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Short Communication

Food toxicity: hazard versus risk

Carla Landolfi*

ToxHub-Consulting, Italy

*Author for correspondence: Email: carla.landolfi@toxhub-consulting.com

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Abstract

Until recently, eating food has usually been regarded as a low risk activity. In the last century, industrialization has changed methods and chemicals used in the food supply chain to improve production, maintenance, and acceptance by consumers. Hazardous substances can be used in these processes. However, despite the many potential health risks associated with food, in practice, the degree of risk associated with modern food supply is extremely low. The presence and levels of hazardous substances in food, such as chemicals intentionally added, or contaminants and residuals, is constantly monitored and evaluated by national and international agencies assuring safe foodstuff to the public. This manuscript reports some examples of different hazardous substances occurring in food and their risk for the population.

Keywords: Food toxicity; Hazard; Risk; Food safety

Short Note

The Pure Food and Drug Act 1906 was the first of a series of significant consumer protection laws attempting to regulate food safety. This act prohibited the use of any colour additive in food if the colour would deceive the consumer, conceal inferiority or damage, or result in misbranding or adulteration [1,2].

Over the years, the issue of food safety has increasingly had a greater socio-economic and regulatory impact as foodborne diseases represent a public health burden and contribute substantially to the cost of health care. The importance of food for mankind is undeniable; there is still no way of living without eating. Therefore, this commodity is of utmost importance for the well-being of people around the world. Although the need for food has proved to be immutable over the centuries, production, preparation, choice and the way we consume food has seen significant changes, sometimes resulting in risks to human health.

Food safety is a responsibility shared by everyone involved in the food chain, from producers of food products, to retailers and consumers. Throughout the food chain, laws and controls are implemented that lead to the elimination of the use of hazardous substances as well as the reduction in the risk of contamination and to ensure that the foods that reach the tables of consumers are safe.

Foods that we commonly eat are generally accepted as being safe to eat. However, all chemicals, including those found naturally in foods, are toxic at some dose. Toxicity testing of a food or ingredient can tell us what the likely adverse effects are and at what level of consumption they may occur, but by itself this does not tell us whether it is safe to eat in normally consumed amounts. The concept of inherent hazard from risk should be distinguished, that is the probability that the substance will produce injury under defined conditions of exposure. The concept of risk takes into account the dose and length of exposure as well as the toxicity of a particular chemical. Consequently, any attempt to examine the safety of food should not be based on the toxicity of a food ingredient or contaminant but rather by the evaluation on the safe use of the substance [3].

Hazardous food substances can be chemicals intentionally added such as additives and flavouring, contaminants such as residue of veterinary medicines or pesticides or chemicals released from packaging materials. Moreover, unavoidable chemicals in the modern food chain can be persistent

organic pollutants, metals, natural toxins from plants or from animals or mycotoxins and nanomaterials.

Among these the most dangerous contaminants are those produced by infestations of bacteria or moulds in food, which can produce toxins that remain in the food even after the biological source has been destroyed.

Recently, the European Food and Safety Authority (EFSA) published a scientific opinion on public health risks related to the presence of ochratoxin A (OTA) in food, a mycotoxin naturally produced by fungi of the genus *Aspergillus* and *Penicillium* and found as a contaminant in various foods including cereals, preserved meats, fresh and dried fruit, and cheese [4]. New data suggest that OTA can be genotoxic by directly damaging DNA, inducing kidney toxicity in different animal species and kidney tumours in rodents. Moreover, OTA resulted genotoxic both *in vitro* and *in vivo*; however, the mechanisms of genotoxicity are unclear. The EFSA panel, considering the available data, calculated relevant Margin of Exposures (MOE) ≥ 200 for non-neoplastic, and an MOE ≥ 10,000 for selected neoplastic effects. The estimation of chronic dietary exposure resulted in mean and 95th percentile levels ranging from 0.6 to 17.8 and from 2.4 to 51.7 ng/kg bw per day, respectively. Median OTA exposures in breastfed infants ranged from 1.7 to 2.6 ng/kg bw per day, 95th percentile exposures from 5.6 to 8.5 ng/kg bw per day in average/high breast milk consuming infants, respectively. Comparison of exposures with the BMDL10 based on the non-neoplastic endpoint resulted in MOEs of more than 200 in most consumer groups, indicating a low health concern with the exception of MOEs for high consumers in younger age groups, indicating a possible health concern. When compared with the BMDL10 based on the neoplastic end point, MOEs were lower than 10,000 for almost all exposure scenarios, including breastfed infants. This would indicate a possible health concern if genotoxicity is direct. Uncertainty in this assessment is high and risk may be overestimated.

Other natural contaminants are aflatoxins. Aflatoxins are one of the highly toxic secondary metabolites derived from polyketides produced by fungal species such as *Aspergillus flavus, A. parasiticus, and A. nomius* [5]. They are widely spread in nature and have severely contaminated food such as cereal crops including wheat, walnut, corn, cotton, peanuts and tree nuts [6,7]. Aflatoxin term typically refers to the sum of Aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), aflatoxin G2 (AFG2) and aflatoxin M1 (AFM1). They can lead to serious threats to human and animal health by causing various complications such as hepatotoxicity, teratogenicity, and immunotoxicity [8-11]. AFB1, AFG1 and AFM1 are carcinogenic when delivered orally via the diet or by gavage to experimental animals. There is limited evidence for the carcinogenicity of AFB2 and inadequate evidence for carcinogenicity of AFG2. AFB1 is the most potent mutagenic in the class [12].

EFSA has just delivered a scientific opinion on the risks to public health related to the presence of aflatoxins in food. In particular for AFB1, AFB2, AFG1, AFG2 and AFM1. Considering the genotoxicity and cancerogenic effects of AFB1 the expert panel deemed that calculation of a BMDL from the human data was not appropriate and the cancer potencies estimated by the Joint FAO/WHO Expert Committee on Food Additives in 2016 were used. The calculated MOEs are below 10,000 for AFB1 and also for AFM1 where some surveys, particularly for the younger age groups, have an MOE below 10,000. From this evaluation, the panel concluded that aflatoxins raise a health concern [13].

Pesticide or veterinary medicine residues are hazardous substance in food. Generally, they are well controlled in modern food supplies.

One debated case is around glyphosate. Glyphosate is an active substance that is widely used as a pesticide. Glyphosate-based pesticides i.e. formulations containing glyphosate and other chemicals are used in agriculture and horticulture primarily to combat weeds that compete with cultivated crops. They are typically applied before crops are sown and as a pre-harvest desiccating treatment, accelerating and evening the ripening process therefore it can be a crop contaminant [14].

Glyphosate is currently approved in the EU and the approval expires on 15 December 2022. In May 2017, EFSA, in line with the scientific opinion of 27 out of 28 Member State experts, concluded that glyphosate is unlikely to be carcinogenic to humans. This conclusion represented a divergence with the International Agency for Research on Cancer (IARC), which in March 2015 classified glyphosate as probably carcinogenic to humans [15]. Recent reports in the media have alleged that parts of the EU assessment of glyphosate were plagiarised from information provided to regulatory authorities by the companies applying for the re-authorisation of this active substance. EFSA replied that these allegations are unfounded and based on a fundamental lack of understanding of the EU pesticides assessment framework [16]. However, the debate is still open even if EFSA reviewed all existing authorised uses of the herbicide in the EU, covering all crops treated with glyphosate, and published a risk assessment which shows that current exposure levels are not expected to pose a risk to human health. For this assessment EFSA compared the diets of adults and children in the EU with the safe intake values that EFSA [17,18].

Food-producing animals may be treated with veterinary medicines to prevent or cure disease. These substances may leave residues in food. The potential occurrence of these contaminants, which could be hazardous to consumers, requires close monitoring by the authorities. In its annual report on residues of veterinary medicines in animals and food of animal origin for 2018, EFSA reported that data showed high rates of compliance with recommended safety levels in the European Union. The percentage of samples that exceeded maximum levels was 0.3%. Compared to 2017, non-compliance increased slightly for antithyroid agents and steroids. Small decreases were noted for antibacterials, and other veterinary drugs (such as non-steroidal anti-inflammatory drugs). Data showed low, but still present, levels of banned substances, such as chloramphenicol, nitroimidazoles and nitrofurans. However, they demonstrate high rates of compliance with recommended safety levels [19].

In the modern food chain, the majority of foods are kept in plastic packaging. Legislation for food contact materials covers materials that contact food or water giving rules to ensure public health [20,21]. The safety of food contact materials must be evaluated as hazardous chemicals can migrate from the materials into food. One of these is bisphenol. Bisphenol A (BPA) is an organic compound used in combination with other chemicals to produce polycarbonate plastics and epoxy resins used in many industries including food. It can be found, for example, in the bottles for drinks, in plastic containers and dishes (plates and cups), in the crockery for microwave cooking, in kitchen utensils and water tanks. In addition, BPA residues are also present in epoxy resins used to produce film and protective coatings for beverage cans and food tin cans [22].

BPA is considered an endocrine disrupter, i.e. a substance that can interfere with the action of hormones, alter homeostasis, and modify physiological processes throughout an individual's life, especially in the stage of fetal development and early childhood. In 2017, the European Chemicals Agency (ECHA) added BPA to the list of extremely worrying substances (SVHC) due not only to its endocrine disrupting properties but also to its potential toxic effects on reproductive capacity. BPA, in fact, having weak estrogenic activity, is able to mimic the action of estrogen and therefore to influence the reproductive function. A Specific Migration Limit (SML) has been set at 0.05 mg/kg [21] of foodstuff and, currently, the Tolerable Daily Intake (TDI) is 4 ug/kg of body weight/day). However, in January 2011, the European Commission prohibited the use of BPA for the production of polycarbonate infant feeding bottles [23] and since 2009 it has been included in the list of banned substances in cosmetic products [24]. Finally, in December 2016, the European Commission decided to limit the use of BPA in thermal paper in the EU [25]. The ban will enter into force in 2020, to give manufacturers, importers and users of thermal paper time to eliminate it and find an alternative. However, the EFSA expert panel evaluated the levels of BPA to which consumers of all ages are exposed. EFSA considered that there are no health concerns as the maximum estimates for food and aggregate exposure (from a set of multiple sources) to BPA are 3 to 5 times lower than the TDI of 4 ug/kg bw/day [26].

Other than contaminants and residues, some 20th century food may have adverse effects on the body if consumed in excessive quantities, such as foods rich in unsaturated fats, or refined flours or foods cooked at very high temperatures. Sometimes alarms rise from publications where normally used food is now regarded as toxic. This is the case for red meat and, more convincingly, of processed red meat.

Red meat is consumed globally and plays an important role in the Western diet. However, its consumption is linked with various types of diseases [27]. Scientific literature is available on this matter. It is reported that long-term consumption of red meat (and even more clearly processed meat) is associated with significant increase in mortality, likely contributing to the current epidemic of cardiovascular diseases [28], type 2 diabetes [29], and to increased risk of certain kinds of adenocarcinomas (cancers of mucosal epithelial origin), particularly colorectal cancer [30]. The concern raised in particular, following the World Health Organization-International Agency for Research on Cancer (WHO/IARC) monograph summary where the carcinogenicity of consumption of red meat and processed red meat was emphasized [31,32]. On October 26, 2015, IARC issued a press release informing the recent evaluation of the carcinogenicity of red and processed meat consumption. The consumption of red meat and processed meat was classified as "probably carcinogenic to humans", and as "carcinogenic to humans", respectively. The substances responsible for this potential carcinogenicity would be generated during meat processing, such as curing and smoking, or when meat is heated at high temperatures [33]. There are many proposed mechanisms for the disease-promoting effects of red meat. These include DNA damage due to N-nitroso compounds (NOCs) and mutagens generation by high temperature grilling; high dietary intake of salt and saturated fat; pro-oxidant effects of heme and iron; and production of Trimethylamine–N-oxide (TMAO) by the gut microbiome [34].

Given all this evidence, why was red meat, particularly processed meat, not banned or limited to the consumer? The IARC classification of carcinogenicity is not a classification of the level of risk, but an evaluation on existing carcinogenicity data. It does not give information on the potency in the tumor induction and mainly on the risk. A paper published in 2017 by the World Cancer Research Fund [35] on the risk of colorectal cancer estimated that a consumption of processed red meat estimated to be 50 grams per day would be associated to an increase in the risk of this cancer by 16 percent. It is, however, the so-called relative risk, which must be added to the absolute risk of individuals. In fact, people who are unfamiliar with colon cancer and cancer in general, have healthy life habits (do not smoke, exercise) but are frequent consumers of cured meats, will increase their risk of getting colorectal tumors by about 16 percent compared to people with the same characteristics and habits except for cured meats. The indications of the IARC must be considered in terms of population and public health.

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