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REVIEW ARTICLE

Azo Dye Toxicity: Sunset Yellow Toxicity in Foods

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ABSTRACT

One of the most important synthetic azo dyes is Sunset Yellow FCF (E110), which is widely used in the food industry. Sunset Yellow continues to be investigated in terms of its adverse properties affecting human health, especially its effect on the development of attention deficit hyperactivity disorder (ADHD) and cancer and other systemic adverse effects due to excessive consumption. The main purpose of this review is to critically discuss the acceptable daily intake (ADI) of Sunset Yellow and the developmental, geno-cytotoxic and immunotoxic effects associated with exceeding the ADI.

Contents

1. Introduction

Since the last century, in addition to preserving the nutritional and health-related properties of foods, the use of dyes in different colours has increased in parallel with the developments in science and technology. Accordingly, a large number of active compounds that are involved in various biological processes of humans are taken into the body with the consumed foods. Today, food dyes used as colour additives are widely applied to make various foods such as dairy products, beverages, cereals, snack foods and ice creams more attractive and appetising. Among various food additives, food colourings in particular play an important role in foodstuffs due to their physical appearance and acceptance by the consumer. Food dyes are categorised as natural and synthetic dyes. However, synthetic food colours are widely used in the food industry compared to natural ones inasmuch as light, oxygen, pH, colour uniformity, microbial contamination, strong colouring ability, stability and low cost are among the important factors during food processing. Synthetic colour additives are organic pigments produced using artificial synthesis methods, usually with coal tar from aniline dyes as raw material. Azo dyes are the largest group (60-70%) of synthetic colourants [1].

Synthetic food colours are mainly divided into two groups: fat-soluble and water-soluble (Sunset Yellow FCF, Tartrazine, Brilliant Blue, Allura Red and Amaranth etc.). One of the commonly used synthetic dyes is Sunset Yellow (SY), which belongs to the group of azo food dyes. Azo dyes

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are the largest group of synthetic dyes with azo (-N=N-) functional group or chromophore, which may also contain aromatic ring structures. SY were recognised as food additives by the FAO/WHO Expert Committee on Food Additives (JECFA) and the EU Scientific Committee on Food (SCF) in 1982 and 1984 respectively. Recently, it has been reported that some synthetic dyes show high stability against spoilage and pose mild toxicity to human and animal health [1]. In China, SY has been reported to be highly used as an additive in some food products due to the toxicity of other food colourings. However, excessive consumption of food colourings can lead to many serious health problems such as allergy and asthma, DNA damage, hepatocellular damage, renal failure, attention deficit hyperactivity disorder (ADHD), potential immunotoxicity and reproductive toxicity [2]. In Malaysia, SY has been reported to be detected in chicken meat as a contaminant to increase the resemblance to natural poultry meat products to mislead consumers [3].

2. Sunset Yellow (SY)

SY ($C_{16}H_{10}N_2Na_2O_7S_2$, molecular weight = 452.38), designated by the IUPAC association as disodium 6-hydroxy-5-[(4-sulfophenyl)azo]-2-naphthalenesulfonate, is one of the synthetic dianionic monoazo food dyes with orange colour, evening yellow and edible yellow No. 3 (SY FCF). SY contains sodium chloride and/or sodium sulphate as the main colourless components. Generally known to form lyotropic liquid crystalline phases as a function of temperature and composition, SY can form NH-hydrazone or -OH hydroxyl azo with the presence of two sulfonate groups leading to high solubility in aqueous solution. SY can be synthesised by diazotising 4-aminobenzenesulfonic acid in the presence of sodium nitrite. The azo-hydrazone tautomerism in SY is common in aqueous solutions. This azo compound has greater affinity to form dye aggregates (H-aggregates instead of J-aggregates) by π-π stacking interactions between aromatic rings in aqueous solution [4, 5]. SY FCF can be oxidised by peroxydisulfate in the absence and presence of the azo-dye Ag and can be photocatalytically degraded by thiocyanate complexes of some transition metals and hydrogen peroxide [6]. SY is normally applied to impart orange or red colour in food and pharmaceuticals. It is commonly used in the production of soft drinks, jellies, custard powders, carbonated drinks, fruit juices, candies, ice creams and jams [1].

The acceptable daily intake (ADI) is defined as the average amount of consumed food colouring multiplied by the average levels of colour additives in foods and then the result divided by the average body weight for each group [7]. The WHO has standardised the maximum permissible limit of CAR up to 200 mg/kg. Meanwhile, the Expert Committee on Food Additives of the EU and FAO/WHO (JECFA) in 1982 and the EU Scientific Committee on Food (SCF) in 1984 allowed the appropriate ADI of SY between 0 and 2.5 mg/kg/body weight/day [1]. However, a maximum level of 100-200 ppm has been allowed in food in India. This value is lower than the ADI set by JECFA and SCF [8]. In Brazil, the ADI level is similar to EFSA for solid juice powder, solid jelly powder and soft drinks [9]. The US FDA has set the ADI at 113 mg/p/day for children under 30 kg and 225 mg/p/day for the US population (60 kg person) [7]. In a study conducted by Lok et al. [7] in Hong Kong, SY was found to be higher than other food colourings in soft drinks and desserts. SY is banned in Norway and Finland [10].

3. Azo Dye Toxicity

Azo dyes are widely used in food and other industries as well as in research laboratories. Excessive consumption can adversely affect human health with allergies, respiratory problems, thyroid tumours, chromosomal damage, urticaria, hyperactivity, abdominal pain [11]. Synthetic dyes are often combined with various toxic compounds such as lead, mercury, arsenic and benzidine, which can affect human health, especially body functions. This combination can result in urticaria, rhinitis, nasal congestion, bronchoconstriction, anaphylactoid reaction, eosinophilotactic response, purpura (bruises), allergies, kidney tumours, chromosomal damage, abdominal pain, vomiting, indigestion and aversion to food. Mikkelsen et al. reported that the combination of Allura Red AC, Amaranth, SY FCF, Ponceau 4R and Tartrazine dyes may cause chronic urticaria or angioedema in patients [12]. Nettis et al. 5 mg tartrazine azo dye was found to cause intolerance in a child with such symptoms as double blindness, facial oedema, urticaria, abdominal pain and mild hypotension [13]. It is reported that there are 2.5 million children with Attention Deficit Hyperactivity Disorder (ADHD) in the United States of America [14]. Bateman et al. [15] reported that an increase in sodium benzoate and two synthetic dyes in the diet may cause hyperactivity in children. In addition, artificial food dyes may contribute to the development of cancer due to the long-term use and maintenance of the artificial colourant in the human body [14].

Liver reductase enzymes can catalyse the reductive cleavage of the azo bond to produce aromatic amines. Chen [16] stated that azo dyes could be reduced by microsomal and cytosolic reductase in liver and extra-liver tissues, which play a vital role in the metabolism process. Azo dyes are metabolised to aromatic amines by intestinal microorganisms following oral intake. Brás et al. [17] reported that carcinogenic aromatic amines might also be formed as a result of azo dye metabolism by anaerobic microorganisms in the human intestine. Bacterial reduction in the colon results in the formation of azo dye metabolites such as sulfanilic acid and aminopyrazolone, which are easily absorbed and excreted in faeces [18, 19]. Azo dye metabolites may cause adverse haematological or biochemical effects. Intestinal microbial azoreductases may be more important than liver enzymes in azo reduction. Azoreductase activity in various intestinal preparations was influenced by various dietary factors such as cellulose, proteins, fibres, antibiotics or supplementation with live lactobacilli cultures. A wide variety of anaerobic bacteria isolated from the contents of the secretum or faeces from experimental animals and humans are capable of cleaving azo bonds to produce aromatic amines. The ability of bacterial azoreductases to catalyse these reactions depends on the presence of oxygen and the flavin requirement for optimal activity [20, 21].

Azo dyes are reported to induce DNA damage in vivo and in vitro [22, 23]. Three different mechanisms have been identified for azo dye carcinogenicity, and all of them

involve metabolic activation to reactive electrophilic intermediates covalently bound to DNA. One of these mechanisms is the metabolic oxidation of toxic aromatic amines formed after reduction of the azo bond of azo dyes, mostly by intestinal anaerobic bacteria, to reactive electrophilic species that can covalently bind to DNA. These reactive electrophilic species may also cause liver damage due to oxidative stress. Another mechanism is the metabolic oxidation of azo dyes carrying a free aromatic amine group without azo bond reduction [24]. Another mechanism is the activation of azo dyes by direct oxidation of azo bonds to highly reactive electrophilic diazonium salts [20, 25]. Each of these mechanisms may be compound-specific, so azo toxicity is likely to arise from more than one mechanism. On the other hand, these mechanisms may affect the absorption and excretion of the food product containing the dyes. Interactions between azo dyes and other food components may also contribute positively or negatively to these mechanisms [26].

Although it is not possible to predict azo dye carcinogenicity with certainty, it is possible to establish certain guidelines. Since some strains of intestinal anaerobic bacteria (and in some cases hepatic azo reductases) can reduce any azo compound to aromatic amines, those containing aromatic amine subgroups of known carcinogenicity, such as benzidines, should be suspected. Information on the human carcinogenicity of other specific aromatic amines is lacking, and various short-term mutagenicity tests may provide some guidance. The other in vitro tests can directly assay new azo dyes. Although it is unlikely that azo dyes can be developed, which can guarantee that no toxic precursor aromatic amines are produced for carcinogenicity, it may be possible to select non-toxic aromatic amines [25].

Sulfanilic acid may affect cell division and contribute to potential carcinogenesis by causing regenerative hyperplasia [27]. However, sulfonate groups can be metabolically cleaved from aromatic amines [28].

4. SY Toxicity

The toxicity and carcinogenicity of SY may result from its interaction with cytosolic receptor molecules in mammalian systems or from the formation of free radicals and arlyamines as a result of azoreduction. Reactive oxygen species (ROS); hydroxy radical (OH), superoxide anion radicals (O_2) and hydrogen peroxide (H_2O_2) etc., will be produced during normal metabolism as a result of an abnormal response to stress. SY shows suppressed effect on behaviour as well as raising the percentage of balanced mitotic abnormality in human cells [29–31].

Initially, JECFA and SCF determined the safe ADI dose to be 0-2.5 mg/kg body weight per day. Higher doses can cause xenoestrogenic activity and reversible inhibition of erythrocyte cholinesterase and plasma pseudocholinesterase [5]. Reassessing the toxicity of SY due to some aromatic amines associated with genotoxicity or carcinogenicity, EFSA stated that the dye molecules were reduced by azo-reduction to sulfonated aromatic compounds with low intestinal absorption as well as azo-reduction to sulfonated aromatic compounds with no genotoxic activity, which could be a possible cause of damage. SY may be absorbed from the gastrointestinal tract and faeces and may contribute to the development of cholestasis in combination with other elements important in the predisposition of primary biliary cirrhosis [32]. In the mouse in vivo model, no DNA damage was observed in the comet assay at doses up to 2000 mg/kg, but DNA damage was identified in actively dividing root tip cells of the plant model (*Brassica campestris* L.) and in human blood lymphocytes. Interestingly, in the light of new data, such as testicular atrophy as well as altered lipid profile in laboratory rodent studies, EFSA has decided to reduce the ADI to 1 mg/kg bw per day for two years. The finding that 99% of consumers ingested less than 1 mg/kg body weight per day confirmed the expected low population exposure and the ADI dose of 1 mg/kg body weight for SY remains valid. Although SY is known to bind to human and bovine serum albumin, triggering complex formation, the low intake in the general population is considered to reduce the likelihood of harm to human health from this colourant [5].

4.1. Developmental Toxicity

Sunset Yellow (SY) may have pathological and biochemical effects on organs if the Acceptable Daily Intake of 2.5 mg/kg/bw is exceeded. In a study in which the effects of SY on the morphological parameters of Swiss Albino mice of different ages (four, eight and ten weeks old) were investigated, treatment and control groups n=6, SY was administered orally for 28 days (30 mg/kg/bw/week). On the last day of the study, mice were weighed and tail, temporal region, femur and crown-rubmp length values were measured using a digital caliper. A statistical significance was observed in the mean body weight in SY groups ($p < 0.05$). SY administration in childhood caused retardation in growth and development parameters. Therefore, SY may cause weight gain and affect morphological parameters [33].

In a chronic toxicity study involving tartrazine and sunset yellow food dyes in the neurodevelopmental processes of zebrafish embryos from 18 hours post-fertilisation (hpf) to 91 days post-fertilisation (dpf), low heart rate, bent tail and abnormal pigmentation were found to be associated with induced neurodegenerative phenotypes. It was observed that locomotor activity decreased for 7 days after exposure and gradually recovered in the following periods, and transcriptome analysis revealed changes in clock genes (Cry2 and Per2) and dopamine-related genes (NURR1 and tyrosine hydroxylase) [34]. Immature male rats were treated with SY (FD&C Yellow No. 6 FCF) and tartrazine (FD&C Yellow No. 6 FCF), when the dyes were included in the stock diet at the 5% level, tartrazine and SY FCF had no apparent toxic effects; however, when fed a purified diet, both tartrazine and SY FCF at the 5% level in the diet caused a marked retardation in growth, a non-grizzled appearance of the fur, and death of 50% or more of the rats over a 14-day experimental period [35].

In the study evaluating the developmental toxicity of SY and other azo dyes on zebrafish embryos, at concentration levels of 5 to 50 mM, the dye caused hatching difficulty and cardiac oedema, decreased heart rate. It was reported that exposure to 100 mM could cause developmental abnormalities such as yolk sac oedema and spinal defects such as spinal curvature and tail distortion, exposure to 100 mM was completely embryolethal, LC50 value for SY 72 hours after fertilisation was 38.93 mM and EC50 value was 29.81 mM and TI (teratogenic index) ratio was calculated as 1.31 [36].

The teratogenic/embryotoxic potential of SY (E110) was tested in the Danio rerio (zebrafish) model, first from the gastrulation stage (~6 hours post fertilisation [hpf]) to hatching, then during the post-hatching period (24 to 168 hpf) for no observed effect concentration (NOEC), median effective concentration (EC 50), median lethal concentration (LC 50) and teratogenic index. The exposure of embryos to 0.1 mM dose caused development to proceed as in controls (NOEC), while exposure to 1-5 mM caused a decrease in body size, dry body mass of emerging larvae and morphological deformities such as microphthalmia, pericardial oedema, yolk sac oedema and spinal curvature. In addition to these abnormalities, embryo larvae exposed to 10-50 mM dose showed, in addition to the abnormalities mentioned, a significant decrease in heart rate and increased cellular apoptosis in the heart region with high mortality rates. In the 100 mM exposure group, all embryos died within 24 hpf. The NOEC and LC 50 were recorded as 0.1 and 42.57 mM, respectively. The EC 50 (96 hpf) values recorded for pericardial oedema and yolk sac oedema were 19.41 and 39.84 mM, and the teratogenic index coefficient was 2.1 and 1.06, respectively [37].

4.2. Genotoxicity/Cytotoxicity

Sunset Yellow may adversely affect brain tissue by causing oxidative damage at ADI level. Sunset Yellow was administered orally to weaned rats at the Acceptable Daily Intake (ADI) level (4 mg/kg/bw) for 40 days, and a significant decrease in tissue protein levels, superoxide dismutase and catalase activity as well as a significant increase in lipid peroxide levels were observed in the frontal cortex, cerebellum and hippocampus. In terms of enzyme activities, Glutathione-S-transferase and Glutathione Reductase were negatively affected, whereas Glutathione peroxidase activity was positively impacted. Biogenic amine levels and Acetylcholinesterase activity were also altered, with frontal cortex and hippocampus being the most affected subregions [38].

In the study investigating the role of Sunset Yellow given at doses of 80.7 mg/kg/day and 161.4 mg/kg/day during mammary gland carcinogenesis induced by intraperitoneal N-methyl-N-nitrosourea (MNU) administration in Sprague-Dawley rats, both doses resulted in a significant dose-dependent increase in tumour incidence, proliferation and volume and decreased tumour latency compared to control. Immunolabelling indices of proliferating cell nuclear antigen, estrogen receptor alpha and progesterone receptor were significantly increased after SY treatment. Oxidative stress markers, serum estrogen, progesterone and prolactin levels were significantly altered by SY treatment. The mRNA expression of estrogen receptor alpha and epidermal growth factor was increased in SY groups compared to control [39].

In the study in which the hypothesis that chronic consumption of Sunset Yellow (SY) food colouring disrupts the composition of the gut microbiota and alters gut integrity was tested by giving SY orally to male rats for 12 weeks, SY-induced microbiome dysbiosis was demonstrated by analysing faecal samples before and after treatment. SY treatment decreased the abundance of beneficial taxa such as Treponema 2, Anaerobiospirillum, Helicobacter, Rikenellaceae RC9 gut group and Prevotellaceae UCG-003 and increased the abundance of potentially pathogenic microorganisms Prevotella 2 and Oribacterium. This dysbiosis disrupted intestinal integrity, altered the jejunal adherens junction complex E-cadherin/β-catenin and decreased Trefoil Factor (TFF)-3. SY administration increased LPS serum levels, matured IL-1β and IL-18 by activating the inflammatory inflammasome cascade TLR4/NLRP3/ASC/cleaved-activated caspase-1, and increased pyroptosis and intestinal permeability by activating caspase-11 and gasdermin-N [40].

SY may have harmful effects on the male reproductive system. CoQ10 supplementation may alleviate the adverse effects of SY exposure. In the study aimed to investigate the effects of SY at both molecular and histopathological levels and the protective benefits of Coenzyme Q10 (CoQ10) supplementation in male rat testes; 42 male Sprague-Dawley rats were randomly divided into six groups (n = 7) and received daily oral gavage for six weeks. The groups were designed as follows: low dose Sunset Yellow (2.5 mg/kg/day), high dose Sunset Yellow (70 mg/kg/day), CoQ10 (10 mg/kg/day), low dose Sunset Yellow plus CoQ10, high dose Sunset Yellow plus CoQ10 and deionised water as control. It was shown that there was a dose-dependent increase in the expression of oxidative stress genes (Sod, Gpx and Cata) and a significant decrease in the expression of steroidogenic acute regulator (Star) gene (P value < 0.05) with increasing SY doses. Gene expression results were found to be supported by histological results. In addition, no significant difference was observed between rats treated with CoQ10 in combination with low doses of Sunset Yellow (CoQ10+LD) and control rats given low doses of Sunset Yellow (SY-LD) [41].

In the study in which the possible toxic effects of Sunset yellow and the possible protective effects of CoQ10 on testicular tight and gap junctions in rats were evaluated by molecular, immunohistochemical and histopathological changes, 60 weaned Sprague-Dawley male rats were randomly divided into six groups (n = 10), and dye was administered by daily oral gavage for 6 weeks. The treatment groups were given low dose sunset yellow (SY-LD) (2.5 mg/kg/day), high dose sunset yellow (SY-HD) (70 mg/kg/day), CoQ10 (10 mg/kg/day), low dose sunset yellow and CoQ10 (CoQ10 + LD), high dose sunset yellow and CoQ10 (CoQ10 + HD) and the control group was given distilled water. At the end of the experiment, rats were anaesthetised, and testes were removed for molecular, immunohistochemical and histopathological (H & E staining) evaluations. By real-time quantitative PCR, Claudin 11 and occludin gene expression was found to be significantly decreased in HD and CoQ10 + HD groups compared to controls, while Connexin 43 (Cx43) expression was significantly higher in control and CoQ10 groups compared to HD group. It was concluded that these findings were largely compatible with immunohistochemical and histopathological data, and that exposure to high doses of sunset yellow caused disturbances in cell-to-cell interactions and testicular function, and that concurrent treatment with CoQ10 had some beneficial effects, but did not completely improve adverse effects [42].

In a study investigating the binding of SY to catalase and trypsin enzymes by fluorescence, isothermal titration calorimetry (ITC), ultraviolet-vis absorption, simultaneous fluorescence techniques and molecular docking, fluorescence spectra and ITC data showed that the intrinsic fluorescence of catalase and trypsin was quenched by the dye effect and that a thermodynamically tight binding was formed [43].

SY and two other food dyes, amaranth and tartrazine, were evaluated for genotoxicity (micronucleated cell frequency) and toxicity (apoptotic and mitotic cells) in the micronucleus assay in the mouse intestine, and each dye compound and its main metabolites (sulfanilic acid and naphthionic acid) were detected in the media of colonic cells. At doses up to 2000 mg/kg bw, no genotoxic effect was found in the micronucleus intestinal test, and in the in vivo comet test, transient DNA damages were not stable in the colon of mice given amaranth and tartrazine, which was determined to be due to local cytotoxicity [44].

In the study in which genotoxic effects of SY and other azo dyes (ponceau 4R, Red 40, tartrazine) were investigated by in vivo micronucleus test, 0.5, 1.0 and 2 g/kg single doses were given orally to healthy and heterogeneous Swiss albinus young adult mice of both sexes. Following euthanasia at 24 and 48 hours, bone marrow was statistically analysed for polychromatic (PCE) and normochromatic (NCE) erythrocytes and micronucleated PCE (MNPCE). MNPCE frequency and PCE/NCE ratio analyses showed significant differences between treatment groups (0.5-2 g/kg) and control groups. Genotoxic and systemic toxic effects of each azo dye were determined in relation to treatment dose, euthanasia time and sex of the animal. Regardless of whether genotoxicity is dose (ponceau 4R, SY and tartrazine), time (ponceau 4R, Red 40 and SY) or sex (Red 40 and tartrazine) dependent, potential clastogenic and/or aneugenic effects have been identified that may increase the systemic toxic risks associated with azo dyes [45]. Single or repeated oral administration of SY may cause chromosomal abnormalities in bone marrow cells and spermatocytes [29].

4.3. Immunotoxicity

In a study in which it was shown that doses as high as 10 times the daily intake of both synthetic (Amaranth and Sunset Yellow) and natural (Curcumin) colouring agents had a suppressive effect on the cellular immune response and did not change the humoral response; Amaranth, Sunset Yellow and Curcumin were administered orally for 4 weeks at doses of 47, 315 and 157.5 mg/kg body weight doses of Amaranth, Sunset Yellow and Curcumin were administered orally for 4 weeks**,** and it was found that these three dyes did not affect body weight gain or spleen weight, whereas Sunset Yellow and Curcumin significantly reduced the weight of the thymus gland of rats. While total leucocyte counts were not affected, a significant decrease in the number of neutrophils and monocytes and an increase in lymphocytes were observed in rats treated with Ambatearanth and Curcumin. In addition, Sunset Yellow caused a significant decrease in the percentage of monocytes, these three types of dyes significantly decreased delayed hypersensitivity, total serum protein, albumin, total globulin and albumin/globulin (A/G) ratio were not affected by the colouring agents, amaranth increased the intensity of albumin band, curcumin treatment decreased the intensity of albumin band. It was concluded that oral administration of any of the tested colouring agents did not change the density of the globulin region compared to the control group [10].

Sunset Yellow may protect against oxidative damage in human keratinocyte-derived HaCaT cells and may show chemopreventive activity in DMBA/TPA-induced skin carcinogenesis. Sunset Yellow (SY) exhibits immunomodulatory properties evidenced by its capacity to partially inhibit the secretion of proinflammatory cytokines, regulate immune cell populations and modulate the activation of lymphocytes. In a study in which the potential anti-inflammatory properties of SY were studied through in-silico, in vitro and physiochemical test systems and in a two-stage model of DMBA/TPA-induced skin carcinogenesis, in vitro experiments showed that pretreatment of SY significantly increased the cell viability of HaCaT cells when exposed to tertiary Butyl Hydrogen Peroxide (tBHP). The increase in cell viability was accompanied by a decrease in ROS levels, restoration of dysregulated mitochondrial membrane potential and a significant reduction of DNA damage in (SY + tBHP)-treated cells. Subsequently, the implications of these findings were tested in a mouse model of DMBA/TPA-induced two-stage skin carcinogenesis receiving topical SY (0.025%, 0.05% and 0.1%) in combination with DMBA/TPA treatment for 21 weeks. By assessing tumour incidence and body weight at regular time intervals, SY was found to significantly reduce tumour mean latency, tumour incidence, tumour yield and tumour burden in a dose-dependent manner [46].

It suggests that non-cytotoxic dose of SY may have immunomodulatory effects [47]. To investigate the immunotoxic properties of SY, Yadav et al. isolated and cultured splenocytes and performed mitogen-stimulated proliferation assay (lipopolysaccharide, LPS or concanavalin A, Con A), mixed lymphocyte reaction (MLR) assay, immunophenotypic analysis of cell surface receptor expression and cytokine release assay in culture supernatants in the presence of SY. It was observed that SY (250 g/ml) significantly ($p < 0.05$) suppressed mitogen-induced proliferation of splenocytes and MLR response. Furthermore, immunophenotypic analysis revealed that SY altered the relative expression of CD3e/CD4/CD8 on T cells and CnoD19 on B cells. Consistent with the suppression of T-cell and B-cell responses and altered surface receptor expression, SY also decreased the expression of IL2, IL4, IL6, IL-17, IFN- and TNF-α cytokines [47].

SY can reduce the weight of the thymus gland and the percentage of monocytes [10]. In the study in which the effects of different doses of E110 (Sunset Yellow) on the embryonic development of primary lymphoid organs, thymus and bursa of Fabricius of chicken Ross 508 line were determined by histological, histomorphometric and histochemical methods, it was determined that although the effect of embryonic development delay in lymphoid organs was observed in each of the groups injected with E110 at doses of 100 ng/egg, 500 ng/egg and 1000 ng/egg, the significant adverse effect occurred in the group injected with 1.000 ng/egg E110 treatment group [48].

Sharma et al. [49] reported the effects of excessive consumption of SY on body weight, haematology and

serology of albino mice, as well as that the infusion may have the same effects on human health.

5. Conclusion

The use of food colourings has been associated with many systemic diseases and disorders, especially allergies, food intolerance, cancer, multiple sclerosis, attention deficit hyperactivity disorder (ADHD), brain damage, nausea, testicular atrophy, other reproductive disorders and heart disease. High consumption of Sunset Yellow may cause cancer, asthma, ADHD, impairment of the reproductive system, lymphoid tissues and brain subregions with genotoxic, cytotoxic and immunotoxic consequences. It is a high-risk azo dye that should be investigated for other possible systemic adverse effects.

Conflict of Interest

Author declares that they do not have any conflict of interest.

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