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Effects of Acid Yellow 23 Food Dye on Environment and its Removal on Various Surfaces – A Mini Review

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Abstract – *This review paper focuses on the impact of Acid Yellow 23 or tartrazine (E102) (in Europe) on health of different organ and tracing out the evidences showing the harm and the benefits of food additives. The method included the search for updates in the database. The study covered the details about the different types of food additives and products consisting Acid Yellow 23 (E102) and its effect on different organs like liver, kidney function, lipid profile, oxidative stress biomarkers, nervous system, hyperactivity, behaviour, cancer, reproductive and developmental toxicity and some bio element levels of Acid Yellow 23 (E102). Many studies were recognised and searched for the benefits and harms of Acid Yellow 23(E102).On briefing, the hazardous effects of Acid Yellow 23(E102) on liver, renal function, lipid profiles, behaviour, carcinogenicity and forthcoming research recommendation are defined. A larger scale evaluation of the precautions and the toxicity effects of Acid Yellow 23(E102) is reinstituted here. The conclusion obtained is that there is a great need for the professional assistance for consumers with regards to food safety problems. Collective evidences suggest the potential threat of Acid yellow 23 (E102), and extremity to avoid its intake. This paper provides understanding about the different isolation and analytical methods used for the determination of Acid Yellow 23 (E102) in the food stuffs and its hazardous impact on the health the consumers and provides incalculable interest to food additives using industries and government regulatory.*

Key Words: Liver, Kidney, Oxidative stress, Cancer, Acid Yellow 23 (E102), Synthetic color, Isolation.

1. INTRODUCTION

Continuous use of synthetic food additives has gained attention towards focusing more on its benefits and food toxicity, specifically in case of the young ones. One of these additives is artificial azo dye tartrazine or Acid yellow 23(E102). A great number of researches have been done for detecting the presence of Acid yellow 23 (E102) in various food products. The techniques of isolation and detection of Acid yellow 23 (E102) is in this review paper. The most popular methods include HPLC (high performance liquid chromatography), TLC (thin layer chromatography), electrochemical sensor, spectrophotometry, capillary electrophoresis and LC-MS (liquid chromatography tandem mass spectroscopy). Isolation techniques such as – LLI (liquid-liquid isolation), (SPI) solid-phase isolation, membrane filtration, cloud point isolation is some widely used methods. Also, a quick analysis on synthesis processes and metabolism of Acid Yellow 23(E102) and the maximum permitted level in varied food products is also elucidated in this paper Colouring food products have widely been practiced in Egyptian cities in early 1500 BC [1]. Later on, it gained popularity among other cultural groups and societies as an essence to increase consumer as well as artistic appeal [2]. Not only this but it also included some pharmaceutical medication and few non–food application [3]. These aesthetically appealing dyes are known to us as azo dyes, few of them are considered highly carcinogenic in nature [4]. However, these are continuously used under the permissible limit set by FDA [5]. The most popularly used azo dyes are Red 40 (Allura dye), Acid Yellow 23 (E102 or tartrazine), Blue 1 which makes up to 90% of all the food dyes in US. Acid Yellow 23 or E102 despite been cited toxic in nature by few researchers the FDA has refused to ban this azo dye in other countries [6]. With Yellow 23 being one of the most widely used food dye in American culture, it can be hard to hairline the health effect of this dye as a very small portion of a control group has been found to ever consume yellow 23 before [7]. Even though not much research has been carried out on this dye, studies have laid out that Yellow 23 can alter the functioning of both reproductive and neurobehavioral of different animals but variegated in humans [8]. The matter of concern with this dye is its possibility of contrastingly disturbing the learning ability and causing behavioural changes in children [9,10]. Few other affects reported were the anxiety and depression among children due to increased stress level also possibly induced by yellow 23 [11,12]. These effects can also include ADHD symptoms after consuming the average amount of Yellow 23 [13]. The yellow 23 has the chemical formula $C_{16}H_9N_4Na_3O_9S_2$, and is found in form of powder at room temperature [14]. A report estimated that children on a day consume 100mg to 200mg of yellow 23 i.e.- chips, soft drinks, cereals, candy [15]. For a fact, eating food with acid yellow 23 dissipates the zinc which is essential for cognitive function, implying zinc to cause detrimental effect

in body with increased intake of yellow 23 [16]. Another study has also shown that this effect can possibly be deferred if sufficient amount of vitamin E is taken along with yellow 23 [17].

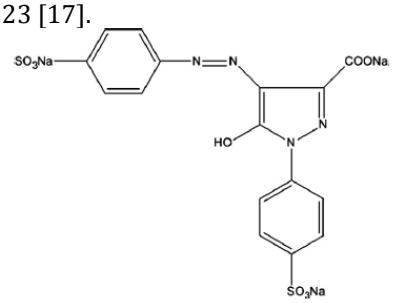

Fig-1: Chemical structure of Acid Yellow 23 (E102) [18].

1.1 Acid Yellow 23 (E102) containing Foods Products

Several food stuffs impart different concentration of Acid Yellow 23 (E102), relying on the industrialist or on the cook administrator. Considering its negative impact nowadays focus has been directed more towards using non synthetic colouring material like annatto, malt colour or beta carotene in place of Acid Yellow 23. Foodstuff containing Acid Yellow 23 (E102) includes sweetmeat, soft drinks, cotton candy, cereals (corn flakes and muesli), flavoured chips (Doritos and Nachos), cake combinations, soups, jam, sauces, ice cream, some rice, candy, chomping gum, marzipan, jelly, gelatins', mustard, marmalade, yogurt, noodles, fruit pleasant and product, chips and several expediency foods together with glycerine, lemon and honey products, soft drinks (Mountain Dew and Mirenda), energy drinks, prompt desserts, and some product containing Acid Yellow 23 (E102) as shown in Fig- 2.

Fig -2:Some products containing Acid Yellow 23 [19].

1.2 Non-food products

Acid Yellow 23 (E102) may be found in nonfood products like soaps, cosmetics, shampoos and other hair products, conditioners, pastels, crayons and stamp dyes.

1.3 Medications

Particular medicinal preparations comprise Acid Yellow 23 (E102)as antacids, vitamins, certain prescription medications and medical capsules. Accruing research has been performed on Acid Yellow 23 and its effect on the health.

Table-1: Maximum reported and Maximum Permitted Levels of use of Acid Yellow 23 (E102) in beverages and foodstuffs used for the refined exposure assessment according to the European Parliament and Council Directive 94/36/EC [20].

S. No.	Beverages and Foodstuffs	Maximum Permitted Level(mg/ L)	Maximum Reported Use Level (mg/L)
1.	Fruit wines, cider and perry	200	1
2.	Non-alcoholic flavoured drinks	100	20
3.	Liquid food supplements/dietary integrators	100	50
4.	Americano, Bitter soda, bitter vino, Spirituous beverages	100	100
5.	Aromatized wines, aromatized wine-based drinks and aromatized wine-product, cocktails	200	200
6.	Desserts including flavoured milk products	150	10
7.	Edible ices	150	20
8.	Flavoured processed cheese, Edible cheese rind and edible casings*Fine bakery wares	100	30
9.	Candied fruit and vegetables, Mostarda di fruttaPreserves of red fruits, Complete formulae for weight control intended to replace total daily food intake or anindividual meal, Solidfood supplements/dietary integrators, Complete formulae and nutritional supplements for use under medical supervision, Soups Extruded or expanded savoury snack products, Savoury snack products and savoury coated nuts,	200	50

	Processed mushy and garden peas (canned)		
10.	Fish paste and crustaceans paste, Smoked fish, Meat and fish analogues based on vegetable proteins	100	100
11.	Decorations and coatings	500	180
12.	Confectionery	300	220
13.	Mustard, Fish roe	300	300
14.	Pre-cooked crustaceans	250	250
15.	Sauces, seasonings, pickles, relishes, chutney and piccalilli	500	425
16.	Salmon substitutesSurimi	500	500

2. FOOD DYES AND THE LAW

Earlier around 1960, US law needed absolutely "harmless" dyes despite of the amount being used – that was a complete implicit [21]. Colour additives amendment 1960 was passed by Congress in order to loosen the requirements of using food dyes, while restraining, along with FDA, concern more on the safety of food dyes were ensured. An adjunct professor at the university of Cincinnati College of Law named James T. O. Reilly (2007), noticed that the Congress favoured the idea of regulating colours for their reasonability and lesser beneficiary to society over other items like food preservatives and common spices [22].

According to the law based on the food dyes-

- According to Congress each batch of the food dyes, excluding the colourings (such as from grape skin or carrots), be examined and certified as to contain only permissible contaminants levels, say for benzidine and lead. Food additives, such as preservations or flavourings, are not employed for examination.
- Congress bounded companies from declaring dyes as "generally recognized as safe" (GRAS), and hence barred further regulation by FDA. On contrary, companies are granted permission for the declaration of Flavourings, emulsifiers, and other ingredients to be GRAS, even when the testing for toxicity is not conducted.
- The FDA's definition of safety for colour additives states that ''safe means that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the colour additive''[23]. 'Convincing evidence" is considered as a stronger standard term of proof than that used for Noncolor additives.

Members of congress stressed more upon high safety standards for artificial colourings, because the colouring do not offer any health benefits to counteract even small risks.

According to Representative Ted Weiss (D-NY) – "The amount is of no concern when the food additive used offers no nutrient as well as therapeutic value" [24]. According to Representative King (It is unclear which Rep. King was quoted in the case: Rep. Cecil King (D-CA) or Rep. David King (D-UT)- The colourants used in the cosmetic products and the food presents no essential good for public and for national security. Consumers will easily get along without (carcinogenic colours).'' [25]. Unfortunately, as evidenced by the continual approval of dyes for which there is evidence of carcinogenicity, enforcement of the 1960 law has been inadequate.

A legal limit has been settled by FDA for cancer causing dye contaminants. Those limits are destined to check that these dyes possess no lifetime threat of greater than one cancer in a million counts [26]. Multiple tests are conducted by the FDA chemists in each batch of dye to ensure if it's not surpassing the settled tolerance limit. Unfortunately, the FDA's process suffers from several problems. Firstly, Per capita usage increases about 50% than from the tolerance limit set up in 1990 for dye usage. Secondly, FDA did not take into account the risk posed by the dyes on children, who are both highly sensitive to carcinogens and consume more dyes per unit of body weight than adults [27]. third, and most importantly, the tests offer clear cut detection of "free" contaminants and not just limited to "Bound" carcinogens. (those that occur as parts of larger molecules and are freed during digestion) [28].

Consumer activist have long sought to persuade the FDA to ban dyes. At the beginning of 1970s the CSPI requested the government to ban violet 1, which was used as a colourant used by USDA's meat inspection stamp, as it was the sole reason for inducing cancer in animals banned in (1973). Latterly, the FDA was sued by the Public Citizen's Health Research Group in the year 1970s and 1980s for ban of food dyes [29]. CSPI also filed petition against FDA in 2008 to ban colours as they were adversely affecting the children's behaviour and health.

Even if all colour additives were deemed safe, many uses of colourings, both synthetic and natural, still could be considered illegal under the Food, Drug, and Cosmetic Act.

Sections402(b)(3) and (b)(4) of that law stipulate that "A food shall be deemed to be adulterated ...(3) if damage or inferiority has been concealed in any manner; or (4) if any substance has been added thereto or mixed or packed therewith so as to...make it appear better or of greater value than itis." Section 403 of the same law says that a food is misbranded "if its labelling is false or misleading in any particular".

The food colourants widely used in stuffs like fruit drinks, gelatin deserts, frozen desserts, salad dressings, child-oriented cereals and snack foods and countless other products are helpful in concealing all the blemishes in appearance and makes them aesthetically appealing. supporters would suggest that the consumer is free to pick the stuff checking the details or the colourants used in it, but this would be unfair to put that burden on consumers. It was suggested that the artificial food colourings used should be clearly mentioned in front as the part of product name [30]. The FDA could require the same of artificially coloured foods. A national poll commissioned by CSPI and administered by opinion research corporation in January 2010 presented a statistical data, showing percentage of respondents favouring this suggestion of labelling which was about 74%.

Table -2: Agriculturally based adsorbents, Acid Yellow 23 (E102) and corresponding adsorption capacities at different temperature and pH.

S. No	Dyes (Adsorbates)	Adsorbents	Temperature	pH	Max. Adsorption Capacity	Reference
1.	Acid Yellow 23	polyanilinenanolayer composite (sawdust)	Room Temperature	4.2	98%	[31]
2.	Acid Yellow 23	Titanium dioxide surface	30^{0}C	11	93.57%.	[32]
3.	Acid Yellow 23	bovine serum albumin	-	7.5	0.5 gm/l	[33]
4.	Acid Yellow 23	saw dust	318 K	3	97%	[34]
5.	Acid Yellow 23	*Annona muricata L seeds*	2	-	23.6310 mg/g	[35]
6.	Acid Yellow 23	Mixed-Waste Activated Carbon	25-50^{0}C	2	74.9mg /g	[36]
7.	Acid Yellow 23	apricot stones	25^{0}C	6.8	76 mg/g	[37]
8.	Acid Yellow 23 and Allura Red	Corncob	-	2.0	94.92%	[38]
9.	Acid Yellow 23	blackthorn fruits (*Prunus spinosa*)	22 ±1 ^{0}C	5.0	100 mg/g	[39]
10.	Acid Yellow 23	Medical Activated Charcoal Tablets/ activated charcoal formulations (AC1 and AC2)	37^{0}C	1.5	272.85 and 456.83 mgg^{-1}	[40]
11.	Acid Yellow 23	Lantana camara	2	303 K	99.2 %	[41]
12.	Acid Yellow 23	Coconut Husks	2.5	50^0 C	76.8 %	[42]
13.	Acid Yellow 23	Bottom Ash and De-Oiled Soya	2.0	30^0 C	85.31 %	[43]

3. METABOLISM AND BIOLOGICAL EFFECTS OF ACID YELLOW 23 (E102)

Acid Yellow 23 (E102) inside an organism is reduced to aromatic amine, that is enormously stimulated as it is a nitrogen containing organic compound i.e. azo group. And the primary metabolite identified is sulfanilic acid. Acid Yellow 23 (E102) is determined to cause allergy such as urticaria and asthma, besides the emphasis of studies on its carcinogenesis and mutagenesis because of its metabolic conversion into aromatic amine (sulfanilic acid) via the gut microflora [44] and possibly by mammalian azo reductase in the hepatic or intestinal wall after consumption [45]. After the complete reduction of the azo dye into aromatic amines, these are further oxidised to N-hydroxy derivatives by P450 enzymatic system [46]. This biological transformation occurs in various species including humans [45], and hence is responsible for varied ailments including anaemia, pathological lesions in the brain, liver, kidney and

spleen, beside allergic reactions, tumour and cancer. But Acid Yellow 23 (E102) can't bring about malignant and benign neoplasia. Moreover, [47] did not pin down any detrimental role of Acid Yellow 23 (E102) in the development of neurobehavior, also, catastrophic impact on reproductive markers were not established at Acid Yellow 23 (E102)dose of 1225 and 773 mg/kg/BW/day for females and males, respectively. In previous determination, Acid Yellow 23 (E102)linked contrary effects on reproduction were not suggested. But, superoxide, anion, hydroxyl radical and hydrogen peroxide reactive oxygen species (ROS) might be formed in the nitrosamine metabolism and raise Oxidative stress [48].

4.ROLE OF ACID YELLOW 23 (E102) ON SENSITIVITY

Acid Yellow 23 (E102)consumption can diversely impact the immunological reactions, comprising fatigue, nervousness, migraines, clinical depression, purple skin spot, and even sleep disruption. Intake or even cutaneous contact with materials containing Acid Yellow 23 (E102) can generate sensitivity symptoms. Some claims Acid Yellow 23 (E102)inducing sensitivity even at minor dosages, and until 72 h following exposure. Kids are likely to suffer from asthma and rashes when exposed to Acid Yellow 23 (E102) upper limits, as well as possible link with chromosomal injury, thyroid cancer and hyperactivity. Few investigators have related hyperactivity and infantile obsessive-compulsive disturbances in kids with Acid Yellow 23 (E102). Some common food additives including Acid Yellow 23 (E102), monosodium glutamate have been suggested as risk factors for aggravation of asthma. Acid Yellow 23 (E102)is also used in medication, and can intensify asthma severity only in countable susceptible individuals, Whereas MSG may escalate asthma severely [49].

Food additives examinations revealed that Acid Yellow 23 (E102) increased sulphido-leukotriene released by peripheral leucocyte in patients with confirmed intolerance to food additives (atopic dermatitis). The mechanism of these changes may be due to a pathophysiological involvement of food additive that facilitated exaggeration of atopic dermatitis [50]. Humans are adversely affected by increased Acid Yellow 23 (E102) consumption, such as vasculitis and urticaria.

EFSA panel (2009) [51] concluded that intolerance responses can be observed in people highly exposed to Acid Yellow 23 (E102)and the sensitive persons can even respond to the level of ADI dose. JECFA (2016) [52] and European Commission SCF (1984) evaluated Acid Yellow 23 (E102). In 2008, the EFSA Scientific Board of Food Additives, flavourings, evaluated Acid Yellow 23 (E102), against claims that it causes hyperactivity in children [53]. In 2009, the EFSA ANS Panel agreed over the re-evaluation of Acid Yellow 23 (E102) as food additives [51]. However, the Brazilian sanitary surveillance agency (ANVISA) asked for an Opportunity of dispersing a ticket warning against scaling of urticaria, asthma and allergic rhinitis in Atopic patient intaking food and drugs having Acid Yellow 23 (E102). While, Pestana et.al (2010) [54] stated that a group of atopic subjects with asthma, nasal allergy, pseudo-allergic or urticarial responses to non-steroidal anti-inflammatory (NSAID) drugs, 35 mg of Acid Yellow 23 (E102)dye, did not produce any kind of significant respiratory, cutaneous or cardiovascular responses when compared with the placebo and there were no demographical alterations among the groups.

5. INTERNATIONAL REGULATORY STATUS

Food Colouring agents have a inimitable status as pharmaceutical excipients and most regulatory agencies hold lists of colours that may be used in medicinal products. Some colouring agents outlawed in few countries, can be permitted for use in some other countries i.e. the same colour (including Acid Yellow 23) may have a distinctive regulatory status in distant province of the world.

5.1 European Union

Acid Yellow 23 (E 102) is approved as a food additive in EU [55] and is permitted to be used in medicine for oral use. The primary regulatory body for colouring agents that may be used in medicinal products is council directive 78/25/EEC of 12 December 19771F [56]. This directive links pharmaceutical requirements with those of foods in EU. A clause in EEC directive states *''Experience has shown that on health grounds there is no reason why the colouring matters authorized for use in foodstuffs intended for human consumption should not also be authorized for use in medicinal products."* On 21 October 1998, the scientific committee on medicinal products and medical devices (SCMPMD) pointed this clause in respect of other colourants; no specific belief of this committee on Acid Yellow 23 (E102) use. But the European Commission has provided guidance on cross references to the current food

colour regulation as contained in Council Directive 94/36/EC [57].

In the EU, Directive 89/107/EEC as well as Regulation (EC) 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives, which has practiced from 20 January 2010, require that food additives must be monitored and re-evaluated whenever necessary in the light of new scientific data. Accordingly, a re-evaluation of Acid Yellow 23 (E102) was undertaken by the European food safety agency (EFSA) in 2009.

5.2 UK

Acid Yellow 23 (E102)is permitted for use in oral medicines and must always be declared on the label.

5.3 Canada

Permitted in drugs for internal and external use (Food and Drug Regulations [C.R.C., c 870, Section C.01.040.2]) [58].

5.4 USA

In the USA, 21 CFR 74.1505, 82.51 and 82.705 clearly state that "FD&C Yellow #5 (and associated lakes) may be safely used for colouring drugs generally, including drugs intended for use in the area of the eye, in amounts consistent with current good manufacturing practice. "There is a restriction in 21 CFR 74.1505 for prescription drugs that states that the labels for these products must bear the following warning statements: "This product contains Acid Yellow 23 (E102) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of Acid Yellow 23 (E102) sensitivity is low in general population, it is frequently seen in patients who have hypersensitivity for aspirin".

6. Toxicological assessment in animal studies or health biomarkers

Acid Yellow 23 (E102) has been reviewed for safety multiple times. The first risk assessment for Acid Yellow 23 (E102) was administered by JECFA and at least three evaluation are made by the EU scientific Committee on Food (SCF, now known as EFSA) in 1975, 1984 and 2009 [59, 60]. Separately, reviews were also administered by the National Health and Welfare Canada [61] and by the Nordic Council of Ministers (2002) [62] in Europe. The sections below discussed about the brief summary of salient features of the toxicology profile of Acid Yellow 23 (E102) from diverging animal studies.

6.1 Toxicokinetic

Studied have been performed to check upon the absorption, distribution, metabolism and excretion of Acid Yellow 23 (E102)in animals and humans. Many of these were originally evaluated mainly by JECFA (1966) [63]. No new studies except one including azo reduction by intestinal bacterial, has been published since JECFA review. Less than 5% oral absorption of Acid Yellow 23 (E102) has been administered in humans and laboratory animals. The Acid Yellow 23 (E102) absorbed is secreted mostly in urine unvaried. The left-over Acid Yellow 23 (E102) is metabolised extensively by intestinal microflora; of which some metabolites are absorbed by intestine. [64, 61, 65, 66, 59]. Among these metabolites the primary metabolite i.e. sulfanilic acid is largely secreted by urine. Kuno&Mizutani (2005), using bovine liver microsomes that mimic human liver microsomes, exhibited that Acid Yellow 23 (E102) is not a substrate for CYP2A6 and UDP-glucuronosyltransferase.

6.2 Acute and chronic toxicity

Acute oral toxicity was checked in rodents. In mice, the LD50 value was determined to be 12750 mg/kg/bw [59, 63] and in rats it was >2000 mg/kg/bw [59, 67]. JECFA (1966) [63] reviewed several short term and sub-chronic toxicity studies in rats, cats and dogs. No corresponding reports on Acid Yellow 23 (E102) related effects for doses up to 500mg/kg/bw was found. A more recent study on rats by Abdel-Zahab et al. 1997 (reviewed by EFSA 2009) [59] investigated the effects of two mixtures of colouring agents (up to 800 mg/kg/bw), consisting Acid Yellow 23 (E102). However, the mixture composition was not reported due to in-confidence affairs. The EFSA panel commutated that it was difficult to assess the results of this study as the exposure of the animals to the individual food colours could not be determined. Studies pin down the effects of Acid Yellow 23 (E102)as increased neurotoxicity, deficit learning and memory in animals [68] at doses above the acceptable daily intake (ADI) of Acid Yellow 23 (E102) (0-7.5 mg/kg/day). However, it could not be ignored that exposure to Acid Yellow 23 (E102)together with other dyes exerted toxicity by mechanism involving synergistic process. Long term toxicity studies in rodents were

reviewed by JECFA (1966) [63]. EFSA (2009) [59] confirmed, these studies have been conducted prior to the introduction of OECD guidelines and prior to establishment of Good Laboratory practice. Majority of studies when examined shows no persisted and dose related effects on behaviour, morbidity, mortality, haematology or on the general physical observations.

6.3Reproductive toxicity

On the basis of the studies performed on reproductivity showed that Acid Yellow 23 (E102) does not have teratogenic effects on rats or rabbits and no negative effects on reproductive parameters were recorded in one generation studies at doses up to 2% in the diet [64] reviewed by [65] Tanaka (2006) [47]. None of the studies were affected in regards with the behavioural development. The No Adverse Effect Level in rats was 5% Acid Yellow 23 (E102) in the diet (2641 and 3348 mg/kg/day in male and female rats, respectively; Borzelleca&Hallagan 1988b) [69] and 1000 mg/kg/day in rabbits (FDA 1972 in Collins et al. 1990) [70]. Also, the reproductive parameters in the chronic toxicity and carcinogenicity studies referred to above were examined and reviewed by EFSA (2009) [59]. No effects related to treatment were ascertained.

6.4 Genotoxicity

Accessible evidences showed that Acid Yellow 23 (E102) possess no mutagenic potential in most of the studies (reviewed by EFSA 2009) [59, 65, 63, 71]. Other studies depicted that Acid Yellow 23 (E102) however has potential clastogenic activity. It presented to cause chromosomal aberrations in Chinese hamster [72, 73] and rat [74] somatic cells, but not in mice [75]. Sasaki et al. (2002), [67] with the help of comet assay, at doses slightly above the ADI Acid Yellow 23 (E102) can induce transient DNA destruction in the colon of mice. EFSA (2009) [59] reviewed these latter studies and concluded that the transient DNA damage observed could be partly attributed to local cytotoxicity of the dye. Even though in more recent study, no genotoxic effect has been revealed in the micronucleus assay in mice at doses up to 2000, g/kg/bw (Poul et al., 2009 reviewed by EFSA 2009) [52].In view of the negative carcinogenicity studies the biological significance of the positive genotoxicity results is ambiguous.

6.4.1Genotoxicity study in vivo

Comet assay inferred that Acid Yellow 23 (E102) possess a genotoxic effect in the white bloods' cells of treated rats. This genotoxic effect was marked as a prominent increase ($p<0.05$) in the percentage of DNA in the comet tail in the nuclei of leucocytes of Acid Yellow 23 (E102)-treated animals as compared to controls. Relating to the genotoxicity of synthetic colours, the obtained results revealed that Acid Yellow 23 (E102) caused DNA damage in leucocytes as identified by comet assay. This genotoxic effect is assumable due to the direct contact of Acid Yellow 23 (E102) with nuclear DNA [76]. Data relevant to the genotoxic effect of Acid Yellow 23 (E102) with positive results are available. This finding agrees with Mpountoukas et al. (2010) [77] who investigated the toxic effect of Acid Yellow 23 (E102)at 0.02-8 mM in human peripheral blood cells in vitro. In addition, Acid Yellow 23 (E102) has been shown to cause chromosomal aberrations in fibroblast cells of Muntiacus muntjac [78]. Hassan (2010) [79] also revealed that application of a daily dose of Acid Yellow 23 (E102)(7.5 and 15 mg/kg/bw) for seven weeks results into liver and kidney DNA destruction.

6.4.2 Genotoxicity study in vitro

One study was JECFA (1966) [63] conducted with Acid Yellow 23 (E102) to evaluate the mutagenic effects [80] in culture of E. coli and no such effect was dogged. No evidence of mutagenic activity was collected in In vitro studies in Salmollea typhimurium [81] and E. coli [82-84].

The widely used food additives were evaluated for their Mutagenicity i.e. (Ponceau 4R, Amaranth, Sunset Yellow FCF and Acid Yellow 23 (E102). And these were examined for causing mutagenicity in salmonella typhimurium TA98 and TA100 in both pre incubation and plate- incorporation assays in the absence and presence of rat-liver S9. Likewise, the former one negative result was collected for these dyes [81].

It was noted down that the metabolic conditions of the standard Ames test protocol were not apt for testing mutagenic activity in Salmonella typhimurium using azo dyes and developed another standard. The prompt use of flavin mononucleotide (FMN) in place of riboflavin to reduce the free amines in azo compounds and hamster liver S9 rather than rat liver S9 for the process of metabolic activation was proposed. The panel hence concluded that no positive results could be drawn out of standard conditions [85].

A study conducted by Ishidate et al. (1984) [86] showed some positive impact of Acid Yellow 23 (E102) on the polyploid cells as by treating theChinese Hamster fibroblast cell line with AY9E10223(E102) for 48h.

The genotoxic character of 21 food dyes consisting acid yellow 23 (E102) at varied concentration (8.5 to 35%) and salt/wheat flour or corn starch as other ingredients were studied by Pollastrini et al. (1990) [84]. In vitro studies were performed along with S. typhimurium (TA98, TA100, TA1535 and TA1538) and E. coli (Wp2, Wp2uvrA and Wp2uvrApkM101) with metabolic activation at concentrations up to 1000 or 5000 µg/plate Acid Yellow 23 (E102). And still the negative results were obtained.

Another study by Das and Mukherjee (2004) [87] using salmonella typhimurium strains were tested for the mutagenic and genotoxic effects of AY23 (E102) with no metabolic activation and in vivo mouse bone marrow assay in Ames test.

In the Ames test, no mutation was induced even at varying concentration (10,100,250,500 and 1000 µg/plate) in TA97a and TA100. Nonetheless, an increase in number of reverent colonies in case of TA 98 was noticed at lower doses but failed to increase as the doses were increased further (up to 2 high doses).

6.5 Acid Yellow 23 (E102) metabolites genotoxicity testing

Rats dosed with gavage presented an unidentified urinary metabolite of AY23 (E102) which had dose dependent mutagenic activities in the Ames test with S. typhimurium TA98 and not with TA100 and all this was in the presence of rat liver S9[82]. Further investigation in case of bile and faeces of treated rats for mutagenicity in S. typhimurium strains TA98 and TA100 were done with or without metabolic activation. A feeble but reproducible dose related response in S. typhimurium strain TA100 was seen in presence of S9 mix. In bile, mutagenic activities exerting from metabolites were not observed.[88] Even in Faecal extracts of treated rats no mutagenic activities of AY23(E102) were identified hence no conclusion on genotoxicity could be drawn.

Sulphonated aromatic amines are produced on azo reduction of Acid Yellow 23(E102). genotoxicity data of a range of sulphonated aromatic amines was reviewed by [89]. The genotoxity of sulphonated aromatic amines were compared with their unsulphonated analogues in order to check the effect of sulphonation on the genotoxic potential of phenyl-and naphthylamines. And it was identified that the azo reduction product of Acid Yellow 23(E102) including sulphonated naphthyl and phenyl amines were non- mutagenic to salmonella typhimurium in the Ames test. Absence of genotoxicity in case of other Sulphonated aromatic amines were also determined with variety of in vivo and in vitro test systems.

Thus, it was concluded that the sulphonated aromatic amines had very low genotoxic potential in comparison with their unsulfonated analogues. Hence, presence of colouring having sulphonated aromatic amines possess no harm and induces no significant genotoxic risk.

Panel thus concluded that in spite of studies suggesting possible mutagenic effects, as per the data available no genotoxic effects of AY23 (E102) have been satisfactorily demonstrated.

6.6 Carcinogenic contaminants

The toxicity of Yellow 23 could be due to the presence of several carcinogens like- benzidine and 4‑aminobiphenyl. The FDA limits free benzidine to 1 part per billion (ppb), though analytical methods can only detect 5 ppb. Essentially, FDA tests in 1990s suggested that about 83 ppb of free and bound benzidine were contained in dyes, with the later presumably being liberated in the GI tract [90]. The FDA doesn't test for bound benzidine when it certifies the purity of dyes. The FDA's 1985 risk assessment (using projections for 1990 consumption levels) calculated a risk for Yellow 23 of 4 cancers in 10 million people, which is slightly smaller than the "concern" level of 1 in 1 million [91]. The Assessment yet fails to acknowledge - (a) greater sensitivity of children to carcinogens (FQPA), (b) greater consumption of Yellow 23 by children than the general population, (c) substantial increase in per capita consumption of Yellow 23 since 1990, (d) possibility that some batches of dye contain large amounts of bound benzidine and other carcinogenic contaminants, and (e) the presence of similar contaminants in Yellow 6.

The Scientists of FDA discovered that one company eliminated benzidine contamination in 1992, suggesting that it could be considered by the other companies as well [92]. However, the routine test for bound contamination should be conducted for all the chemicals that are consistently been imported from countries like China, India, others.

6.7 Hypersensitivity and intolerance study in human beings

A number of studies relevantly on humans were reviewed by Arden and Ram in 2001 [93], and all were found indecisive as none of them conducted Acid Yellow 23 challenge or avoidance in diet nor did they significantly change asthma consequence. Schab and trinh (2004) [94] carried a meta- analysis of findings from previously performed clinical trials that tried to show a distinct relationship between intakes of artificial food colours, including Acid Yellow 23, changes in children behaviour. However, the limitation of the study was in analysing objective behavioural measures such as clinical/psychological evaluations, activity monitoring or behavioural testing; and got criticism worldwide for its emphasis on behaviour ratings as described by parents, teachers or clinicians [95, 65, 96, 97].

No distinctive relationship between ingestion of food colour and the heightened attention deficit hyperactivity in children [95] or growth of in tolerance reaction [65] was identified. The use of non-standardised diagnosis, questionable sample selection, imperfect blinding and non-standardised outcome measures utilised by previous investigators may have been key factors aiding to the ambiguity surrounding Acid Yellow 23 consumption and these reactions. The relationship between the food colour and hyperactivity in children was again revisited in 2007 when a study conducted at Southampton University by McCann et.al (2007) [98] got published. The study signified that the food colour mixture and the sodium benzoate could possibly raise the behavior mean level of hyperactivity in children of the age group 3-4 years old and 8-9 years old from the general population. But due to result inconsistency with respect to the age and sex of the children and the observer type (parent, teacher, or independent assessor), the effects of measure of the unknown clinical relevance , the mixture study use, and lacking dose responses data resulted in the rejection of the suggestion of link between artificial food colours and hyperactivity by European Food Safety Authority (EFSA) [97].

In answer to a petition from The Centre for Science in Public Interest (CSPI 2008) [99] emerging from the Southampton study, a complete review of McCann et.al (2007) [98] study along with the previously conducted clinical (33 trials), trials publications were administered by the FDA, which also included the 2004 Meta- analysis by schab and Trinh (2004) [94].

The FDA neurotoxicology/Toxicology panel worries were same with the previously identifies deficiencies of McCann et.al (2007) [98] study by the EFSA (Watson 2008) [97]. Thus, FDA figured that a causal relationship between exposure to Acid Yellow 23 or other food additives and hyperactivity in children fails to ascertain. None of them (EFSA and FDA) could alter the current regulations on acceptable daily intake of Acid Yellow 23 in foods, drugs, and cosmetics as no promising evidences were detected.

6.8 Biochemical studies of Acid Yellow 23

Biochemical Results reported that significant ($p<0.05$) increase in the aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) activity were observed in treatments with Acid Yellow 23 as compared to controls. An increment in level of plasma uric acid, urea and creatinine in animals treated with Acid Yellow 23 was also reported in our result. The rats showed a significant increase ($p<0.05$) in plasma lipid peroxidation and nitric oxide (NO), on the contrary treatment with Acid Yellow 23, the total of antioxidant decreased.

The activity of ALT, AST and ALP greatly elevated along with the administration of Acid Yellow 23. The increase in the level of the enzyme activity in the liver is an indication to the possible damage in the tissue. These results reported were in line with the data previously observed and reported by the investigators studying liver function and hepatocellular impairment. More than the normal level of intracellular enzyme in the blood could thus be an indication to greater liver damage [100, 76, 101, 102].

The Glomerular filtration efficacy and proximal tubular secretion rate, both significantly changes with change in level of creatinine and urea [103]. Any such damage in the Kidney filtration increases the blood level of creatinine and urea. Our results show significantly elevated serum levels of creatinine, uric acid and urea in Acid Yellow 23- treated groups as compared to controls. Tawfek et. al. (2015) [104] also found significant increase in serum creatinine and urea in rats following the consumption of different types of food additives including Acid Yellow 23, sunset yellow and sodium benzoate. Hence, an agreement in the results was checked. Similar study was conducted by Ashour & Abdelaziz (2009) [105] in rats dosed with organic azo dye (fast green) orally for 35 days and showed agreement with data reported by Amin, Abdel Hameid&AbdElsttar (2010)

[100]. A recent study, conducted by Nabila et.al (2013) [106] pointed out the significant elevation in urea and creatinine levels on application of Acid Yellow 23 and resulted in the impaired renal functions and the kidney inactivity in filtering out the body fluids.

6.9 Toxicity mechanism of Acid Yellow 23 (E 102) in Vivo (as oxidative /antioxidant biomarkers)

According to the biochemical studies, the reactive oxygen species (ROS)/antioxidant imbalance is what we call as oxidative stress. The oxidative stress is the outcome of elevated level of ROS beyond the antioxidant potential. So, oxidative stress may occur because of speeding ROS production, a drop of antioxidant mechanism, or both [107]. In present study, the oxidative stress in the Acid Yellow 23 treated rats is presented completely as a result of elevated levels of malondialdehyde (MDA, end product of lipid peroxidation) and nitric oxide (NO). These results along with the recorded data is owned by Omca, Zhang & Ercal (2012) [46], as they studied the oxidative effects of Acid Yellow 23 on Chinese hamsters and other azo dyes. As a result of Acid Yellow 23 application, the level of ROS increases along with the increases lipid peroxidation. Acid Yellow 23 gets metabolised inside the body into aromatic amines by intestinal microflora (azo group compound). These amines than easily could interact with the active amino groups with nitrite or nitrate containing foods and results into production of ROS as part of their metabolism [108]. Energy metabolism could be altered by another free radical source i.e. NO, nitric oxide. A study showed that oxidative stress to epithelial cells could cause elevation in NO synthesis which results in further NO release, production of nitrite and decreased cell viability [109]

The Oxidative stress reaction could be easily estimated by examining the raised level of tissue antioxidant capacity (TAC) [110]. In the work presented, the relation between decreased level of TAC in the serum of Animals treated with Acid Yellow 23 and increased free radical generation due to administration of Acid Yellow 23 and /or impaired antioxidant machinery suggested the increased oxidative stress. The administration of Acid Yellow 23 led to distortion of hepatic architecture as well as degeneration in kidney structure of rats, this is very well shown with the help of Histological and ultrastructural results. The figures obtained with light microscope explained Acid Yellow 23 induced necrosis of most hepatocytes, congestion of blood sinusoids, infiltration of white blood cell, activated Kupffer cells, damaged glomerular and renal tubule membranes. These results obtained were in line with those of Himri et al. (2011) [76], Mehedi et al. (2013) [111] and Saxena & Sharma (2015) [102] as their study indicated the very alteration in the histological structure of Liver and kidneys in animals as ours on subjecting them with Acid Yellow 23. A study conducted by Rus et al. (2010) [112] showed that congestion, stasis and edema in kidney and liver of guinea pigs were all because of administered Acid Yellow 23 and carnosine and turns fatal by causing apoptosis in hepatocytes and atrophy of renal structures.

Table -3: Field report and Effect of Acid Yellow 23 both low and high doses, on liver, lipid profile renal function and oxidative stress

Product Names	Company Names	Parameter	Low and high level of Acid Yellow 23	References
Tito wefer	Candy makers food industry	Liver function	Increase	[113, 76]
Beco-biski	EL-Jawharafor food industry			
Sposa Cake	Over seases Co. for food products			
Fruity, juice powder	Dream A.S.E.			
Ice man, icecream,	Egyptian Co. for food industries			
Lika, Gum	Sima Food industry			
		Renal function	Significant increase	[105, 113, 76]
		Lipid profile	Increase	[105, 113]
		Oxidative stress/antioxidant markers	Decrease	[46, 114]

7. The safety effect of Acid Yellow 23 as food additive

Over a long time, investigations on a number of sub chronic and chronic role of Acid Yellow 23 in mice and rats with no significant opposing role has been formally defined and continuously been checked [51]. With the administration of doses of about 10g/kg and above (greater than ADI of Acid Yellow 23) animals showed some insignificant changes such as discoloration of fur, faecal and urinary output [58]. The author suggested that the discolouration of body fluid could certainly be because of the introduction of Acid Yellow 23 in children's food. The authorities need to be updated. Several publications have been provided in this review recently. This is the first and former paper that covers the complete literature on the relation between Acid Yellow 23, oxidative stress biomarkers, hyperactivity, behaviour, carcinogenicity, reproductive and developmental toxicity and some bio element levels. And also provides with some health effects due to food additives and some recommendation for the better health of the customer. Still much evidences are required to support the Acid Yellow 23 related health effects.

8. Isolation Techniques for the determination of Acid Yellow 23 in foodstuffs

Before the step of detection, the priority should be given to the isolation of impurities out of the system in order to avoid any kind of interruption in result. And the method of isolation may vary according to the nature of sample taken [115]. Some popularly used methods are- liquid-liquid isolation, solid phase isolation, membrane filtration and cloud point isolation.

8.1 Liquid-liquid isolation (LLI)

On the basis of relative solubility, the compounds can be separated out by Liquid-liquid isolation (LLI) or solvent isolation methods such as – water, ethanol, methanol, isopropyl alcohol, acetate, and ammonia [115]. For the isolation of synthetic dyes in chilipowder and syrup preserved fruits the acetonitrile was used by Tsai et al. [116]. Sample was than extracted twice, centrifuged and filtered before introducing it in the vial. The acetonitrile possesses some remarkable properties like good isolation yield and less fat solubility, carbohydrate precipitation and protein precipitation. Bento et al. [117] however used methanol- ammonium hydroxide for the isolation of colouring in yogurts and milk drink. Methanol-ammonium hydroxide solution (8:2) is extracted synthetic food colorants but not natural colorants using the proposed method specify to synthetic colour. A green method approach was appreciated and used by Pávai et al. [118] and no hazardous chemical has been used in the preparation of sample which is diluted with the deionised distilled water. Another solvent the LLE was used for the isolation of synthetic food colouring in beverage, preserved fruits, candy and gelatin by Tang et al. [119]. Water ammonia aqueous solvent was the solely used for the mixture of sample, which was than sonicated and diluter afterwards. Methanol solvent was used for the isolation of food additives in red wine by Ma et al. [120]. Before the process of detection, the mixture was degassed, centrifuged, acidified and filtered.

8.2 Solid-phase isolation (SPI)

Sorbents like C18, polyamide, gel permeation chromatography (GPC) and styrene-divinylbenzene polymer are used in Solid phase isolation (SPI) to extract the azo dyes from food matrices. It is essential to select apt solvent for the isolation of synthetic colourant depending on the analytical structure [115]. SPE is considered as a simple and easy method for extracting the colourants with no contaminants. Preconditioning and washing of cartridges should be very well ensured while conducting SPE method. Methanol and acetic acid are generally used for this purpose of conditioning. [121-124]. recently, isolation of colourants from sugary and gummy confectionary, ice cream and chocolate sweets through adoption of SPS method was reported by Martin et al. [123]. The SPE cartridges are preconditioned with acetic acid and the colorants are eluted with ethanol-ammonia solution. n- Hexane have been used to eliminate fat from flour and meat foodstuffs as by Qi et.al. [125].

For the sample isolation of methanol- ammonia water is added. After loading the extracted sample into the Strata X-AW cartridges, elution with ethanol containing ammonia-water is accomplished. SPE cartridges are used for both solid food matrices and for soft drinks. Sep-Pack C18 have been used for extracting the colourants by Andrade et al. [121]. Acetic acid and isopropyl alcohol were used for preconditioning of Cartridges. The sample is made to pass down thru cartridges following the colorant elution through isopropyl alcohol. Yoshioka and Ichihashi [126] have prepared the column by making slurry of polyamide and packed it into a column to extract 40 synthetic dyes in drinks and candies. The column is preconditioned with

methanol followed by elution with ammonia-ethanol solution. Huang et al. [127]. Polyamine SPE column that has been preconditioned with methanol and water for extracting colourant from the milk sample is mixed with ethanol at a pH of about 2. The acidified sample induces greater adsorption of synthetic colourants [126]. The mixture is centrifuged and flowed through cartridges, followed by elution with 0.55 ammonia and methanol solution.

In order to extract the colourant from drink, syrup, candy, jelly gum, chocolate, coloured rice, saffron and gum new approach of using polyamide sorbent into the treated sample was conducted by Khanavi et al. [128] and Hajimahmoodi et al. [129]. Sorbent is filtered out after vigorously stirring. Alkaline ammonia is used for removing colourants from polyamine. Polyamide with aqueous ammonia is used for the exaction of colourants from the fish roe and caviar by Kirshbaum et al. [130]. The collected supernatant is defatted by three-fold treatment with nhexane and acidified prior to addition of polyamide. Contrastingly, white commercial wool yarn as a sorbent have been used for colouring coated chocolate, commercial cakes and soft drinks by Gan et al. [131] and Sorouraddin et.al. [132]. The samples are diluted with distilled water, centrifuged and mixed with acetic acid. Washing of white wool yarn with detergent is followed along with water addition into the sample mixture and is heated. After an hour the yarns taken out and washed with plenty of distilled water. The colourant elution is achieved by placing thee yarn in ammonium solution followed by heating.

Multiwalled carbon nanotubes have been used to separate Acid Yellow 23 compound from the food matrices by Soylak and Cihan [133] The dye is extracted out from tap water, powdered beverages and from drug samples. Before analysing the colourant, us eluted using DMSO. Further, magnetic solid -phase isolation (MPSI) method has been used for soft drinks, cocktails, solid beverages, ice cream, sugar-based and gelatin-based confection by Wu et.al. [134] Magnetic SPE method used Fe3O4-poly (ionic liquid) core shells microspheres as sorbent. On the other hand, diverse hemimicelle solid-phase isolation (MHSPI) method have been used by Tavakoli et al. [135] which is based on cetyltrimethylammonium bromide-coated (CTAB) Fe3O4/SiO2 nanoparticle to extract synthetic colorants. Homogenization is required for samples such as saffron rice, saffron dessert, honey cream, fruit juice-coated ice cream, and saffron ice cream, followed by dilution with water and pH adjustment (pH= 9) using alkaline ammonia. Based on MHPSE method the samples are centrifuged and kept for preconcentration process. Liquid samples are first filtered and then used for isolation. For analyte preconcentration the NPs solution CTAB along with the alkaline food samples are added into the vial in sequence.

8.3 Membrane Filtration

A thin layer of semi- permeable membrane is used in filtration for the isolation of components of the samples when an external force is applied across the membrane with water as a diluent [115]. For the isolation ofcolourants from juice and gelatin membrane filtration methods have been used by Vidotti et al. [136]. The samples are dissolved in water by heating, cooled, diluted to 50 mL with water and filtered through a 0.45 μm membrane filter. Filter membrane isolation method have been used to extract colourant from alcoholic beverages by Prado et al. [137]. Mechanical agitation aid in degasification and homogenisation of samples. Sample is then filtered using cellulose ester. Sample filtration through a folded paper filter and it making up to 50mL had been performed by Minioti et al. [138], and the samples were reduced before filtering by placing it on an ultrasonic bath. The diluted sample is then filtered through 0.45 μm disposable syringe before analysis. Serdar and Knezevic [139] The degassed and the diluted soft drink was filtered using folded paper filter before its refiltration with 0.45 μm membrane filter.

8.4 Cloud Point isolation

A green alternative technique i.e. Cloud point isolation (CPI) is used for LLI method, analyte preconcentration and sample clean-up. CPE uses small quantities of mildly toxic surfactants (following principles of green chemistry) and not toxic organic solvents. Besides, surfactants are not particularly volatile and non-flammable. Clouding behaviour in CPE method is observed when a solution consisting polyoxymethylene-type non-ionic surfactant is allowed to settle after heating and stirring. Dehydration of liquids result into isolation of aqueous and surfactant rich phase after completion of settling process. [140,141]. The lesser volume of surfactant rich phase predicts achievement of high enrichment factor. This enhanced the analysis sensitivity without further sample clean up or evaporation process. [142].

8.5 Other Isolation methods

With the outbreak of green chemistry researchers now emphasizes their studies more on developing miniaturized, efficient, and environmental moderate sample isolation procedures and processes. And have developed green chemistry techniques like solid-phase micro- isolation (SPMI) [143, 144] and liquid-phase micro isolation (LPMI) [145, 146]. Although SPME is a solvent-free isolation method, the SPME fiber used in this isolation method is high-priced, fragile, and short lifetime [147]. Membrane-protected solvent and exposed solvent [148] are two divided broad categories of LPME method. Single-drop micro-isolation (SDMI) and dispersive liquid-liquid micro-isolation (DLLMI) are also green techniques used in the exposed solvent mode to extract food colorants [149, 150]. For the isolation of complex solids, semi-solid or viscous samples the most preferred isolation technique is the Matrix solid-phase dispersion (MSPD) method. This could clean up and extract the sample at the same time, and ultimately reduces the amount of the solvent. The isolation of synthetic colourant from meat and condiments have been recently performed by MSPD [151-153]. On basis of ionic liquid micro isolation (IL-ATPI) technique an aqueous two-phase system is introduced which can fulfil the purpose of isolation of five synthetic dyes including Acid Yellow 23 from soft drink, instant powdered drink, sugar-based and gelatin-based confectionary. The agent here used for the isolation is 1-alkyl-3-methylimidazolium bromide and salt [154].

By using the ultrasound- assisted isolation (UAI) method isolation of colourants from soft drinks is efficiently conducted by Antakli et al. [155]. The aliquots of the sample are taken after complete degasification by ultrasonication. By UAE method Shen et al. [156] have extracted four artificial food colorants including Acid Yellow 23 and three carotenoids. The mixing of sample is carried using methanol and an ultrasonic probe is immersed in the mixture to undergo ultrasonic-assisted isolation. The supernatant was separated thru centrifugation and methanol was extracted after repeatedly extracting for about 3 times.

Table-4: Analytical methods and Isolation procedure for identification of Acid Yellow 23 in food products

S. No.	Analytical Methods	Isolation Procedure	FoodProducts	References
1.	Liquid chromatography electrospray ionization tandem mass spectrometry	The prepared sample was loaded into SPE cartridge and eluted out with ethanol-ammonia solution	Sugar and gummy confectionary, ice cream, and chocolate sweets	[126]
2.	HPLC-PAD	Methanol ammonium hydroxide was added to the sample to extract the colorants.	Yogurt and milk drink	[159]
3.	Glassy carbon electrode modified with poly (L-phenylalanine) coupled with differential pulse voltammetry (DPV)	Carbonated beverage sample was degassed with slight boiling and diluted to 50 mL with water. Instant juice powder was dissolved and diluted to 50 mL with water. Sugar coated tablet sample was grinded and dissolved in water. The sample was then filtered and the step was repeated for 3 times. The supernatants were collected and diluted with water to 50 mL.	Beverage, instant juice powder, and sugarcoated tablets	[157]
4.	LC-MS	Acetonitrile was used as solvent. The sample was extracted twice, centrifuged and filtered before injected into the vial	Chilli powder and raisin	[119]

5.	Spectrophotometric	The candy sample was dissolved in distilled water and transferred to volumetric flask. Soft drink sample was degassed and the aliquot was taken for analysis. For chewing gum, the sample was dissolved in distilled water and centrifuged	Soft drinks, candy, juice powder and chewing gum	[158]
6.	Cellophane test strip	Deionized distilled water was used to dilute the sample and no hazardous chemical was used	Soup powder, yogurt, sweet cream cheese, jams, sparkling tablet, and beverages	[121]
7.	HPLC	Magnetic SPE method that used Fe3O4-poly (ionic liquid) core shells microspheres as sorbent was used for isolation steps. The diluted and filtered sample was flowed into MSPE system along with the sorbent to be extract	Soft drinks, cocktails, solid beverages, ice cream, Sugar based and Gelatin based confection	[137]
8.	HPLC-UV Vis	Aqueous two-phase system based on ionic liquid micro isolation (IL-ATPS) was used as isolation method. The separating agent used was 1-alkyl-3 methyl imidazolium bromide and salt	Soft drink, instant powdered drink, sugar based and gelatin based Confectionnary	[157]
9.	HPLC coupled with DAD and MS/MS	Methanolammonia-water solution was added to extract the sample and the sample extracts were loaded into Strata-X-AW cartridges and eluted out with ethanol that contained ammonia-water	Flour and meat foodstuffs	[128]
10.	Polyamide TLC method coupled with on-plate SPE and backlight-assisted detection	Water-ammonia aqueous solution was used as the solvent and the mixture of the sample and solvent was sonicated and diluted	Beverages, gelatins, solid samples	[122]
11.	HPLC-UV Vis	Mixed hemimicelle solid-phase isolation (MHSPS) method, based on catyltrimethyl ammonium bromide coated (CTAB) Fe3O4/SiO2 nanoparticle was used for isolation of the colorants. NPs solution, CTAB solution and alkaline food sample was added into a vial in sequence to pre-concentrate the analytes	Saffron rice, saffron dessert, honey cream, fruit juice coated ice cream, and saffron ice cream, beverages	[138]
12.	Silica gel chromatography plate and ion-pair HPLC	Sep-Pack C18 cartridges were used to extract the colorants. The cartridges were precondition with isopropyl alcohol and acetic acid. The sample was flowed through the cartridge and the colorants were eluted with isopropyl alcohol	Soft drinks	[124]
13.	Ultra-performance liquid chromatography coupled with electrospray Ionization tandem mass spectrometry (UPLC-ESIMS/MS)	Methanol was added as solvent for the isolation. The mixture was degassed, centrifuged, acidified and filtered prior to the detection steps	Red wine	[123]
14.	1-alyl-3- methyl imidazolium tetraflouroborate ionic liquid modified carbon ceramic	The sample was transferred into 50-mL flask and adjusted for the volume with doubly distilled water	Soft drink	[162]

	electrode			
15.	Graphene and mesoporous TiO2 modified carbon paste electrode	Candy, royal jellies, ice cream, solid custard jelly powder and juice powder sample was dissolved and diluted to 100 mL and filtered with filter membrane. Soft drink sample was used directly. Colouring coated chocolate sample was added into water to dissolve the coloured shell. The remaining solution was separated, centrifuged and diluted with	Candy, royal jellies, ice cream, solid custard jelly powder, juice powder, soft drink, colouring coated chocolate	[134]

9. CONCLUSIONS

From the previously available literature and collected evidence it is pointed out that Acid yellow 23(E102) has differing adverse effects on several organs and health system. It is clearly evident, food additives consisting AY 23 (E102) when used in low doses negatively affect and changes the biochemical biomarkers in essential organs. (specially in liver and kidney)

And risk factor elevates when consumed repeatedly for about 30 days with higher dosage, as a result of increase in hepatic oxidative stress due to genesis of ROS. Children are however at a great risk as they are the primary consumer of food stuff incorporated with doses of Acid Yellow 23(E102) i.e.- chocolates, gum, chips, drinks.

- The acid yellow 23 (E102) can release ROS as by converting the intestinal flora into amines that ultimately transforms into Nitrosamine. Nitrosamine than releases ROS. That is why consumers need to be made aware of the high-risk factors of consuming AY 23 (E102) or the food azo dyes.
- These food additives also affect the body weight and the growth of children as by reducing the consumption value of other essential food nutrients in their body. Some side effects of consuming AY 23 (E102) can be marked as hypersensitivity and allergic reactions. A limit must be imposed for the consumption of such food stuffs, especially in children.
- A continuous update of the safety evaluation of the effect of AY 23 (E102) on health is advised by means of developed methodological techniques and all the current data on the effects on other system should be provided concerning genotoxicity, reproductive toxicity and chronical carcinogenicity.

- Companies using food additives in the actual amount or doses should be mentioned clearly on the products. The consumers should be made aware about the concentration of Food additives they are consuming and specially by the children. The industries should focus more on labelling products with complete details about the ingredients added along with the food Colourant used with added values concerning more about the persons who are intolerant to such additives.

Finally, all the evidences support the potential harmfulness of Acid Yellow 23 (E102) and its worthlessness in providing any nutritive value. Thus, it is highly advised to avoid consuming food stuff consisting Acid yellow 23 (E102).

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