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Mini Review | Journal of Nutritional Health & Food Science | Open Access

Special Issue: Food Safety & Hygiene

Food Additives of Public Concern for their Carcinogenicity

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Received: May 13, 2015; Accepted: August 12, 2015; Published: 20 August, 2015

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Abstract

No-Observed-Adverse Effect Level (NOAEL) of food additives has been long determined on the basis of toxicological studies. Acceptable Daily Intake (ADI) levels of food additives for human are derived from these NOAEL, and their legal limits are then established for the food products, intentionally added with food additives. However, recent studies demonstrated that consumption of some processed food containing certain food additives might have increased the risk of cancer in human although the legal limits of these additives in processed foods are well respected by the manufacturers. Possible reasons for increased carcinogenicity risk in processed foods containing these additives can be due to various factors: -interaction of additives with some food ingredients, -food processing may change the chemical formula of food additive to a formula to be acting similarly as carcinogenic compound, -a negative synergistic effects when combined with other additives, -improper storage conditions, and -unknown carcinogenic by-products occurring during the food processing. Due to the above mentioned factors we recommend that an additive, intentionally added to the food during processing must be traced officially for its carcinogenicity. In this review, we overviewed all of the food additives authorized in European Union. Therefore, the traceability issues of processed foods containing certain food additives, which have a negligible probability of carcinogenicity in legal limits, must be reinforced in the perspective of public health concerns.

Keywords: Food additives; Cancer; Side effects; Carcinogenicity; Processed food

Abbreviations

ADI: Acceptable Daily Intake; BHA: Butylated hydroxyanisole; BHT: Butylated hydroxytoluene; EFSA:European Food Safety Authority; FDA: Food and Drug Administration; IARC: International Agency for Research on Cancer; JECFA: Joint FAO/WHO Expert Committee on Food Additives; MNNG: N-methyl-N'-nitro-N-nitrosoguanidine; NOAEL: No-Observed Adverse-Effect Levels; NOC: N-Nitroso compound; NSRL: Level of No Significant Risk; WHO: World Health Organization

Introduction

Due to gradually increased mortality rate, cancer is considered one of the most serious and life-threatening diseases after the cardiovascular diseases. The data provided by World Health Organization (WHO) indicates that cancer would be the first leading cause for death in 2030 [1]. Therefore, the scientific attempts for prevention from cancer and to overcome the main causative factors accounted for the disease are important.

Foods and Cancer

Cancer is a multifactorial disease, in which either heredity or environmental factors are involved. Nutrition is being responsible for the increased rate of cancer. The nature, consumed portion and additive contents of the food products may be important in the possible cancer occurrence. For instance, the refined foods in the form of carbohydrates may stimulate the occurrence of colon cancer [2]. The consumption of excessive amount of red meat may also increase colon cancer [3]. Other factors for increasing cancer risk are due to the additives that are added to the processed foods [4,5,6].

Food Additives and Cancer

Food additives are subjected to toxicological studies for their safety evaluation. The additives, scientifically and officially proven as safe are authorized to be used in the food sector. However, the consumption of some processed foods containing certain food additives might increase the risk of cancer in human, although the legal limits of these additives in these foods are being respected. For instance, the new reports indicated that the processed meat containing preservatives such as nitrite and nitrate increases colon and pancreatic cancer risks [4,7]. A soft drink such as coke may also increase some cancer types as shown by the work of Belpoggi et al. [5]. In this research, the rats fed on a standard diet for life span was taken into a trial where half was given normal tap-water, while other half given a coke as source of drinking water. It was shown that the incidence of breast cancer in females and pancreatic tumor mass in both males and females was higher in the group receiving coke than the normal tap-water group. A similar work reported that drinking beverages containing food additives may increase cancer risk [6]. In this report, 600 Singaporean consumed non-alcoholic beverages

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of two glasses or more per week for 14 years have increased pancreatic cancer, whereas no such evidence was observed in those drinking fruit juices.

It can be clearly seen from these cases where some processed foods containing safe additives may increase carcinogenicity risk despite the fact that there was no safety concern of these additives officially declared. Therefore, one can speculate the following reasons on the fact that why these additives may pose a degree of carcinogenicity in the food products while no carcinogenic risks were demonstrated in experimental studies in which they used *per se*: possibility of food structural changes, possible negative synergistic effects with other carcinogenic by-products in commercial additives, possible exposure to long and improper storage conditions, and possibility of exceeding the safe limits.

Possible Causes of Increase in Carcinogenicity of Additives

Structural changes

Chemical structure of food additives may have been changed in the food products during physical, chemical and enzymatic processing when coming in contact with other food ingredients. For instance, nitrates and nitrites are converted to nitrosamines in meat products [8].

The most frequently present nitrosamines in meat and dairy products are N-nitrosodimethylamine and N-nitrosopyrrolidine. In Belgium, 101 dry fermented sausages were analyzed for the residual sodium nitrite and nitrate contents, biogenic amines and volatile N-nitrosamine concentrations. The results showed that N-nitrosopiperidine and N-nitrosomorpholine were detected in a high number of samples (resp. 22% and 28%) [9].

Catsburg et al. [10], examined the role of dietary sources of N-Nitroso compounds (NOCs) and NOC precursors as potential bladder cancer risk factors in a case-control study in Los Angeles. They reported that consumption of processed meats (sources of amines and nitrosamines) such as salami/pastrami/corned beef and liver were both significantly associated with the risk of bladder cancer.

Negative synergistic effects

Interaction effects between various food additives on carcinogenicity could have been overlooked when evaluating their single carcinogenic risks. The risk could have been increased for one of the food additives, which is adversely interacted. There are scientific evidences available to support this hypothesis. For instance, the additives of potassium sorbate, ascorbic acid and ferric or ferrous salts have been shown to cause mutagenicity and DNA-damaging activity, when all combined together, but not when used separately [11]. In another study, the synergistic effect of a mixture of six typical artificial food colors (erythrosine, allura red, new coccine, brilliant blue, tartrazine, and fast green) on the toxicity of carcinogen 3-amino-1,4-dimethyl-5H-pyrido[4,3-b] indole (Trp-P-1) has been investigated using primary cultured rat hepatocytes and found that the food-color mixture enhanced cytotoxicity of Trp-P-1 [12].

Getting contact with other carcinogenic by products in commercial additives

There can be unknown compounds in a given food, and presumably the consumers could have a risk of consuming them. For instance, some undesirable by-products such as 4-Methylimidazole can be formed during the production of caramels when ammonium is used. The derivate of 4-Methylimidazole cause's lung cancer in both male and female mice at high doses and causes leukemia in females [13,14]. The caramel products contained in some coke products were found to contain higher levels of 4-Methylimidazole than no significant risk level (NSRL), and the center for Science in the Public Interest in February 16th, 2011 has called a public petition to apply United States Food and Drug Administration (FDA) for banning to use these caramels in these products [15].

Improper and longer storage conditions

Unsuitable conditions may cause, change in chemical structure. Benzoates (benzoic acid, sodium benzoate, potassium benzoate, and calcium benzoate) are typical examples. They can be converted by decarboxylation reactions to benzene, which is a carcinogenic compound when they present with ascorbic acid and/or erythorbic acid under suitable pH, UV light or temperature conditions [16].

Exceeding the safe limits

Food additives are placed in the market after their provisions of ADI levels are legally established. Then the provision for a maximum amount that can be added into foods is calculated according to these ADI levels. However foods containing additives are consumed on a daily basis, and this is then followed by the sustainable production of such foods to meet the market demand. Thus, this legal provision for maximum may somehow has been exceeded during the routine production lines.

In a study investigating the role of microparticles in Crohn's disease, it was found that a microparticle titanium dioxide was comsumed more than ADI [17]. In a similar study conducted in Italy, it was shown that an antioxidant Butylated hydroxytoluene (BHT) was consumed more than ADI [18]. It was documented that phosphorus had been consumed more than the ADI level in the US [19].

The dietary exposure of nitrate and nitrite taken along with natural foods was assessed in France. As a result of the study, dietary intake of nitrite was found higher than the ADI level in 0.7%-16.4% of adults, and in 10.5%-66.2% of children, respectively [20]. Similarly, the amount of nitrite-nitrate in meat products was assessed in Estonia, and it was found that nitrite intake exceeded the ADI level by up to 140% for 1 to 6-year-old children [21].

In a study determining the intake of artificial food colors on 3141 children in Kuwait, it was found that tartrazine, sunset yellow, carmoisine and allura red were comsumed more than the ADI level [22,23].

Some "Safe Additives" Might Be Linked to Cancer

According to IARC (International Agency for Research on Cancer) classification, carcinogenicities of food additives are listed in table 1 [24-29]. These are considered as safe due to no significant risk level (NSRL) even they have small degree of risk for cancer. For them, only safe amount are allowed for human consumption. All additives mentioned in this paper are safe when they are consumed in legal limits. However due to above mention reasons, some additives may have lost their scope of safetyness, and thus their carcinogenic effects or risks would have been high, especially when used in processed food.

The main objective of present study is not to carry out a scientific evaluation of these additives. This has been routinely done and reviewed by several authoritative bodies (i.e., European Food Safety Authority (EFSA), Joint FAO/WHO Expert Committee on Food Additives (JECFA) and FDA). Full evaluation reports and ADI levels can easily be accessed via their web pages. Our aim is to gather safe food additives, which have probabilities:

- Promoting carcinogenicity at high exposure doses,
- Stimulating carcinogenicity of other carcinogenic compounds at high doses.

Table 1: Classification of food additives with carcinogenicity by IARC.

Groups* / Food Additives	Group 1	Group 2A	Group 2B	Group 3
Cyclamic acid and its Na and Ca salts [24]				X
Butylated hydroxyanisole (BHA) [25]			X	
BHT [26]				X
Saccharin and its Na, K and Ca salts [27]				X
Talc not containing asbestiform fibres [28]				X
Carrageenan, native [29]				X
Carrageenan, degraded [29]			X	

* IARC classification of carcinogens: **Group 1**: Carcinogenic to humans (Sufficient evidence in humans or sufficient evidence in animals and strong mechanistic data in humans)
Group 2A: Probably carcinogenic to humans (Limited evidence in humans and sufficient evidence in animal)
Group 2B: Possibly carcinogenic to humans (Limited evidence in humans and less than sufficient evidence in animals)
Group 3: Not classifiable as to its carcinogenicity to humans (Inadequate in humans and inadequate or limited in animals)

Table 2: Food additives promoting carcinogenicity at high exposure doses.

Food Additives	Cancer Types
Cyclamic acid and its Na and Ca Salts	Colon and Hepatocellular tumors, Prostate adenocarcinoma, Thyroid and Uterus adenomas [30]
Allura Red AC	Colon tumor [31]
Acesulfame potassium	Urinary track tumor [32]
Aspartame	Urinary track tumor [32] Lymphoma, Leukemia and Breast tumor [33]
BHA	Breast tumor [34]
BHT	Bladder tumor [35]; Lung tumor [36]
4-Hexylresorcinol	Adrenal gland pheochromocytoma and Herderian gland tumor [37]
Hexamethylenetetramine	Kidney tumor [38]
Carboxymethyl cellulose, Sodium carboxymethyl cellulose	Fibrosarcoma at the side of subcutaneous injection [39,40]
Xylitol	Adrenal medulla tumor [41]
Nitrates, Nitrites	Colorectal cancer [42] Bladder tumor [43] Non-hodgkin lymphoma [44] Thyroid tumor [45] Brain [46] Hepatocellular tumor [47] Advanced prostate cancer [48]
Propionic acid and its salts	Forestomach tumor [49]
Saccharin and its salts	Bladder tumor [50]; Thyroid tumor [51]
Talc	Adrenal gland and lung adenoma/carcinoma [52] Endometrial cancer (in genital usage of women as talcum powder) [53,54,55,56]
Polyoxyethylene stearate	Bladder papilloma [57]

Table 3: Food additives stimulating carcinogenicity of other carcinogenic compounds at high doses.

Food Additives	Cancer Types and Cancer Causing Compounds
Carrageenan	*Degraded carregeenan:* Colorectal carcinoma without any carcinogenic agents [58] *Native carregeenan:* Colon carcinoma in the presence of azoxymethane or methylnitrosourea [59]
Sodium Saccharin	Bladder carcinoma in the presence of N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide or N-butyl-N-(4-hydroxybutyl) nitrosamine [60]
Sorbitan monolaurate	Stomach adenocarcinoma and gastric sarcoma in the presence of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) [61] Skin tumor in the presence of dimethylbenz[a]anthracene [62,63]
Antioxidants related to cancer promoting	Urinary bladder cancer caused by ascorbic acid and sodium erythorbate in the presence of N-butyl-N-(4-hydroxybutyl) nitrosamine [64] Forestomach and urinary bladder carcinomas caused by sodium ascorbate in the presence of butylated hydroxyanisole, urinary bladder carcinoma enhanced by sodium erythorbate [65,66] Forestomach carcinoma caused by propyl gallate in the presence of sodium nitrite [67] Gastric carcinoma caused by the combination of sodium nitrite and ascorbic acid in the presence of MNNG [68]

We overviewed all of the food additives, which were approved to consume in EU. Selected additives were listed in table 2 and 3[30-68].

General Conclusion

The official monitoring of processed products in respect with their cancer causing effects due to the quality and quantity of their additive contents are significant for the protection of public and consumer health. This review may facilitate to track processed foods containing these additives. It also provides the reader an easy access to the concise information on the relationship between carcinogenicity and food additives. We strongly believe that this review would help to conduct the official controls of processed products containing these food additives since it provides a concise piece of information regarding their possible carcinogenic risks.

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