Chapter 5

Risks of Environmental Genotoxicants

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/62454

Abstract

Humans have throughout their development been exposed to various environmental genotoxicants through food, air, water, and soil. Environmental exposure to genotoxic compounds may induce damage to human health and thereby increase risks of human cancers and other diseases. Environmental genotoxic chemicals have the ability to induce mutations. Such mutations can give rise to cancer in somatic cells. However, when germ cells are affected, the damage can also have an effect on the next and successive generations. Because of the potential health hazard represented by exposure to genotoxic chemicals, it is important that all chemicals for which there is possible human exposure be screened for genotoxic activity. If genotoxic hazard is detected, then the risks of exposure can be assessed and the use of the chemical controlled and when appropriate eliminated from the market and the environment. In this chapter, a general overview of the genotoxicity and the genotoxicity of some environmental genotoxicants are discussed. This is followed by a description of the genotoxic properties of some environmental genotoxicants such as bisphenols and mycotoxins, which are prominent environmental contaminates, and is believed to be genotoxic agents that contribute to the high incidence of carcinogenicity among populations.

Keywords: Environmental genotoxicants, mutations, carcinogenicity, mode of action, risk assessments

1. Introduction

DNA is constantly damaged by both endogenous and exogenous sources, and genotoxicity can be considered as an imbalance between DNA damage and DNA repair mechanisms. Maintenance of DNA integrity is essential for proper cellular and organismal function, and the capacity to withstand genotoxic challenge is important to avoid long-term genetic instability and population vulnerability. Unrepaired DNA damage can lead to mutations, cellular senes-

cence, apoptosis, progression of cancer, and the process of aging [1]. Mutation is a broad term covering a whole range of changes to the informational molecule, DNA packaged into chromosomes, of an organism from gene changes to modifications of the number and/or structure of chromosomes. Mutagenicity in normal cells is one of the most serious problems due to the possibility of inducing secondary malignancies and abnormal reproductive outcomes such as Down, Klinefelter, and Turner syndromes [2]. Such changes can be assessed directly by measuring the interaction of agents with DNA or more indirectly through the assessment of DNA repair or the production of gene mutations or chromosome alterations.

Genotoxicity covers a broader spectrum of endpoints than mutagenicity. For example, unscheduled DNA synthesis, sister chromatid exchanges, and DNA strand breaks are the measures of genotoxicity, not mutagenicity, because they are not themselves transmissible from cell to cell or generation to generation. Mutagenicity on the other hand refers to the production of transmissible genetic alterations. Although all cells of an organism contain the same DNA, somatic cells in different organs and tissues of the adult body become specialized to perform defined functions so that only some parts of the genome are expressed. A common feature of mutations in cancer-causing genes, such as those controlling cell division and proliferation, is that this results in genes being expressed in the wrong tissue at the wrong time. The effect of a mutation will depend upon the position of the mutation within the DNA and the location and activity of the particular gene in which the mutation has been induced. Mutations in the many genes that have been implicated in the multistage events leading to cancer can be produced by a variety of mechanisms and interactions and modifications of the genetic material [2, 3].

With the recent focus on environmental problems, increasing awareness of the harmful effects of industrial and agricultural pollution has created a demand for progressively more sophisticated pollutant and toxicity detection methods. In recent years, there has been a growing concern about the increasing number of environmental pollutants that may disrupt normal endocrine function in exposed humans and animals. Endocrine disrupting compounds comprise a large group of synthetic chemicals that mimic the actions of natural hormones, act as antagonist, or block their synthesis, release, or metabolism. The xenoestrogen bisphenols have received much attention due to their high production volume and widespread human exposure. Recent research in various animal models has shown the genotoxic activity of bisphenols using *in vivo* and *in vitro* assays. Nevertheless, notable differences have been reported, leading to opposite conclusions, which may well have been caused by differences in the screening test, the organisms used, and the exposure conditions assayed [4].

Many important agricultural products, especially those rich in carbohydrates, are attractive colonization sites for fungi. Some toxic secondary metabolites of fungal growth are identified as mycotoxins and may be found to contaminate agricultural products [5]. Mycotoxins are virtually ubiquitous at some concentration in the average human diet. Mycotoxins are able to resist decomposition or being broken down by mammalian digestion, even by ruminant livestock, allowing these compounds to persist in meat and even dairy products [6]. This gives rise to certain partially metabolized mycotoxins, such as aflatoxin M1, which are present in milk from cows or humans that consumed feed or food contaminated by aflatoxins. Even

http://dx.doi.org/10.5772/62454

temperature treatments, such as cooking and freezing, do not inactivate some mycotoxins. This section broadly discusses the genotoxic properties of the environmental genotoxicants bisphenols and aflatoxins, which are prominent environmental contaminates, and is believed to be genotoxic agents that contributes to the high incidence of genotoxicity and carcinogenicity among populations.

2. Bisphenols

2.1. Bisphenol A and its analogues

Bisphenols are a group of chemicals known as diphenylmethanes, which contain two benzene rings separated by one central carbon atom, usually with a 4-OH substituent on both benzene rings (e.g., bisphenol A, bisphenol F, bisphenol AF, and bisphenol Z). Bisphenol A is employed to make certain plastics and epoxy resins (**Figure 1**). In some bisphenols, the central carbon atom is replaced by a sulphone group (e.g., bisphenol S or bisphenol 1) or sulphide moiety (e.g., bisphenol 2). Some bisphenol A analogues seem to be safer alternatives to bisphenol A in industrial applications. For example, the production of bisphenol S, which is stable at high temperatures and resistant to sunlight, is increasing from year to year [7, 8]. The largest US manufacturer of thermal paper has been using bisphenol S as a replacement for bisphenol A since 2006. However, insufficient data are available to tell whether these bisphenol S-containing papers are safer than bisphenol A-containing papers. While bisphenol A is moderately susceptible to environmental breakdown, bisphenol S may be more persistent [9].

Figure 1. Some industrial applications of bisphenols.

From the viewpoint of biodegradability in the aquatic environment, bisphenol F is more biodegradable under aerobic and anaerobic conditions than bisphenol A and may replace bisphenol A to lower environmental risks [10]. Bisphenol AF also occurs as a monomer of phenol-formaldehyde resin. Bisphenol AF is a component of certain plasters and used as a rubber bridging material, while bisphenol A is a monomer that is polymerized to manufacture polycarbonate plastic products, epoxy, and polyester resins (**Figure 2**). Polycarbonate plastics have many applications including use in some food and drink packaging such as water and

baby bottles, compact discs, impact-resistant safety equipment, and medical devices including those used in hospital settings. Epoxy resins are used to coat metal products such as food cans, bottle tops, and water supply pipes. Bisphenol A can also be found in certain thermal paper products, including some cash register and ATM receipts. Some dental sealants and composites may also contribute to bisphenol A exposure [11, 12].

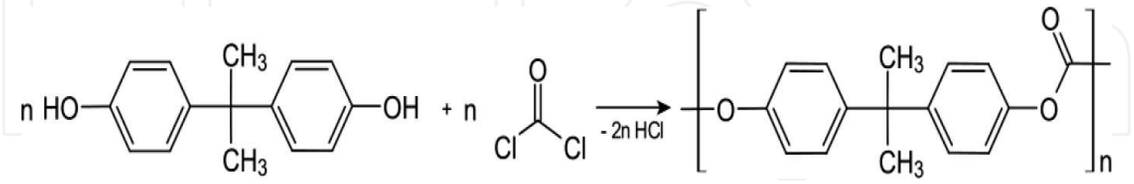

Figure 2. Synthesis of the polymer polycarbonate from bisphenol A and phosgene.

2.2. Human exposure to bisphenols

Human exposure to bisphenols may occur in the workplace through inhalation during production, but the most common route of exposure is by oral intake. Small amounts of bisphenol A are eluted from canned beverages, foods, and baby bottles, especially when heated [12]. At higher temperatures, longer contact with, and higher pH of the contact medium, bisphenol A monomer can hydrolyse and leach into food and beverages. Recent studies also suggest that the public may be exposed to bisphenol A by handling cash register receipts. In accordance with its widespread use in many applications, bisphenol A has been detected in dietary items [13] and human biological samples [14]. Moreover, bisphenol A was detected in environmental media as well [15].

2.3. Risks of exposure to bisphenols

In general, bisphenol A levels in humans have measured well below 50 mg/kg/day, which is the maximum acceptable dose set by the UA EPA [16]. Its ubiquitous presence and widespread distribution have provoked worldwide concerns about its possible association with human diseases such as obesity, diabetes, cardiovascular disease, reproductive disorders, and cancer [17, 18]. Despite its presence in human populations and its association with reproductive and developmental toxicity in animals, most countries have not imposed regulations on the manufacture, import, or sale of bisphenol A products. That has been due largely to conflicting scientific evidence for a direct association between low-level exposure and adverse health effects in humans. Some countries and regions, including Canada, Europe, Sweden, and the United States, on the other hand, have formally banned bisphenol A from infant and children's products, including, variously, cans of infant formula, baby bottles, and sippy cups. Current efforts are focused on replacing bisphenol A with safer food contact materials. All of these alternative materials need to be assessed for appropriate functionality and safety using state-of-the-art methodology and scientific knowledge.

Bisphenol A is a known endocrine disruptor compound. While initially considered to be a weak environmental estrogen, several recent publications have demonstrated that bisphenol

A may be similar in potency to estradiol in stimulating some cellular responses. Furthermore, emerging evidence suggests that bisphenol A may affect multiple endocrine-related pathways [19]. In men, exposure to endocrine disruptors may be associated with decreased fertility and increased risk of testicular or prostate cancer [20]. In women, exposure may increase the risk of endometriosis, reproductive or other endocrine-related cancers, and impaired oocyte competence, ovarian function, or menstrual cycle [21]. Because females have higher levels of natural estrogens in their blood, the impact of estrogen-like compounds on females may be different from that on males. In women, high urinary bisphenol A levels were associated with reduced antral follicle counts in a cohort of 209 women undergoing infertility treatments [22], whereas no correlation was found between serum bisphenol A levels and antral follicle counts in another study on a smaller cohort of 44 patients [23]. Nevertheless, several data suggest a negative impact of bisphenol A on woman fertility. Urinary bisphenol A levels were negatively correlated with numbers and quality of oocytes retrieved in stimulated cycles for assisted reproduction [24]. Increased urinary or serum bisphenol A concentrations were also associated with decreased peak oestradiol levels [25]. Moreover, a study on 137 patients undergoing assisted reproduction suggested that high urinary bisphenol A levels might be associated with up to 50% higher chance of implantation failures, in comparison with patients with low or no evidence of bisphenol A exposure [26].

Because the chemical structure of bisphenol A is similar to that of diethylstilbestrol, which is carcinogenic to mammals, the possible genotoxicity of bisphenol A has been widely tested in a variety of *in vitro* and *in vivo* studies, but the results are controversial. Several studies have shown that bisphenol A can induce chromosome aberrations and DNA adducts formation in Syrian hamster embryo cells [27] or micronuclei formation in human MCL-5 cells [28]. Aneugenic properties were also observed in Chinese hamster V79 cells after bisphenol A exposure [29]. Moreover, in estrogen receptor-positive MCF-7 cells, bisphenol A caused DNA strand breaks that were estrogen receptor-dependent [30]. A recent study has reported that the genotoxic and cytogenetic effects of bisphenol A in Chinese hamster ovary cells were manifested in the form of DNA strand breaks, micronucleus formation, and chromosome aberrations [31]. Conversely, bisphenol A is considered non-genotoxic because it was negative to a set of basic genotoxicity tests. It was not mutagenic in the Salmonella/microsome assay [32], did not induce gene mutations [27, 32] or chromosomal aberrations [33] in mammalian cells *in vitro,* and failed to induce chromosomal aberrations and micronucleus formation *in vivo* in mice [34]. Bisphenol A is considered to lead to genotoxicity through oxidative stress. Bisphenol A-3,4-quinone, which is yielded by oxidative metabolism of bisphenol A, may cause genotoxicity by reacting with DNA [35].

By now, there is increasing evidence supports the notion that low bisphenol A concentrations adversely affect the epigenome of mammalian female germ cells, with functional consequences on gene expression, chromosome dynamics in meiosis, and oocyte development and quality [36]. An epigenetic impact of bisphenol A was demonstrated also on male germ cells. Male offspring of rats perinatally exposed to bisphenol A had reduced sperm counts and other changes in phenotypes not only in the first generation but also in the *F3* generation [37]. Induction of sperm epimutations and male-mediated trans-generational inheritance of obesity

and reproductive disturbances were also shown after bisphenol A exposure of rats [38]. When female mice were exposed during gestation and lactation to low bisphenol A doses deregulated, glucose homeostasis in the *F2* generation was observed; decreased global methylation and differential methylation of a specific CpG site in the glucokinase promoter in the *F1* sperm suggested that the *F2* phenotype could be caused by epigenetic alterations induced in the male paternal germline by bisphenol A prenatal exposure [39].

While comprehensive information is available about the adverse health impacts of bisphenol A, toxicological properties of alternative bisphenols are yet to be investigated. Alternative bisphenols are structurally similar to bisphenol A, and therefore expected to possess similar biological activities. However, most available toxicological information is limited to endocrine disrupting potentials, and only very little is known about the genotoxicity of alternative bisphenols [7]. In turn, bisphenol F has been reported to induce DNA strand breaks, but not micronuclei, in HepG2 cells [40]. In human HepG2 cells, bisphenol F induced histone H2AX phosphorylation, an indicator of DNA double strand breaks [41]. Moreover, bisphenol F induced metaphase arrest and micronucleus formation in V79 cells [29]. In Syrian hamster embryo cells, bisphenol F did not induce gene mutation or chromosomal aberrations, but induced aneuploidy and morphological changes [42]. Bisphenol A may cause oxidative stress, and induce DNA adduct and aneuploidy in rodents [43]. Nevertheless, eight bisphenols including bisphenol A showed no positive responses based on *umu*-test suggesting no genotoxicity [44]. Similarly, other alternative bisphenols are expected, but to date, very little efforts have been made on this aspect.

3. Aflatoxins

3.1. Sources of aflatoxins

With worldwide increases in population, the need for nutrient-rich food is rising. Contamination of foods by toxins, bacteria, viruses, parasites, allergens, and prions may lead to serious diseases; unhealthy foodstuffs are implicated in approximately one-third of cancer cases. Controlled storage conditions, improved packaging, and strict hygiene regulations for food production, preservation, and distribution are essential to diminish such problems. Aflatoxins are toxic metabolites produced by certain fungi in/on foods and feeds. They are probably the best-known and most intensively researched mycotoxins in the world. The occurrence of aflatoxins is influenced by certain environmental factors; hence, the extent of contamination will vary with geographic location, agricultural, and agronomic practices, and the susceptibility of commodities to fungal invasion during pre-harvest, storage, and/or processing periods. Aflatoxin B1 is a prevalent food pollutant, which is found typically in tropical countries. It imposes great costs on the world's economy and health [45]. Thus, it is important to eliminate aflatoxin B1 from food resources and prevent production of the toxin. Due to lack of infrastructure, poor and third world countries are the major victims of aflatoxin B1. The established carcinogenesis, teratogenesis, and severe multi-organ toxicity associated with aflatoxin B1 have made it a substantial challenge for scientists [46, 47].

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Figure 3. Some major sources of aflatoxins.

3.2. Human exposure to aflatoxins

Aflatoxins are a type of mycotoxin produced by *Aspergillus* species of fungi, such as *A. flavus* and *A. parasiticus*, which grow in soil, decaying vegetation, hay, and grains [48]. Aflatoxins have received greater attention than any other mycotoxins because of their demonstrated potent carcinogenic effect in susceptible laboratory animals and their acute toxicological effects in humans. Aflatoxins are regularly found in improperly stored staple commodities such as cassava, chili peppers, corn, cottonseed, millet, peanuts, rice, sorghum, sunflower seeds, tree nuts, wheat, and a variety of spices (**Figure 3**). Aflatoxin B1 is highly resistant to traditional detoxification protocols, such as heat, solvents, and radiation, which have consequences for food quality and safety. However, biological procedures using microbial or enzymatic tools that possess great specificity with minimal consequences are the appropriate choices for the treatment of contaminated foodstuffs; they also offer ease of application, affordability, and environmentally friendly behavior. The use of biological procedures requires optimized conditions, such as pH and temperature, for maximum efficiency. When contaminated food is processed, aflatoxins enter the general food supply where they have been found in both pet and human foods, as well as in feed stocks for agricultural animals [49]. Moreover, animals fed contaminated food can pass aflatoxin transformation products into eggs, milk products, and meat. The four major naturally produced aflatoxins are known as aflatoxin B1, aflatoxin B2, aflatoxin G1, and aflatoxin G2 (**Figure 4**), which are based on their fluorescent color when exposed to ultraviolet light on thin-layer chromatography plates (B = blue fluorescence, G = yellow-green fluorescence), while the subscript numbers 1 and 2 indicate major and minor compounds, respectively. Aflatoxin M1 and M2 compounds are not found on cereal products themselves but are metabolites expressed in milk of mammals whose diet was contaminated by aflatoxins B1 and B2, respectively [50].

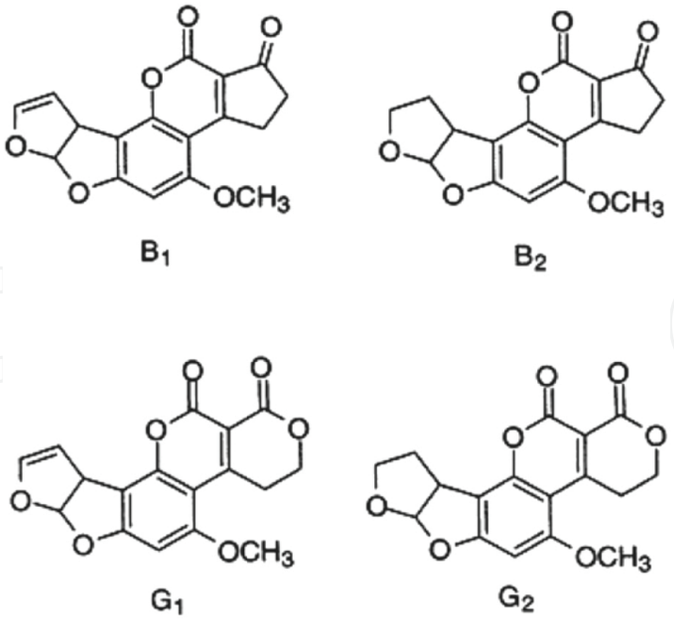

Figure 4. Chemical structures of the four major naturally produced aflatoxins: aflatoxin B1, aflatoxin B2, aflatoxin G1, and aflatoxin G2.

3.3. Risks of exposure to aflatoxins

Aflatoxins have been reported to have several serious deleterious effects in humans and diverse animals with the species reacting differently to the toxicological effects. The target sites of this toxicant are also diverse and effects include hepatotoxicity, teratogenicity, immunotoxicity, hematological disorders, renal dysfunction, induction of chromosome aberrations, and mutations in somatic and germinal cells of animals and humans [51–53]. Aflatoxin B1, the most toxic, is a potent carcinogen and has been directly correlated with adverse health effects, such as liver cancer, in many animal species. Aflatoxin B1 is one of the major risk factors for the occurrence of liver injury and carcinogenesis, especially when it is combined with hepatitis B infection. Epidemiological investigations revealed that dietary contamination with aflatoxin B1 might be responsible for 5–28% of global hepatocellular carcinoma cases [54]. A great deal of evidence has demonstrated that aflatoxin B1 belongs to the indirect-acting carcinogens. Aflatoxin B1 is mainly metabolized in the liver to produce the genotoxic intermediate aflatoxin B1-exo-8,9-epoxide by the liver-specific cytochrome P450 enzymes, P4501A2, and 3A4. These epoxides can form aflatoxin B1-guanine adducts by binding covalently to DNA, thereby introducing GC-TA transversion that leads to DNA mutations and genomic instability [55]. For instance, a frequent hotspot mutation at codon 249 in the human p53 gene gives rise to a Ser to Arg substitution in the p53 protein that decreases its tumor suppressor activity [56]. Another major detoxification pathway of aflatoxin B1 in mammalian species is the glutathione conjugation of aflatoxin B1-8,9-epoxide, which is catalyzed by glutathione S-transferases [57]. Experimental studies conducted in rats have shown that rGSTA5, barely expressed in adult male liver, exhibits a greater activity toward aflatoxin B1-8,9-epoxide than other glutathione S-transferases subunits [58].

Aflatoxin B1 is a clastogen that has been tested for genotoxicity *in vivo* and *in vitro* and giving consistently positive results. It induces chromosomal aberrations, micronuclei formation, sister chromatid exchanges, and DNA strand breaks in several published works [53, 59–61]. An important mechanism responsible for the genotoxic potential of aflatoxin B1 is the formation of DNA adducts. Biotransformation plays a crucial role in the toxicity and carcinogenicity of aflatoxin B1. The enzymatic detoxification of aflatoxin B1 was studied [62], and the pro-oxidant properties and mutagenicity of the detoxification products were compared with those of aflatoxin B1. The results indicated that the metabolized aflatoxin B1 was more toxic than the non-metabolized form of it. A previous study also demonstrated that an epoxide metabolite had an important role in aflatoxin B1-mediated genotoxicity [63]. In the Ames mutagenicity test, the T98 strain exhibits a frame-shift mutation, and T100 exhibits a base-pair substitution. Virtually, all of aflatoxin B1 toxic and carcinogenic effects are attributable to the action of its reactive metabolites that are capable of reacting with cellular macromolecules such as DNA [64]. Furthermore, DNA repair activity and modulation of repair by aflatoxin B1 seem to be also major determinants of susceptibility to aflatoxin B1-induced carcinogenesis [61].

Since the discovery of these deleterious effects induced by aflatoxin B1, a large number of studies have explored the mechanisms and pathways involved in aflatoxin B1-mediated genotoxicity. However, few studies have focused on the epigenetic events involved in the induction of genotoxicity. Recently, several studies reported that cellular epigenetic aberrant changes, such as DNA methylation, histone modifications, and miRNA profiling alterations, also contributed to the hepatotoxicity and genotoxicity induced by chemical toxicants. A genome-wide miRNA-profiling analysis in an acute rat liver injury model induced by aflatoxin B1 predicted that several miRNAs and their potential targets were relevant to acute hepatotoxicity, although functional tests were not performed [65]. However, it is clear from gene expression profiling that the pathways involved in acute poisoning and chronic poisoning are not completely consistent. A recent study investigated alterations in miRNA profiles of rat liver tissues by Illumina deep sequencing and evaluated their roles in aflatoxin B1-induced hepatocellular genotoxicity and hepatotoxicity [66]. The authors demonstrated alterations in the miRNA profile in rat liver tissue, including rnomiR-34a-5p, rno-miR-200b-3p, rno-miR-429, and rno-miR-130a-3p, after aflatoxin B1 exposure. Functional tests showed that the increase in miR-34a-5p by p53 activation after aflatoxin B1 exposure led to cell cycle arrest *via* inhibiting cell cycle-related genes and affecting the micronuclei formation induced by aflatoxin B1, indicating that rno-miR-34a-5p played a critical role in aflatoxin B1-induced rat hepatogenotoxicity. Furthermore, the combination of circulating miR-34a-5p and the aflatoxin B1 level may be considered as a sensitive method for the detection of the genotoxic stress induced by chronic aflatoxin B1 exposure.

As it is realized that absolute safety is never achieved, many countries have attempted to limit exposure to aflatoxins by imposing regulatory limits on commodities intended for use as food and feed [67]. The FDA has established specific guidelines on acceptable levels of aflatoxins in human food and animal feed by establishing action levels that allow for the removal of violate lots from commerce. The action level for human food is 20 ppb total aflatoxins, with the exception of milk, which has an action level of 0.5 ppb for aflatoxin M1. The action level for

most feeds is also 20 ppb. However, it is very difficult to accurately estimate aflatoxins concentration in a large quantity of material because of the variability associated with testing procedures; hence, the true aflatoxin concentration in a lot cannot be determined with 100% certainty. However, the ability of aflatoxin-producing fungi to grow on a wide range of food commodities and the stability of aflatoxins in foods mean that control is best achieved by measures designed to prevent the contamination of crops in the field and during storage, or detection and removal of contaminated material from the food supply chain.

Acknowledgements

This work was funded by the National Plane for Science, Technology, and Innovation (MAARIFAH), King Abdulaziz City for Science and Technology, Kingdom of Saudi Arabia, Award Number (12-MED2648-02).

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