	Terrein
D-Altritol Species	Physcionanthrone	Hydroxysydonic acid	Terremutin
Deacetylaustin	Preechinulin	Indole Species	Terretonin
Dechloronidulin	Questin	Isodihydroauroglaucin	Territrem
Desmethylkotanin	Regulin	Isoflumigaclavines	Parasiticol
Destruxin	Roridin A, D, E, H (Diepoxyroridin)	Itaconic acid	
Dihydroalterperylenol	Aspyrone	Janthitrems	

Table 3. Test protocol for cell and tissue types used in genotoxic studies

Test Materials	**Tissue and cells**	**Test Protocols**	**References**
S. typhimurium	LT2 strains	Ames Test	(Maron & Ames, 1983)
S. typhimurium	SV50 ara	Forward Mutation Assay	(Xu et al., 1984)
E. coli	PQ37 strains	SOS Chromotest	(Quillardet et al., 1982)
E. coli	WP1 and WP2 UvrA	UvrA reverse Mutation Assay	(Nestmann et al., 1981)
S. cerevisiae	Haploid, diploid strains	Gene Conversion and Mitotic Recombination Tests	(Nestmann et al., 1981)
D.melanogaster	Wing	SMART Test	(Graf et al., 1984)

Test Materials	Tissue and cells	Test Protocols	References
Rodents and other animals	Bone marrow cells	*In vivo* CA, SCE and MN Methods	(DeMarini et al., 1987; Wangenheim & Bolcsfoldi, 1988) (OECD, 1996; Rencuzogullari & Aydin, 2018)
Rodents and other animals	Erythrocytes	Mammalian Erythrocyte Micronucleus Tests	(OECD, 2013; Rencuzogullari & Aydin, 2018)
Rodents and other animals	DT40 or other tissue cells	CometAssay	(Yamamoto et al., 2011)
Rodents and other animals	Hepatocytes and orther tissues cells	DNA Repair Test	(Mori et al., 1984)
Rodents and other animals	Germ cells	Germ Cells Mutation Test	(Hassanane et al., 2000; Marchetti et al., 2018)
Rodents and other animals	Lymphoma TK 4/-	Forward Mutation Assay	(Wangenheim and Bolcsfoldi, 1988; DeMarini et al., 1987)
Human and Rodents	Peripheral blood cells or other tissues cells	*In vitro* CA, SCE and MN Methods	(Evans, 1984; Perry and Thompson, 1984; Kirsch-Volders et al., 1997; Albertini et al., 2000; Rencuzogullari & Aydin, 2018)
Human	Cancer cells	MTT Test or Comet Assay	(Prata-Sena et al., 2016)

When Table 1 is examined, it can be seen that the genotoxic or mutagenic effect of many mycotoxins is investigated with only one test (46 mycotoxin) or two tests (24 mycotoxin) system. These mycotoxins may also be considered among mycotoxins that have not been determined genotoxic or mutagenic toxins because the genotoxic effect of any mycotoxin or a chemical is only tested with a test battery in order to say that the results are reliable. The test group, called the test battery, should contain an *in vitro* or *in vivo* test and should consist of a bacterial test system such as the Ames test. The results will be more reliable when molecular tests such as RAPD-PCR included in the system. Therefore, the number of mycotoxins that we do not know about their genotoxic effects increases when we take these mycotoxins among the unexplained ones.

Cytochalasin and fumagillin are the two mycotoxins effects of which were studied *in vivo* in rodents and *in vitro* human lymphocytes without any bacterial test system. Cytochalasin has genotoxic effect only in human lymphocytes, while fumagillin has genotoxic and mutagenic effects in all tests (Banerjee & Paruthy, 2016). In particular, *in vivo* tests are extremely important in terms of presenting mycotoxin metabolism. Floccosin, iridoskyrin, islandicin, mycophenolic acid, nidurufin, norsolorinic acid, rubroskyrine, and skyrin are the mycotoxins genotoxic effects of which were investigated by both *in vivo* and bacterial test (Aleksic et al., 2017). It can be said that there is a non-genotoxic or suspected genotoxic effect in all of the mentioned mycotoxins.

It is important to study candudisin B, fumitremorgen B, fusaric acid, 3-hydroxyterphenyllin, ochratoxin alpha, oosporein, penitrem A, physcion, stemphltoxin, verrucosidin, and verruculogen, which were studied with only one *in vitro* and one bacterial test, and beauvericin and fusarenon X mycotoxins that were studied using only two different *in vitro* tests by *in vivo* testing system for demonstrating genotoxic or mutagenic activity. Among these mycotoxins only oosporein, stemphltoxin, verrucosidin, and beauvericin showed positive results in terms of genotoxic effects, but other mycotoxins showed either negative or unclear/suspicious results (González-Peñas, Vettorazzi, Lizarraga, Azqueta, & López de Cerain, 2019).

Among the studied mycotoxins, actinomycin D, aflatoxin, alternariol, chrysazin (dantron), citrinin, fumonisin, mytomycin C, nivalenol, ochratoxin A, patulin, sterigmatocystin, versicolorin A and B, vomitoxin, and zearalenone can be evaluated as genotoxic or mutagenic (Kaynarca, Hecer, & Ulusoy, 2019).

Acetoscripenol appears to be genotoxic in mouse bone marrow and germ cells, but not in Drosophila wing spot test and bacterial tests. It may have a genotoxic risk due to its effect in *in vivo* studies in mice. Although averufin, azaserine, cyclosporin A, emodin, girseofulvin, kojic acid, lysergic acid, moniliformin, 3-nitropropionic acid, and T-2 toxins give genotoxically positive results in most tests, additional further tests are required to determine whether they are genotoxic or mutagenic (Bennett & Klich, 2003). The same matter is applied for chyrsophanol, gliotoxin, luteoskyrin, penicillic acid, PR toxins, rugulosin, secalonic acid D, and sporidesmin, which are negative in most tests because some of the tests that are supposed to be in the test battery are not used in the studies.

4. Discussion

Genotoxicity and mutagenicity are terms that are used to describe damage caused by chemicals on chromosome and DNA structure and lead to gene mutations, chromosome abnormalities, and DNA chain breaks. Such mutations can cause foremost congenital defects and many other diseases such as cancer, aging, and infertility. Identification of such effects of chemicals is extremely important in terms of minimizing the frequency of abnormality and disease (Phillips & Arlt, 2009).

Mutagenicity refers to a chemical or physical agent's capacity to cause mutations (genetic alterations). Agents that damage DNA causing lesions that result in cell death or mutations are genotoxins. All mutagens are genotoxic but not all genotoxins are mutagens as they may not cause retained alterations in DNA sequence (Bełdowski, Been, & Turmus, 2017).

Of the 109 genotoxically and mutagenically studied mycotoxins, only 14 (actinomycin D, aflatoxin, alternariol, chrysazin (dantron), citrinin, fumonisin, mytomycin C, nivalenol, ochratoxin A, patulin, sterigmatocystin, versicolorin A and B, vomitoxin, and zearalenone) were found to be genotoxic. Of the mentioned mycotoxins, aflatoxin, sterigamatocystin and fumonisin are complete animal carcinogens and only aflatoxin is a human carcinogen. There is no sufficient information on the genotoxic and mutagenic effects of the remaining 95 mycotoxins. In particular, additional tests should be performed to detect the genotoxic effects of mycotoxins that are investigated by using only two test systems in case

of genotoxicity in one of the test systems but non-genotoxicity in the other test system.

When genotoxic studies are performed, application of *in vivo* tests is especially important because many mycotoxins may show genotoxic effects in *in vivo* or by being metabolized in the presence of metabolic activators in *in vitro*. These mycotoxins must undergo biotransformation processes in order to be able to show genotoxicity (Aydın et al., 2017; Bayram, Rencüzoğulları, Almas, & Genç, 2016; Flajs & Peraica, 2009; Yourtee & Kirk-Yourtee, 1986). Wehner, Marasas, & Thiel (1978a) found out that toxins such as austdiol, austocystins A and D, kojic acid, and viridicatum toxin had mutagenic effects after biotransformation. The same can be said for many other mycotoxins (Wehner, Thiel, van Rensburg, & Demasius, 1978b).

In some cases, oxidation reactions can expose genotoxicity. Arbillaga Azqueta, Ezpeleta, & López de Cerain (2007) reported that ochratoxin A is not directly genotoxic; however, oxidative stress in human renal cells affects genotoxicity. It was also found that ochratoxin A enhances radical oxygen production by Russo and colleagues (Russo et al., 2005).

Sometimes *in vivo* nitrosylation can lead to more severe genotoxic activity. Some studies reported that some alternaria metabolites such as altenuene, alterotoxin I, alternarol, alternarol monomethyl ether, and radicinin mycotoxins have very strong genotoxic effects after nitrosation (Schrader, Cherry, Soper, & Langlois, 2006; Schrader, Cherry, Soper, Langlois, & Vijay, 2001).

The chemical structure of mycotoxins or some groups they contain may affect its genotoxic effect. For example, norsoloronic acid, averufin, and versiconal acetate contain anthraquinone. Therefore, their mutagenic effects are weak. However, versicolorin, which is another anthraquinone and contains the bisfuran ring, has high mutagenic activity. Sterigmatocystin also has an anthraquinonedur and xanthone content that contains 2 times more mutagenic effect compared to versicolorin. Aflatoxin B1 contains an anthraquinone and xanthone but the xanthone has been transferred onto a coumarin. This makes aflatoxin B1 10 times more genotoxic (Wong, Singh, & Hsieh, 1977).

Perhaps the greatest risk for mycotoxins is the combined synergistic effect of multiple mycotoxins. Because many Fusaria can produce more than one mycotoxin at the same time (Scott & Stoltz, 1980). Aupanun, Poapolathep, Giorgi, Imsilp, & Poapolathep (2017) showed that some mycotoxins could be present together. It was reported that ochratoxin A and citrinin mycotoxins (Bouslimi, Bouaziz, Ayed-Boussema, Hassen, & Bacha, 2008) and also cyclopiazonic acid and aflatoxin mycotoxins (Sorenson, Tucker, & Simpson, 1984) show strong synergistic effects.

One of the greatest risks of mycotoxins is causing cancer. Hsia, Wu, Lu, & Li (1988) found out that humans eating corn that is contaminated with the trichothecenes group mycotoxins and nivalenol and deoxy-, 3-acetyldeoxy, 15-acetyldeoxy derivatives developed esophageal cancers. Brugger et al. (2006) reported that alternariol also causes esophageal cancer. It was also reported that aflatoxin A1 and B1, sterigmatocystin, and luteoskyrin are hepatocarcinogen (Müller, 1987). Fuminisin was reported to be associated with esophageal cancer as well as with liver cancer in rats (Aranda, Pérez-Alzola, Ellahueñe, & Sepúlveda, 2000). Mirsalis, Tyson, & Butterworth (1982) found out that azaserin is a pancreatic carcinogen.

Some carcinogenic mycotoxins are known to cause cancer through genetic damage. In previous studies, it was reported that mycotoxins that are likely to be genotoxic carcinogens are aflatoxin B1, sterigmatocystin, luteoskyrin, ochratoxin A, azaserine, mitomycin C, and actinomycin D (Beljanski, Le Goff, & Beljanski, 1982; Hashimoto, Nakajima, Matsumura, & Chatani, 2010; Mori et al., 1984) and non-genotoxic carcinogens were reported to be penicillic acid, patulin, griseofulvin, and rugulosin (Mori et al., 1984).

Although mitomycin C and actinomycin D are known to be genotoxic carcinogens, these two mycotoxins also have anti-cancer effects due to their direct-acting alkylating agents (Gupta & Singh, 1982; Parkes & Scott, 1982) and they have also been used as anti-cancer drugs. Similarly, cytochalasin is also a mycotoxin and has anti-tumor effect (Chang et al., 2016; Chen et al., 2015) because it is a cytokine-blocking agent (Fenech & Morley, 1985). These chemicals are used as positive mutagenes in genotoxicity studies due to their high genotoxic effects. Duclauxin and danthron have also been reported to be important anticancer compounds (Anisha, Sachidanandan, & Radhakrishnan, 2018; Fuska, Kuhr, Nemec, & Fusková, 1974; Kuhr et al., 1973). Therefore, it is also understood that some mycotoxins may be used as anticancer drugs, antibiotics, antibacterials or as medicines for other purposes. Many mycotoxins, such as penicillin, griseofulvin, danthron, emodin, luteoskyrin, cyclochlorotine, rugulosin, rubroskyrin, lumiluteoskyrin, pibasterol, skyrin, cyclosporine, chrysophanol, islandicin, iridoskyrin, fumagillin, and mevinolin (lovastatin) are used as antibiotics or other therapeutic agents (Anisha et al., 2018; Flint, Forsey, & Usher, 1959; Henninger et al., 2012; Liberman et al., 1980; Mengs, Schuler, & Marshall, 2001; Mok & Tey, 2018; Nesslany, Simar-Meintières, Ficheux, & Marzin, 2009; Sakai et al., 1992; Schafhauser et al., 2016; Stark et al., 1978; Stevanovic, Stanimirovic, Radakovic, & Stojic, 2008; van den Heever, Thompson, Curtis, & Pernal, 2015; Yang et al., 2018). Nevertheless, it should not be forgotten that mycotoxins may cause adverse effects in humans such as high blood pressure, headache, kidney problems, increased hair growth, vomiting, liver problems, and increased risk of lymphoma (Cho, Davis, Wetter, Bartley, & Brewer, 2018; Geller et al., 2018; Ivandić & Bašić-Jukić, 2014). When mycotoxin is used as a medicine, it will be beneficial for the health of the patient to be under special care.

Mycotoxins, such as alternariol, fusarin, and zearalenone are defined as mycoestrogens. They may cause a number of physiological events in the reproductive tract by exhibiting high estrogenic activity (Ayed-Boussema, Ouanes, Bacha, & Abid, 2007). Although some articles state that zearalenone is non-steroidal estrogenic (Pfohl-Leszkowicz, Chekir-Ghedira, & Bacha, 1995), Abid-Essefi et al. (2003) reported that zearalenone increased estrogenic and anabolic properties by binding to human estrogen receptors. It was reported that some mycotoxins may have different effects depending on sexual difference although they are not mycoestrogens. In a genotoxicity study that has been done in male and female mice, it was

shown that aflatoxin B1 causes higher genotoxic effects in males than females (Madle, Korte, & Beek, 1986).

5. Conclusions

Mycotoxins are toxins that are naturally produced as secondary metabolic products of Fusarium and constitute the greatest risk to humans by causing contaminations in food. Mycotoxins are a large group of toxins that cause various abnormalities in living things, especially cancer, infertility, and congenital defects during pregnancy. Very few of them are known to have genotoxic effects (El Khoury, Fayjaloun, Nassar, Sahakian, & Aad, 2019). However, the mutation-formation effects of a large part of the remaining mycotoxins have not been investigated. Knowing the genotoxic effects of a mycotoxin ensures the explanation of the disease molecular levels. This is extremely important in terms of reducing the abnormality of the chemistry and the frequency of the disease.

There are also mycotoxins that are used as therapeutics for many diseases, especially antibiotics, and even as anti-cancer drugs. Mycotoxins, which are used as drugs, are biotechnologically produced and purified chemicals. These drugs naturally may give adverse effects and cause some unwanted effects in the living system (Loi, Fanelli, Liuzzi, Logrieco, & Mulè, 2017).

As a result, since mycotoxins are produced at specific temperature and humidity grades, storage of food in appropriate conditions from the time of production to consumption can reduce mycotoxin contamination. This is extremely important for the protection of human health.

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