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Evaluating Hazards Posed by Additives in Food: A Review of Studies Adopting a Risk Assessment Approach

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ABSTRACT

Processing and packaging has increased the use of food additives in the food industry. Some of these additives have associated health risks. This review looks at studies on risk assessment of food additives published between 2000-2015. These studies have majorly focused on synthetic food colors and preservatives like benzoate, sorbate, nitrite and nitrate. Most of the studies have shown that the intake was below the acceptable daily intake (ADI) for average consumers. For extreme consumers (95th percentile), intake was found to be above the ADI or approaching ADI for additives like sunset yellow FCF, erythrosine, tartrazine, sulphite, benzoate and nitrite. It is advisable to look at multiple scenarios of dietary exposure while evaluating risk. A surveillance system which documents adverse effects to food additives as well as monitors risk on a regular basis is important for every country to have. Such data would be beneficial to regulatory authorities as well as the industry in fixing usage levels of the additive in an effort to minimize health risk.

Key words: Dietary exposure; Risk analysis; Artificial sweetener; Food colour; Preservative.

INTRODUCTION

With changing lifestyle and dietary transition, there is an increase in intake of processed and packaged foods which tend to have a number of food additives. This has increased our consumption of these chemical substances raising the risk of exceeding acceptable daily intake levels [1]. To make matters worse food laws and regulations in different countries vary. With increase in trade between nations, this disharmony in regulations creates barriers on one hand and allows for sub-standard and unsafe products to enter markets in developing countries where they may not be subjected to rigorous scientific testing.

Risk assessment is a component of the process of risk analysis. Before approval of any food additive, vigorous scientific evaluation of hazards associated with that additive is carried out. Even after approval of the additive, with time, newer safety evaluations of that additive are carried out as exposure may change over time, making risk assessment a cyclic process. The present paper examines the studies, published between 2000-2015, on risk assessment of certain food additives.

Systematic literature search of scientific databases was done and published articles / reports related to risk assessment of food additives were selected. The following keywords were used to search each database: “risk analysis”, “risk assessment”, “food additives”, “processing aids”, “preservatives”, “artificial sweeteners” and “food colours”. Search engine like Google Scholar, Cite U Like, Academic Search, RefSeek and Academic Info was used to retrieve relevant literature from databases like Scopus, PubMed, Medline, Ingenta Connect, Agricola, CAB abstracts, ProQuest, JSTOR, DOAJ, Embase, Springer link and reports published by WHO and JECFA.

The extent to which a food additive can pose a health risk depends upon its toxicity and the dietary exposure. Joint FAO/WHO Expert Committee on Food Additives (JECFA) and Scientific Committee on Foods (SCF) establishes Acceptable daily intake (ADI) values for food additives. ADI values are calculating using a safety factor which ensures that if the additive is consumed daily at that level for the rest of one's life, there would be no "appreciable health risk" [2,3]. Food additives require to undergo a vigorous risk assessment procedure before their approval and entry into the market. Components of the process of risk assessment are hazard identification, hazard characterization, exposure assessment and risk characterization [4]. JECFA evaluates the safety of food additives and contaminants in food. [2]. All food additives that are used in a food-stuff are declared on the package using E-number given by European Union (EU) [5] or by an International Numbering System (INS-No.) signifying approval by JECFA [6].

Member countries may request FAO / WHO or the Codex Committee on Food Additives and Contaminants (CCFAC) to initiate the process for risk assessment to be carried out by JECFA[7]. The scientific process of risk assessment not only estimates human risk associated with consumption of food additives but also assists in arriving at and establishing the ADI values for food additives [8].

Risk assessment process

The risk assessment of food additives is purely a scientific process that requires the nutritionist and the toxicologist to work together [9]. The four steps of risk assessment are being discussed here.

Step 1: Hazard identification

The step of hazard identification identifies intrinsic properties of a food additive which can potentially affect health [10]. This is done by using the "weight-of-evidence approach". For this, review of appropriate published scientific databases is done for searching human and animal toxicological studies related to the food additive of concern. Epidemiological studies are given preference over lab based research data [4].

Step 2: Hazard characterization

The safety of food additives is assessed by evaluating toxicity data. Hazard characterization involves both "dose-response extrapolation" and "dose scaling". In dose-response extrapolation, the toxicity levels estimated for animals need to be extrapolated both qualitatively and quantitatively to much lower doses for comparison with human exposure levels. In dose-scaling, JECFA uses mg / kg body weight for "inter-species" scaling as equivalence in toxic doses is difficult to establish [4]. Hazard needs to be characterized using multiple methods and using different approaches. Mathematical modelling can be used to characterize dose-response relationships [11].

Step 3: Exposure assessment

Estimating consumption of food additives is not simple and requires the assistance of experts in the field of nutrition. Usually the 24-hour dietary recall / record or the food frequency questionnaire (FFQ) is the tool of choice for estimating the intake of foods likely to contain additives. Other direct and indirect methods used for collecting data on food consumption are reviewed elsewhere [1]. Concentration of the additive in different foods is chemically estimated to ultimately calculate the dietary exposure to the additive. Some studies have also used the maximum permissible levels (MPLs) in foods or used industrial usage data to determine exposure.

Step 4: Risk characterization

In this step, the probability of occurrence of adverse toxic effects in humans as a result of exposure to food additive is assessed. This is usually done by comparing ADI values of the additive with exposure levels among humans [4]. Risk can be characterized using different exposure scenarios as depicted in Table 1. Scenarios 1 and 2 give the best estimate of the population where the exposure is assessed among the part of the population which only consumes foods containing the selected food additive and the level of added additive is average. Scenarios 3 and 4 covers the part of the population that always consume the same brand (brand loyal customers), and it is assumed that they are loyal to the brand with the highest reported level of food additive [12]. The worst case intake scenario is where content of additive in permitted food products is the maximum permissible levels specified by regulatory authorities and it is assumed that all consumed food

products, in which addition of additive is permissible, contain that additive. This approach has been used in a number of studies [13-18] for assessing risk associated with consumption of certain food additives.

Hazard Index (HI) has also been used for characterizing risk and is calculated by the average daily dose (ADD) for an additive from the diet expressed as a percentage of ADI. If the HI is less than 100 % then there is no harm from exposure to that additive [19]. Characterization of risk from food additives not only focuses on the data generated for general population but also focuses on the at risk population who may be extreme consumers of the additive for instance, sub-groups like diabetics in case of artificial sweeteners. According to JECFA, occasionally exceeding the ADI of a food additive for individuals is not usually a big concern. However, monitoring of such groups of individuals would be wise in order to estimate the frequency of such exposures as well as the dose of the additive to which these individuals are regularly exposed.

Review of studies done from 2000 onwards on risk assessment of food additives

Studies from various countries between the period of 2000-2015 on assessment of risk of food additives have been reported here. A total of twenty-four studies on risk assessment of food additives were obtained after careful search of databases which used the keywords "risk assessment" in their title or while giving their results or discussion. The summary of these studies have been presented in Table 2 covering artificial sweeteners, artificial colours and chemical preservatives.

Artificial sweeteners

High doses (> 1500 mg / kg body weight / day) of artificial sweetener like saccharin have shown toxic effects like swelling of renal glomeruli, growth depression and carcinoma in rats [36]. Acute, sub-acute and chronic toxicity studies done for aspartame have shown no adverse effects [37]. However a study has reported that intake at half the ADI for aspartame may lead to neurobehavioral effects like irritable moods, depression, lower performance among human adults [38]. The emerging data for sucralose based on human and rodent studies have shown that high sucralose intake alters glucose, insulin and glucagon-like peptide-1 levels. It has been found to be mutagenic in nature in some studies [39-40].

Only three studies on artificial sweeteners could be retrieved. The artificial sweeteners studied were acesulfame, aspartame, cyclamic acid, saccharin and sucralose in beverages. Exposure to selected sweeteners in one study [12] was assessed using all the four scenarios of exposure assessment. In two studies, individuals from all age-groups were studied [12, 21] and in the third study dietary exposure of school children was studied [20]. Either chemical analysis using high performance liquid chromatography (HPLC) was used [20] or usage levels provided by manufacturers were used [21] for estimating sweetener content in foods. The data on food consumption was collected using a semi-quantitative FFQ. In the studies, the content of sweeteners in food items was below the MPLs. Hazard index for both average and high consumers in the studies was lower than 100% for all age-groups. Thereby, the risk was considered to be miniscule but more such studies for susceptible sub-groups like diabetics need to be carried out where the dietary exposure is likely to be higher.

Artificial colour

In most of the studies, colours studied were carmoisine, erythrosine, indigo carmine, ponceau 4R, sunset yellow FCF and tartrazine. Other colours studied were brilliant blue FCF, fast green FCF, allura red, azorubine, brilliant black, brown HT, green S, quinolline yellow, annatto, amaranth and riboflavin. Presence of non-permissible colours like auramine, rhodamine, orange II, blue VRS and malachite green in foods were detected in developing countries like India, where use of these colours as adulterants has been documented [24-26, 28]. In all studies, levels of colours in food-stuffs manufactured by the un-organized sector were found to exceed their MPL's.

High doses (40 mg / kg body weight / day) of erythrosine administered to rats have shown toxic effects like thyroid follicular cell adenomas [41]. Doses between 1500 – 2250 mg / kg body weight / day of Sunset Yellow FCF when administered to rats have shown toxic effects like body weight reduction and diarrhea [4] and Ponceau 4R (500 – 1000 mg / kg body weight / day) has shown toxic effects like hepatic cirrhosis and renal problems in rats [42]. Although humans are not likely to be exposed to such high

doses as used in animal studies, exceeding the ADI is not an unlikely scenario here.

Usually in most of the studies risk due to additive exposure was assessed using scenario 1 which is the best estimate of actual consumption of colour by the targeted population. Only one study [22] assessed the risk using scenario 1 and 3. The exposure was studied in individuals of all age groups. In some studies, exposure to colours was studied only for children probably because foods likely to be coloured are consumed mostly by children. Also children are at a greater risk of exceeding ADIs because of lower body weights. Chemical analysis has been done to analyze colour content in most of the studies except one [30] where maximum permissible levels for colours (worst-case scenario evaluation) in food products was used. The method used for collecting data on food consumption varied from semi-quantitative FFQ to one-day 24-hour recall. In one study [23] a 7-day food diary was also used.

In some Indian studies [25-26, 28] seasonal variation was also taken into account by conducting the study twice in a year. This was done as consumption of coloured food products like beverages and ice creams tends to be higher in summer months. Adulteration with non-permissible colours like Rhodamine and Orange II were reported in studies [25-26]. Children appeared to have a higher risk of being an extreme consumer and sunset yellow FCF, tartrazine and erythrosine were the colours for which the HI was exceeding 100% in high consumers. Major contributors to the intake of artificial colours were desserts and beverages. In studies in Thailand, fish balls were found to be the major contributor to colour intake.

Synthetic preservatives

High doses (280 mg / kg body weight / day) of sulphite in rats have shown several toxic effects like irritation of stomach and intestinal lining, vomiting reflexes and hemorrhages while in humans (at doses of 1-50 mg /day), adverse reactions like urticaria, angioedema and aggravation of asthmatic symptoms have been observed [43]. High dosage (75mg) of benzoates administered to human participants in a study showed toxic effects like urticaria and angioedema [44]. Anaphylactic reactions were observed in humans when they were administered an oral dosage of 25 mg of sodium nitrite [45].

The chemical preservatives for which risk assessment studies have been reported in literature are benzoic acid, sulphite, sorbic acid, nitrate and nitrites. In certain studies exposure to preservative was studied for one specific food item i.e. beverages [21] ,sauces [27] ,red curry paste [34] and meat products[33] assuming that exposure to the additive was majorly from one food item. In most of the studies risk was assessed using scenario 1 of exposure. In the Norway study [12] exposure to the selected preservative was assessed using all the four scenarios of exposure assessment.

In case of two studies [19, 35] total diet study was conducted where consumption of all food items was studied. Exposure was assessed for all individuals above 1 year of age in almost all studies. Only in one study[21] usage levels provided by industry was used for defining preservative levels in foods.

Table 1: Different risk scenarios assessing exposure to food additive [12]

Concentration of additive (mg/kg or mg/l)	**Intake of additive(mg / kg body weight / day)**	
	The actual consumption of food containing the food additive using dietary surveys.	**It is assumed that all foods consumed (in which addition of additive is permissible) contain that additive.**
The average level of additive in the food.	SCENARIO 1	SCENARIO 2
The highest reported level of food additive in the food.	SCENARIO 3	SCENARIO 4

Table 2: Summary of risk assessment studies on food additives

Food Additive	Country (Reference)	Study Participants	Risk Characterization				
			Mean Additive Intake vs. ADI	High Consumer Intake vs. ADI	Major Food Contributor to Additive Intake	Age Group at Maximum Risk from Additive	Comments
Artificial Sweeteners	China (20)	967 secondary school students	Mean intake for all sweeteners was below the ADI.	Intake for all sweeteners was well below the ADI.	Packaged drinks only.	No risk for secondary school students.	Risk was assessed using scenario 1.
	Norway(12)	1674, 2 year olds and 1787, 18-70 year olds	Mean intake for all sweeteners was below the ADI.	Intake for all sweeteners was well below the ADI.	Packaged drinks only.	No risk for any age group.	Risk was assessed using all four scenarios.
	Norway (21)	8821 individuals >1 year of age	Mean intake for all sweeteners was below the ADI.	Intake for all sweeteners was well below the ADI.	Packaged drinks only.	No risk for any age group.	Risk was assessed using scenario 1.
Artificial Food Colours	Australia(22)	13,858, 2-70 year olds	Mean intake for all colours was below the ADI.	Intake was below the ADI.	Soft drinks and sugar confectioneries.	No risk for any age group.	Risk was assessed using scenario 1 and 3.
	France(23)	3003 individuals > 3 years of age	Mean intake for tartrazine was below the ADI.	Intake for tartrazine was well below the ADI.	Soft drinks, bakery wares and sugar confectioneries.	No risk for any age group.	•Some products like soft drinks, bakery wares and sugar confectionery items contain tartrazine exceeding the permissible levels. • Risk was assessed using scenario 1.
	India (24)	300 households and 556, 6-15 year old	Mean intake for all colours was below the ADI.	For school children intake exceeded for colours like	Soft drinks, bakery wares, sweetmeats and sugar	School children (8-10 year olds) from colours like	•Colours like rhodamine and orange II were used

		children		tartrazine, sunset yellow FCF and erythrosine.	confectioneries.	tartrazine, sunset yellow FCF and erythrosine.	for adulteration. •For products such as soft drinks, bakery wares and sugar confectionery items contain colours exceeding the permissible levels. •Risk was assessed using scenario 1.
	India(25)	791 individuals >4 years of age	Mean intake for all colours was below the ADI except for sunset yellow FCF where it approached the ADI in case of children.	For school children intake exceeded for sunset yellow FCF,	Soft drinks, bakery wares, sweetmeats and sugar confectioneries.	School children from sunset yellow FCF.	• Colours like rhodamine and orange II were used for adulteration • Products such as soft drinks, bakery wares and sugar confectionery items contained colours exceeding the permissible levels. • Risk was assessed using scenario 1.
Artificial Food Colours	India (26)	2771 individuals > 1 year of age	Mean intake for all colours was below the ADI.	For children and young adults intake exceeded for sunset yellow FCF, tartrazine, carmoisine and erythrosine.	Soft drinks, bakery wares, sweetmeats, ice lollies and sugar confectioneries.	Children and young adults from colours like sunset yellow FCF, tartrazine, carmoisine and erythrosine.	• Colours like rhodamine and orange II were used for adulteration. •Products such as soft drinks, bakery wares, crushed ice, ice lollies and sugar confectionery

						items contain colours exceeding the MPLs. • Risk was assessed using scenario 1
	(27)	238, 5-70 years of age	Mean intake for all colours was below the ADI.	Intake for all colours was well below the ADI.	Sauces.	No risk for any age group.	Risk was assessed using scenario 1.
	(28)	2378 individuals > 1 year of age	Mean intake for all colours was below the ADI.	For children and young adults intake exceeded for sunset yellow FCF, tartrazine, carmoisine and erythrosine.	Soft drinks, bakery wares, sweetmeats, ice lollies and sugar confectioneries.	Children and young adults from colours like sunset yellow FCF, tartrazine, carmoisine and erythrosine.	• Colours like rhodamine and orange II were used for adulteration. • Products such as soft drinks, bakery wares, crushed ice, ice lollies and sugar confectionery items contain colours exceeding the permissible levels. • Risk was assessed using scenario 1.
	Korea (29)	25628 individuals > 1 year of age	Mean intake for all colours was below the ADI.	Intake for all colours was well below the ADI.	Soft drinks, bakery wares and sugar confectioneries.	No risk for any age group.	Risk was assessed using scenario 1.
	Thailand Nakhon Pathom Province (30)	430 school age children	Mean intake for all colours was below the ADI.	For children intake exceeded for sunset yellow FCF and erythrosine.	Soft drinks, bakery wares, fish balls and sugar confectioneries.	Children from sunset yellow FCF and erythrosine.	Risk was assessed using scenario 1.

	Suratthani Province (31)	430 school age children	Mean intake for all colours was below the ADI.	For children intake exceeded for sunset yellow FCF and erythrosine.	Soft drinks, bakery wares, fish balls and sugar confectioneries.	Children from sunset yellow FCF and erythrosine.	Risk was assessed using scenario 1.
Synthetic Preservative Sulphite	China (32)	2, 72, 023 individuals > 1 year of age	Mean intake below ADI for all age groups.	In all age groups intake was below the ADI.	For Children and Teenagers: fruit juice and soft drinks; Adults: dried fruits, sausages and beer	Children (1-6 year olds) had the highest risk.	Risk was assessed using scenario 1.
Benzoate	India (27)	238, 5-70 years of age	For all age groups intake was below the ADI.	For all age groups intake was below the ADI.	Sauces	Children were at the risk because their intake from sauces was approaching ADI.	Risk was assessed using scenario 1.
	Norway(12)	1674, 2 year olds and 1787, 18-70 year olds	For all age groups intake was below the ADI.	For 2-year olds intake exceeded the ADI for specific brand of beverages (Scenario 3 and 4).	Packaged beverages	2 year old children	Risk was assessed using scenarios 1-4 where average intake for all age groups was below the ADI but for 2 year olds for high consumers using scenario 3 and 4, intake exceeded the ADI from beverages.
	Norway (21)	8821 individuals > 1 years of age	For all age groups intake was below the ADI.	For 1-2 year olds, intake exceeded the ADI for specific brand of beverages.	Packaged beverages	1-2 year old children	Risk was assessed using scenario 1 where average intake for all age groups was below the ADI but for 1-2 year olds for high consumers, intake

	Taiwan (19)	6104 individuals > 1 years of age	For all age groups intake was below the ADI.	Intake was below the ADI for all.	Soft drinks, fish and cheese	No risk for any age group.	exceeded the ADI from beverages. Risk was assessed using scenario 1. Hazard index was below 100% for both average and high consumers of all age groups.
	Thailand (33)	726 individuals > 3.5 years of age	For all age groups intake was below the ADI.	For all age groups intake was below the ADI.	Sausage and processed minced pork	No age group was at risk.	Risk was assessed using scenario 1.
	Thailand (34)	726 individuals > 3.5 years of age	For all age groups intake was below the ADI.	For all age groups intake was below the ADI.	Red Curry Paste	No age group was at risk.	Risk was assessed using scenario 1.
Nitrates and Nitrites	New Zealand(35)	4398 individuals > 1 year of age	For all age groups intake was below the ADI.	For all age groups intake for both was below the ADI.	Nitrite: processed meat products and cheese; Nitrate: lettuce and potato	No age group was at risk.	Risk was assessed using scenario 1.
Sorbates	Thailand (33)	726 individuals > 3.5 years of age	For all age groups intake was below the ADI.	For all age groups intake was below the ADI.	Sausage and processed minced pork	No age group was at risk.	Risk was assessed using scenario 1.
	Thailand (34)	726 individuals > 3.5 years of age	For all age groups intake was below the ADI.	For all age groups intake was below the ADI.	Red Curry Paste	No age group was at risk.	Risk was assessed using scenario 1.

*ADI- Acceptable Daily Intake; MPL - Maximum Permissible Levels.

The data on food consumption was collected using either a 24-hour recall or a semi-quantitative FFQ.

Studies have shown that average intakes of preservatives studied were lower than the ADI for all the age-groups probably because only one major contributor to the preservative intake was assessed. HI approached 100% for benzoate, nitrate / nitrite in case of children [21, 33, 35] and exceeded 100% for children in some studies [21, 32-33]. The reason for intakes exceeding the ADI was the use of preservatives at levels above the maximum permissible in food stuffs which is again a problem of unregulated small scale manufacturing in developing countries.

Most of the risk assessment studies have looked at exposure only according to scenario 1 which uses data on actual consumption of food containing the additive at average concentration levels. Changes in food habits, industry usage levels, brands used etc. can alter intake levels over a period of time. Hence risk should be examined at any point using multiple exposure scenarios in order to cover all possibilities. The process of risk assessment has to be carried out on a regular basis at periodic intervals to capture changes in exposure environment.

Although a big safety margin is incorporated while setting ADI levels, and occasionally approaching or exceeding ADI may not pose appreciable risk, adverse effects occurring in individuals at intake levels below ADI have also been documented. Food additives are valuable in the food processing industry. Responsible usage and monitoring are the keys to ensuring safety of the consumer. Risk assessment studies are hence important food safety tools.

CONCLUSION

The risk assessment process is used to evaluate risk associated with intake of food additives. Various studies have been published between 2000-2015 on risk assessment of food additives. The studies have majorly focused on synthetic food colors, preservatives like benzoate, sorbate, sulphite, nitrite and nitrate and artificial sweeteners. No new dose-response data have been reported in any of the studies reviewed. In most of the studies the concentration of the additive in the food has been determined chemically, whereas in a few studies MPLs and usage levels provided by manufacturers have been used. The dietary intake data has been collected mostly using either 24-hour dietary recall or semi-quantitative food frequency questionnaire. The intake data has been collected either for individuals of all the age groups or children who are considered to be a vulnerable age group by virtue of choosing foods which are processed and packaged and because of the fact that they have lower body weight.

Most of the studies have shown that the intake was less than the ADI for average consumers. For high consumers (95th percentile), intake was found to be above the ADI or approaching ADI for additives like sunset yellow FCF, erythrosine, tartrazine, benzoate and nitrite. Risk in most of the studies has been assessed using scenario 1.

A monitoring and surveillance system especially in developing countries is needed to document episodes of adverse health effects related to additive intake in the population which may escape detection because of symptoms being non-specific. This epidemiological data will be vital to evaluate the actual risk to consumers. It will also help to re-evaluate usage levels of the additives by the industry as well as ADI levels.

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REFERENCES

1. Jain A, Mathur P. Estimation of Food Additive Intake- Overview of the Methodology. *Food Reviews International*; **31**(4): 355-384: (2015).
2. International Programme on Chemical Safety (IPCS). Principles for safety assessment of food additives and contaminants in food. Environmental Health Criteria. No. 70. WHO, Geneva: (1987).
3. Galli C.L, Marinovich M, Lotti M. Is the acceptable daily intake as presently used as an axiom or a dogma. *Toxicology Letters*; **180**: 93-99: (2008).
4. FAO/WHO. Application of risk analysis to food standard issues. Report of the Joint FAO/WHO Expert consultation. WHO/FNU/FOS/95.3. Geneva, Switzerland. 13-17 March, 1995. Available from: http://www.fao.org/docrep/008/ae922e/ae922e00.HTM. Accessed 2015 March 3.
5. Haen D. The paradox of E-numbers: ethical, aesthetic and cultural concerns in the Dutch discourse on food additives. *Journal of Agriculture Environmental Ethics;* **45**: 324-340: (2003).
6. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Evaluation of certain food additives and contaminants. Sixty-ninth Report of The Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Technical Report Series 952. WHO, Geneva: (2009). Available from: http:// whqlibdoc.who.int/trs/WHO_TRS_952.pdf. Accessed 2015 March 3.
7. FAO/WHO. Codex Alimentarius Commission. 2005. Joint FAO/WHO Food Standards Programme. Procedural Manual. 15th edition. WHO. FAO. Rome. ISBN 92-5-105420-7: (2005). Available from: ftp://ftp.fao.org/docrep/fao/008/a0247e00.pdf. Accessed 2015 March 3.
8. Food and Agricultural Organization (FAO). United Nations (UN). Food quality and point (HACCP) system. Food quality and standards service food and nutrition division. Publishing Management Group, FAO Information Division : (1998) Available from: http://www.fao.org/ag/agn/CDfruits_en/others/docs/sistema.pdf. Accessed 2015 March 14.
9. Larsen J.C. Risk assessment of chemicals in European traditional foods. *Trends in Food Science & Technology*; **17**: 471–481: (2006).
10. Huggett A, Petersen B.J, Walker R, Fisher C.E, Noterman S.H.W, Rombouts F.M, Abbott P, Debackere M, Hathaways S.C, Paakkanen J, Smith M.R, Tennant D, Wagstaffe P, Wargo J, Wurtzen G. Towards internationally acceptable standards for food additives and contaminants based on the use of risk analysis. *Environmental Toxicology and Pharmacology;* **5**: 227-236: (1998).
11. Varzakas T.H, Arvanitoyannis I.S, Labropoulos A.E. Food additives and contaminants. Chapter 13. In: Yildiz F (eds); Advances in Food Biochemistry. CRC Press. p. 409-457: (2010).
12. Vitenskapskomiteen for Mattrygghet (VKM). Risk assessments of aspartame, acesulfame K, sucralose and benzoic acid from soft drinks, “saft”, nectar and flavoured water. Opinion of the panel of food additives, flavourings, processing aids, materials in contact with food and cosmetics of the Norwegian Scientific Committee for Food Safety. Norwegian Scientific Committee for Food Safety: (2013).
13. Jain A, Mathur P. Intake of processed foods and selected food additives among adolescents (13-19 year olds) of Delhi, India. *Asian Journal of Multidisciplinary Studies*; **22**(2): 64-77: (2014).
14. Bilau M, Matthys C, Vinkx C, Henauw S.De. Intake assessment for benzoates in different subgroups of the Flemish population. *Food and Chemical Toxicology*; **46**: 717-723: (2008).
15. Singhal P, Mathur P. Availability and consumption pattern of artificial sweeteners among diabetics, overweight individuals and college girls in Delhi. *Indian Journal of Nutrition and Dietetics*; **45**(26): 26-33: (2008).
16. Sinkova T, Janekova K. Dietary intake of sulphites by children in the Slovak Republic. *Central European Journal of Public Health*; **14**(1): 18-21: (2006).

17. Suh H.J, Chung M.S, Cho Y.H, Kim J.W, Kim D.H, Han K.W, Kim C.J. Estimated daily intakes of Butylated hydroxyanisole (BHA), Butylated hydroxytoulene (BHT) and tert-butyl hydroquinone (TBHQ) antioxidants in Korea. *Food Additives and Contaminants;* **22**(12): 1176-1188: (2005).
18. Gisele C, Maziero C.B, Cecilia M, Toledo F. Estimates of the theoretical maximum daily intake of phenolic antioxidants BHA, BHT and TBHQ in Brazil. *Food Additives and Contaminants;* **18**(5): 365-373: (2001).
19. Hsieh D.P.H, Huang H.Y, Ling M.P, Chen Y.S, Huang L.L, Wu C.H, Ni S.P, Hung H.C, Chiang C.F. Total dietary studies and food safety assessment in Taiwan-food preservative as an illustration. *Journal of Food and Drug Analysis*; **20**(4): 744-763: (2012).
20. Centre for Food Safety (CFS). Risk Assessment Studies. Report No. 15. Chemical Hazard Evaluation. Risk assessment on artificial sweeteners in beverages. Food and Environmental Hygiene Department. The Government of the Hong Kong Special Administrative Region: (2003). Available from: http://www.cfs.gov.hk/english/programme/programme_rafs/programme_rafs_fa_01_02_ra.html. Accessed 2015 March 3
21. Husoy T, Mangschou B, Fotland T.O, Kolset S.O, Notvik H.J, Tommerberg I, Bergsten C , Alexander J , Frost L.A. Reducing added sugar intake in Norway by replacing sugar sweetened beverages with beverages containing intense sweeteners – A risk benefit assessment. *Food and Chemical Toxicology*; **46**: 3099–3105: (2008).
22. Food Standards Australia and New Zealand (FSANZ). Survey of added colours in foods available in Australia- study of concentration in foods including dietary exposure assessment and risk characterization: (2008). Available from: www.foodstandards.gov.au/ srcfiles?Colours%20Survey Final%20Report%2022% 20Oct%2008% 20_2_.pdf. Accessed 2015 March 14.
23. Elhkim M.O, Heraud F, Bemrah N, Gauchard F, Lorino T, Lambre C, Fremy J.M, Poul J.M. New considerations regarding the risk assessment on Tartrazine. An update toxicological assessment, intolerance reactions and maximum theoretical daily intake in France. *Regulatory Toxicology and Pharmacology*; **47**: 308–316: (2007).
24. Mathur P, Sharma S, Bhat R.V. Estimating the intake of food colours-a risk assessment approach. In: Chanana, B.; Kalra, MB. New Technologies and Methodologies for Sustainable Development. Global Book Organization Pvt. Ltd. p 39-50: (2014).
25. Dixit S, Khanna S.K, Das M. All India Survey for Analyses of Colours in Sweets and Savouries: Exposure Risk in Indian Population. *Journal of Food Science;* **78**(4): T642-647: (2013).
26. Tripathi M, Dixit S, Khanna S.K, Das M. Intake pattern of synthetic colours by different age and socio-economic consumer groups of Lucknow, India. *International Journal of Food Safety, Nutrition and Public Health*; **3**(1): 1-19: (2010).
27. Dixit S, Mishra K.K, Khanna S.K, Das M. Benzoate and synthetic colour risk assessment of fast food sauces served at street food joints of Lucknow, India. *American Journal of Food Technology*; **3**(3): 183-191: (2008).
28. Rao P, Sudershan R.V. Risk assessment of synthetic food colours: a case study in Hyderabad, India. *International Journal of Food Safety, Nutrition and Public Health*; **1**(1): 68-87: (2008).
29. Suh H.J, Choi S. Risk assessment of daily intakes of artificial colour additives in food commonly consumed in Korea. *Journal of Food and Nutrition Research;* **51**(1): 13–22: (2012).
30. Benjapong W, Srianujata S, Nitithamyong A, Karnpanit W, Visetchat P, Wonglek J, Peeratikorncharoenkul R. 2010. Risk assessment of synthetic food colour exposure in Thai population. *Toxicology Letters; 196*S: S37–S351: (2010).
31. Peeratikorncharoenkul R, Benjapong W, Visetchart P, Phattanakulanan P, Karnpanit W. Risk Assessment of Synthetic Food Colours from Food Consumption of School Children in Urban and Rural Areas of Suratthani Province, Thailand. *Thai Journal of Toxicology*; **24**(1): 5-10: (2009).
32. Zhang J.B, Zhang H, Wang H.L, Zhang J.Y,

Luo P.J, Zhu L, Wang Z.T. Risk analysis of sulfites used as food additives in China. *Biomedical Environmental Sciences*; **27**(2): 147-154: (2014).

33. Sripanaratanakul P, Benjapong W, Visetchart P, Phattanakulanan P, Karnpanit W. Risk Assessment of Exposure to Benzoic Acid and Sorbic Acid from the Consumption of Sausage and Processed Minced Pork (Moo Yor) in Thai People. *Thai Journal of Toxicology*; **24**(1): 15-20: (2009).
34. Wongsaprom P, Benjapong W, Karnpanit W, Phattanakulanan P. Risk Assessment of Benzoic Acid and Sorbic Acid Exposures from Red Curry Paste Consumption in Bangkok and Suphanburi. *Thai Health Science Journals*; **24**(1): 25-30: (2009).
35. Thomson B.M, Nokes C.J, Cressey P.J. Intake and risk assessment of nitrate and nitrite from New Zealand foods and drinking water. *Food Additives and Contaminants;* **24**(2): 113-121: (2007).
36. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Evaluation of certain food additives and contaminants. Forty-first Report of The Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Technical Report Series 837. WHO, Geneva: (1993). Available from: http:// whqlibdoc.who.int/trs/WHO_TRS_837.pdf. Accessed 2015 March 3.
37. Magnuson B.A, Burdock G.A, Doull J, Kroes R.M, Marsha M, Farzia M.W, Spencer P.S, Waddell W.J, Walker R, Williams G.M. Aspartame: a safety evaluation based on current use levels, regulations, toxicological and epidemiological studies. *Critical Reviews in Toxicology*; **37**(8): 629-727: (2007).
38. Lindseth G.N, Coolahan S.E, Petros T.V, Linseth P.D. Neurobehavioral effects of aspartame consumption. *Research Nurse Health;* **37**: 185-193: (2014).
39. Schiffman S.S, Rother K.I. Sucralose, a synthetic organochlorine sweetener: overview of biological issues. *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*; **16**(7): 399-451: (2013).
40. Grice H.C, Goldsmith L.A. Sucralose-an overview of the toxicity data. *Food Chemical and Toxicology*; **38**(2): S1-6: (2000).
41. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Evaluation of certain food additives and contaminants. Thirty-seventh Report of The Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Technical Report Series 806. WHO, Geneva: (1991). Available from: http:// whqlibdoc.who.int/trs/WHO_TRS_806.pdf. Accessed 2015 March 3.
42. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Evaluation of certain food additives and contaminants. Seventy-fourth Report of The Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Technical Report Series 966. WHO, Geneva: (2011). Available from: http:// whqlibdoc.who.int/trs/WHO_TRS_966.pdf. Accessed 2015 March 3.
43. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Safety evaluation of certain food additives. Fifty-first Report of The Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Report Series 42. WHO, Geneva: (1999). Available from: http:// http://www.inchem.org/documents/jecfa/jecmono/v042je01.htm. Accessed 2015 March 3.
44. Nettis E, Colonardi M.C, Ferranini A, Tursi A. Sodium benzoate induced repeated episodes of acute urticaria / angioedema: randomized controlled trial. *British Journal of Dermatology*; **151**: 898-902: (2004).
45. Hawkins C.A, Katelaris C.H. Nitrate anaphylaxis. *Annals Allergy Asthma Immunology*; **85**: 74-76: (2000).