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Toxicological and ecotoxicological aspects of tartrazine yellow food dye: a literature review

Aspectos toxicológicos e ecotoxicológicos do azocorante alimentar amarelo tartrazina: uma revisão de literatura

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ABSTRACT

The use of the tartrazine yellow additive in food products for human consumption is permitted within the acceptable daily intake of 7.5 mg/kg of body weight per day (following the Joint Expert Committee on Food Additives standards). However, studies have described this as a toxic component. The dye, which is intensively used in the industry and commerce, enters the aquatic environment through releases of non-treated or inadequately treated effluents; however, further ecotoxicological research is needed. We addressed studies reporting the toxic effects of the exposure to this dye developed in humans, guinea pigs, and *Danio rerio* (a fish with molecular bases and genomes similar to humans). Based on this review, the doses allowed for acceptable daily intake, or even lower, toxic effects, can be evidenced for different organisms, life stages, and tested times. The reported values may not be protective to aquatic life. In a paper about the exposure of *D. rerio* from embryos to larvae kept at values lower than 0.05 and 0.5 $g.L^{-1}$ for pure and commercial tartrazine, there was ecotoxicological effect for embryos and larvae 48 hours after hatching, which implied cardiac edema, changes in the yolk sac, scoliosis, and tail distortions.

Keywords: CENO; food additive; environmental legislation; *Danio rerio*; mutagenicity.

RESUMO

O uso do aditivo amarelo tartrazina é legalizado para aplicação em produtos alimentícios para consumo humano dentro do valor de ingestão diária aceitável (IDA) de 7,5 mg/kg de peso corpóreo por dia (seguindo os padrões da *Joint Expert Commitee on Food Additives*). No entanto, estudos descrevem este aditivo como tóxico. O corante, usado intensamente na indústria e no comércio, adentra o ambiente aquático por meio de lançamentos de efluentes sem tratamentos ou tratados inadequadamente; no entanto, novas pesquisas ecotoxicológicas são necessárias. Portanto, esta pesquisa elencou estudos cujos efeitos tóxicos da exposição ao referido corante se desenvolveram em seres humanos, cobaias e *Danio rerio* (peixe com bases moleculares e genoma similares aos humanos). Concluímos, de acordo com a literatura, que mesmo em doses permitidas para a IDA, ou até menores, há evidências de efeitos tóxicos para diferentes organismos, fases de vida e tempos testados. Os valores relatados podem não ser protetivos à vida aquática. Em um trabalho de exposição de *D. rerio*, desde embriões até larvas, mantidos em concentrações de 0,05 e 0,5 $g.L^{-1}$ para tartrazina pura e comercial, observou-se que, na menor concentração, houve efeito ecotoxicológico em embriões e em larvas após 48 horas da eclosão, que implicou em edema cardíaco, alterações no saco vitelínico, escoliose e distorções na cauda.

Palavras-chave: CENO; aditivo alimentar; legislação ambiental; *Danio rerio*; mutagenicidade.

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Introduction

Colors fascinate human perception. In food, they are related to health and taste. Although these additives do not add nutritional value to the food, their use is intended, among other purposes, to intensify the natural color and extend their shelf life (FREITAS, 2012; ANASTÁCIO *et al*., 2016). The most used dyes include those from the azo group (-N = N-), due to their high solubility, low cost, and better fixation on food. This group represents more than 65% of the commercial dyes (ZANONI; YAMANA, 2017). In Brazil, 11 artificial organic dyes are allowed, of which six are azos: tartrazine yellow, twilight yellow, amaranth, azorubin, ponceau 4R, and red 40.

The application of these additives to food must not exceed the maximum quantity allowed by the legislation: 0.5 g.1000 mL) (Resolutions 382, 383, 385, 388 e 389 – BRASIL, 1999a; 1999b; 1999c; 1999d; 1999e). However, quantitative analyzes of dye intake by the population require the identification of food products with additives in the consumer's diet, the estimation of additive concentration in these products, and the daily consumption knowledge, which should not exceed the acceptable daily intake (following the Joint Expert Committee on Food Additives – JECFA). For the tartrazine yellow dye, which is one of the most used in the food industry, the acceptable daily intake is 7.5 mg.kg of body weight per day, which would not cause health risks.

Morais (2010) studied individuals prone to allergic rhinitis, bronchial asthma, urticaria, or sensitivity to non-steroidal anti-inflammatory drugs, providing them acceptable daily intake doses of tartrazine yellow dye for seven days. The investigator observed that these individuals had a significant reduction in the peak of expiratory flow and presented angioedema, nasal congestion, rhinorrhea, wheezing, itchy skin, and urticaria, corroborating the data obtained by Doguc *et al*. (2013), Khayyat *et al*. (2017), and Bhatt *et al*. (2018).

Corder and Buckley (1995) proved in clinical respiratory studies that patients sensitive to tartrazine developed bronchoconstriction with consequent decrease in the respiratory volume. There is a group of people whose sensitivity to this dye is manifested as asthma, urticaria, and hypersensitivity to tartrazine, which occurs in approximately 3% of the population, mainly in individuals sensitive to salicylates. As the chemical structure is close to that of benzoates, salicylates, and indomethacin, allergic cross-reactions may occur. (POLÔNIO; PERES, 2009). Matsuo *et al*. (2013) analyzed the effect of tartrazine on histamine release (a hormone responsible for several allergic symptoms) in basophils (important cells of the immune system) of individuals that had chronic allergy-related conditions, such as urticaria.

Tartrazine has also been associated with behavioral changes, such as attention deficit and hyperactivity. Baterman *et al*. (2004) applied dye mixtures in the presence of sodium benzoate, in a double-blind experimental study using placebo in children at preschool age, and demonstrated that artificial dyes have a relevant influence on the hyperactive behavior of children aged about three years old.

Al-Shabib *et al*. (2017) showed that tartrazine can cause amorphous aggregation of proteins in the cationic form, which is known to cause various diseases and metabolic irregularities. Sasaki *et al*. (2002) proved the occurrence of DNA damages in mice colon in a comet assay at doses of 10 mg.kg.pc.day (mg per kilogram of body weight per day). They concluded that the azo dye, when ingested, is absorbed by the intestinal epithelium and metabolized by azo reductases elaborated by microorganisms from the intestinal flora and by hepatic reductases, which convert it into aromatic amines.

As toxicological effects were detected in humans and guinea pigs, it is likely that its release in water bodies can interfere with aquatic biota. Some papers were performed with the *D. rerio* organism, a model organism widely used in various biological, biomedical, toxicological, and ecotoxicological research, due to its 70% genetic homology with humans and to the advantages provided by its transparent embryos that permit detailed analyses of its development. These studies showed that the dye is harmful to embryos and larvae, for which development was negatively affected (JOSHI; KATTI, 2017; GUPTA *et al*., 2019; JIANG *et al*., 2020; SILVA; FRACÁCIO, 2020).

Despite the existence of maximum acceptable limits for daily human intake in national and international laws, there is still no specific legislation regarding the safe limits of food dyes for the discharge of effluents into water bodies aiming at aquatic life protection. Studies have indicated that approximately 12% of the synthetic dyes are lost during manufacturing and processing operations (ANUNCIAÇÃO *et al*., 2015), which is one of the industrial sectors with increasing development. In 2019, according to the Brazilian Food Industry Association (ABIA), there was a 2.3% growth with revenues of approximately $ 700 billion.

Currently, in the state of São Paulo, regulation 333/2012 prohibits the release of dyes in rivers, lakes, dams, and other freshwater bodies without proper treatment. It includes the dyes as contaminating substances that, thus, contribute to a greater control over water quality and public health (ALSP – regulation 333/2012).

According to those pieces of information, the present paper intends, through literature data, to evaluate whether the conditions and limits of use established for the tartrazine yellow dye are safe for aquatic environments. Therefore, we intend to answer:

- the relationship between the human use of this dye and the impact on aquatic environments;
- safe exposure concentrations in the literature for aquatic life protection that can be used as a basis;
- main biological effects to test organisms.

This review aimed to contribute to further clarification on the interactions between tartrazine yellow food coloring and humans, as well as between tartrazine and aquatic life.

Methodology

A review was carried out using the PubMed database (National Library of Medicine of the United States) and CAPES journals (Coordination for the Improvement of Higher Education Personnel), in the period from 2010 to 2020. We were interested in the effects of tartrazine on both humans and aquatic life. The keywords "toxicity" and "tartrazine food" were used for analyzing their impacts on humans, whereas for aquatic life, we applied: "ecotoxicology", "tartrazine food", "ecotoxicology", "tartrazine dye" and "ecotoxicology", "tartrazine dye", "zebrafish". The searches returned 235 papers, of which only four were on aquatic life. The 231 papers on humans were analyzed to investigate selection criteria and were eliminated if they:

- dealt only with dye degradation;
- analyzed other dyes simultaneously, which could imply in synergistic processes;
- used food to analyze the toxicity (this is because foods rarely contain only one color and many foods contain other forms of additives that would require further study);
- toxicity was not significant or doubtful.

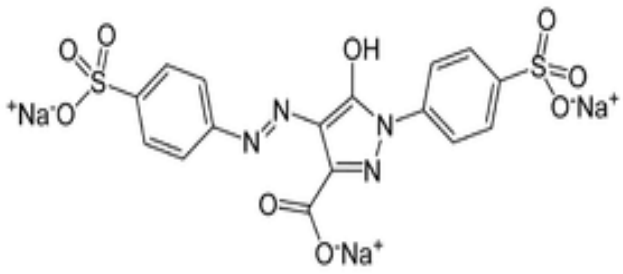
Composition and chemical structure of the tartrazine yellow dye

Tartrazine yellow is a regulated artificial organic dye used by several industrial segments. It is prepared from diazotization of 4 – amino – benzene acid with nitric acid and sodium nitrite. The diazo compound is coupled with 4,5-dihydro-5-oxo-1-(4-sulfophenyl)-1H-pyrazole-3-carboxylic acid, methyl ester, ethyl ester or a salt of carboxylic acid, which is isolated and purified as the sodium or calcium salt (FOOD AND DRUG ADMINISTRATION, 2019). As the main non-colored component, it is possible to find sodium chloride and/or sodium sulfate in its composition.

The purity degree of the dye should not be less than 85% in its total color components (calculated as sodium salt), and the remaining 15% could be composed of sodium chloride or sodium sulfate (which is never explicitly mentioned by the FDA, 2019). The water-insoluble matter must not exceed 0.2% and the subsidiary coloring, no more than 1.0% with 0.5% of organic compounds (hydrazobenzene 4-aminobenzene-1-sulfonic acid, 5-oxo-1-(4-sulphophenyl)-2-pyrazoline-3-carboxylic acid, 4,4′ -diazoaminobenzene (benzene sulfonic acid), tetrahydroxy succinic acid). Non-sulfonated primary aromatic amines can be present at levels of ≤0.01% (calculated as aniline), which were originated in the manufacturing process.

In the manufacturing process of the dye, impurities can reach 10% in the final compound (RESENDE, 2015) and many of them are metals, 4-aminobiphenyl, 4-aminoazobezene (sulfanilic acid) and benzidine (aromatic amine, formed by the oxidation of aniline). In the process of benzidine diazotization, a small part remains as free bendizine, but the majority remains in the form of subsidiary dyes, such as the diazo benzidine T-pyrazolone dye (Figure 1). According to Prival, Peiperl and Bell (1993) and Davis and Bailey Jr. (1993), if these compounds are present in the dye and mammals consume it, they will be reduced in the intestine, releasing benzidine in its free form. Compounds like benzidine are considered mutagenic and/or carcinogenic, since the electrolytes interact with DNA through their metabolism and induce mutations or generate tumors (MATHUR; BHATNAGAR; SHARMA, 2012).

The high solubility of this dye is due to the azo bond to two sulfonic groups, in addition to the functional carboxylic acid group (AL-SHABIB *et al*., 2017). They have a high standard of fixation, resistance to light and humidity, and pH and oxygen variations (HUNGER, 2003; SHORE, 2002; ZOLLINGER, 1991). The dye can be identified through ultraviolet–visible spectrophotometry (UV-Vis), with a wavelength close to 426 nm (PARLAMENTO EUROPEU, 1995). This characteristic occurs due to the presence of chromophores, carboxylic, nitro, hydroxy and amino groups that can increase the specific absorption intensity (DEL GIOVINE; BOCCA, 2003) (Figure 1).



Usual name: Tartrazine yellow.
Chemical Name: Trisodium salt 4,5-dihydro-5-oxo-1 (4-sulfophenyl) -4-[4-sulfophenyl-azo] -1H-pyrazol-3-carboxylate.
Synonyms: Tartrazine; FD & C Yellow No. 5, Food Yellow No.4. Class: Monoazo.
Molecular Formula: C16H9N4Na3O = S2.
Molar Mass: 534, 35781. CAS: 1934-21-0.
Number Color Index: (C.I.) 19140.
Maximum Absorption λ max. = 426nm.
Solubility in water: 38 mg / L at 2°C, 200 mg / L at 25°C. LD 50 - 2,000 mg / kg, in mice (at this dosage, research has shown genotoxic damage).

Figure 1 – Structure of the tartrazine yellow azo dye.
Source: Prado and Godoy (2003) and Cosmoquímica Indústria e Comércio LTDA (2009).

Regulations on the use of tartrazine yellow dye

Human food

In 1943, the United Nations Conference on Agriculture and Food created the United Nations Food and Agriculture Organization (FAO). In 1948, it formed the first group of experts with responsibilities on human health to establish food standards, the FAO/World Health Organization – WHO, which promoted the creation of the JECFA in 1956 to:

- assess the risks of consumption by animals and humans;
- assign functional classes;
- check the identity and purity specifications;
- evaluate methods of analyses and develop standards or codes, such as labeling.

In 1961, the FAO and WHO created the *Codex Alimentarius* (CA) in an attempt to establish an international standard for the use of these additives. CA also resulted in the formation of the Codex Committee on Food Additives (CCFA), a group specialized only in food additives that establishes the maximum permitted levels of these products and acts together with the JECFA.

In 1989, CA from the FAO/WHO created the International Numbering System (INS), with the purpose of providing an international numbering system for identifying additives in lists of food ingredients and for using the specific name of the additive (name of color index – CI), based on the identification number (CI). The INS does not require toxicological approval of the substance.

In 2001, the European Food Safety Authority (EFSA) was created, providing independent scientific advice on the food-related risks, which can be existent or still emerging.

The JECFA guides the FAO and WHO on the use of food dyes, and this committee meets every two years to assess, among other demands concerning food, food additives.

In Brazil, the National Health Surveillance Agency (ANVISA) is the agency responsible for regulating the use of dyes, based on the principles of risk analyses of EFSA. ANVISA establishes the maximum limits and types of foods in which dyes can be applied without offering risk to human health. The organization also carries out surveillance activities through the Standing Committee on Food Additives – CPAA (FÁVERO; RIBEIRO; AQUINO, 2011).

In 1999, ANVISA, through Resolutions 382 (BRASIL, 1999a) to 389 (BRASIL, 1999e) of 5 August, determined the permission of only 11 artificial colors in Brazil, including the tartrazine yellow dye, which must, mandatorily, have its name declared in full on the labels of the products (Resolution No. 340 of 12/13/2002 — ANVISA/Brazilian Department of Health). The additive is listed in Appendix III of Resolution 04/88 from the National Health Council, Brazilian Department of health (BRASIL, 1988), which allows its use in food following the acceptable daily intake of 7.5 mg/kg per body weight (JECFA). Therefore, a 30-kg child can consume up to 225 mg of tartrazine per day and a 60-kg adult can consume up to 450 mg per day of the dye without a probable health risk.

In 2009, ANVISA adapted the Mercosur Group Technical Resolution GMC n. 11/2006 on food additives within the scope of Mercosur (BRASIL, 2009).

ANVISA, through Resolution No. 285/2019 (BRASIL, 2019) on May 22, 2019, prohibited the use of food additives containing tartrazine and aluminum lacquer. Lacquers are preparations of salt from the dye (Resolution No. 37 of 1977 — BRASIL, 1977). It is a combination with the basic radical of aluminum, calcium and/or sodium, which can be sold under the name aluminum, calcium and/or sodium lacquer. They are used on confectionery surfaces, processed cheeses, melted cheeses, soups, chemical yeast present in flours, pastries and pizza doughs, as well as bread and cookies, among many other food products.

Regulation for discharge of effluents with dyes

Synthetic dyes are added in the category of emerging pollutants, which are defined as any chemical substance that has not been included in monitoring programs, nor in legislation relevant to environmental quality, but is constantly being introduced into the environment due to anthropic activities (HORVAT *et al.*, 2012).

Synthetic organic dyes, most of which are recalcitrant, are used universally in different manufacturing processes. The dyes are released into the environment in industrial effluents and are highly visible even at low concentrations (< 1 mg/L) (ALMEIDA *et al.*, 2004).

The determination of color in liquid samples is based on the methodology proposed in the Standard Methods by the American Water Works Association (AWWA, 2005), whose principle is the determination of the color spectrophotometrically in a wavelength range between 450 and 465 nm, using a standard solution of platinum-cobalt (Pt-Co). However, effluents whose colorations of the samples are very intense, hinder the satisfactory application of the method, and in practice, they are diluted to samples with strong colors so that they can be measured on the curve scale standard of 0.005 and 0.8% of absorbance of light at predefined wavelengths – Abs (AWWA, 2005). In addition, different dyes with equal concentrations can visually present different color intensities or even completely different shades (BELTRAME, 2006).

As to Brazil, there is still no specific legislation that defines color standards for effluents. However, in CONAMA 357/2005 (BRASIL, 2005), on articles 15-III and 16-I, it is understood that, in the absence of defined standards, one should adopt those available for the class in which the receiving bodies are included. Thus, for freshwater bodies classified as Classes 2 and 3, the tolerable value of real or true color would be up to 75 mg Pt/L (platinum scale per liter). CONAMA 430/11, in its article 18, shows that effluents of any nature should not have the potential to cause toxicity in the aquatic biota.

Tartrazine toxicity

Toxicity assessment by the Joint Expert Committee on Food Additives Commission

The tartrazine yellow dye was first evaluated in 1966 by JECFA experts in food additives, and later in 1975 and 1984 by the Scientific Committee for Food (SCF), when the value of the IDA was set at 7.5 mg/kg/pc/day for humans. In a more recent meeting (WHO, 2017), the committee reassessed this value, analyzing some research produced in recent years.

The committee considered that toxicological research in recent years is insufficient to alter the value of the IDA, considering that tartrazine is not highly toxic. The analyses considered three studies as a toxicity parameter: Sasaki *et al.* (2002), who described an LD50 value greater than 2,000 mg/kg/pc/day in studies with mice; Borzelleca and Hallagan (1988a), performed with mice for 104 weeks, in which the unobserved adverse effect level (NOAEL) of 9735 mg/kg/pc/day was established, and Borzelleca and Hallagan (1988b), with rats at maximum exposure of 125 weeks, in which the NOAEL of 2,641 and 3,348 mg/kg/day were established.

A study by Axon *et al.* (2012) concluded that the dye can act as an activator of estrogen receptors (xenoestrogen), increasing the risk of primary biliary complications and cirrhosis in postmenopausal women. However, according to the committee's evaluation, it is unlikely that cosumption could reach the levels of exposure (220 and 160 nM) used in the research.

Research by Patterson and Butler (1982) reported significant increase in chromosomal aberrations in fibroblastic cells of *Muntiacus muntjak* in vitro (5 to 20 µg/mL), but it did not report cytotoxicity.

Maekawa *et al.* (1987) studied concentrations of 0, 1 or 2% administered in rats that were statistically significant, presenting mesothelioma in the abdominal cavity in males and stromal polyps of the endometrium in females, but the incidence of these tumors was not dose-dependent and was within the historical control range for these tumors and within this strain of mice.

Mpountoukas *et al.* (2010) studied human peripheral blood cells in concentrations of 0.02 and 8 mM and did not find genotoxicity, but there was cytotoxicity (which can cause cell death) in high concentrations (4.0 and 8.0 mM), and the dye also demonstrated ability to bind to DNA.

Tartrazine would have the ability to bind to human and bovine serum albumin, forming a complex with these proteins, potentially limiting their physiology and function (PAN *et al.*, 2011). However, it is poorly absorbed, and this effect would probably not have an important role; only in case of greater exposure or association with other dyes or drugs capable of binding to plasma or proteins.

Toxicity research in rats showed significant changes in some blood parameters that indicate liver and kidney malfunction (ABOEL-ZAHAB *et al.*, 1997; MOUTINHO; BERTGES; ASSIS, 2007; AMIN; HAMEID II; ELSTTAR, 2010; EL-WAHAB; MORAM, 2013; GHONIMI; ELBAZ, 2015). However, the daily intake of 8,103 and 9,735 mg/kg/day in males and females, respectively, for 104 weeks, resulted in no adverse effects (BORZELLECA; HALLAGAN, 1988b).

Another issue raised by the commission was the difficulties in the toxicity analyses of the tartrazine dye when studied in mixture with other dyes (GIRI *et al.*, 1990; POLLOCK; WARNER, 1990; COLLINS *et al.*, 1990; 1992; ABOEL-ZAHAB *et al.*, 1997; SASAKI *et al.*, 2002; MCCANN *et al.*, 2007; ELHKIM *et al.*, 2007; AXON *et al.*, 2012; EL-WAHAB; MORAM, 2013; CEYHAN *et al.*, 2013; SAXENA; SHARMA, 2014; 2015; ERICKSON; FALKENBERG; METZ, 2014), due to the interactions that can occur between chemical substances.

The committee criticized the relevance of some in vitro genotoxicity tests because the azo linkage and desulfonation in the tested metabolic products were not broken. They have also noted that the potential for tartrazine to cause mutations is in occasional cases, which, if present, would be directed to cells lining the intestine during the transit of metabolites before excretion in feces. The committee cites a personalized protocol for the reverse mutation assay, using flavin mononucleotides to accelerate azo-reduction in hamsters, with a lesser tendency to inactivate azo-reduction products, which produced negative results (PRIVAL; MITCHELL, 1982; PRIVAL *et al.*, 1988).

In assessing the reproductive parameters and offspring development, the Committee's report cites again the paper of Borzelleca and Hallagan (1988a; 1988b). It concluded that the administration of 2,641 and 3,348 mg/kg/pc/day did not affect the reproduction of rats. Tanaka (2006) also found no neurotoxic effects after providing doses of 83, 259, and 773 mg/kg/day during five to nine weeks to F0 and F1 rat lineages.

Neurological studies, in juvenile mice and rats that received tartrazine orally at doses of up to 700 mg/kg/pc/day for 30 days, revealed some neurobehavioral and neurochemical effects (GAO *et al.*, 2011). The committee, however, noted that only a small number of animals per group/dose was used and in very high doses, which prevented the use of these studies for evaluation. Ceyhan *et al.* (2013) administered tartrazine with an IDA dye mixture (7.5 mg/kg/pc/day) in female rats, before and during pregnancy, but no effects on reproductive parameters were observed.

Collins *et al.* (1990; 1992) administered doses of 60, 100, 200, 400, 600, and 1,000 mg/kg/pc/day in pregnant rats from 0 to 19 days of gestation, but no maternal toxicity or dose-related effects prevented fetal development. Subsequently, the dye was administered to rats throughout the gestational phase in doses of 0.5; 0.1; 0.2; 0.4; 0.7% diluted in drinking water and 67.4; 131.8; 292.4; 567.9 and 1064.3 mg/kg/pc/day in food, and there were also no changes in viability, size, weight, or teratogenic effects on fetal development.

In humans, many reports concluded that the tartrazine yellow dye causes intolerance or hypersensitivity reactions. However, the reports analyzed by the committee were of foods consumed by the population, which rarely contain only the dye, but a mixture of dyes. In the study carried out by Elhkim *et al.* (2007), these symptoms were observed in only 0.12% of the analyzed population, which was considered poorly relevant by the committee.

Based on studies associating the consumption of food and drinks containing tartrazine with hyperactivity in children (POLLOCK; WARNER, 1990; BATEMAN *et al*., 2004; MCCANN *et al*., 2007; STEVENSON *et al*., 2010), the committee warned about the presence of the substance sodium benzoate in these products. However, these studies were considered limited due to inconsistencies in the conclusions and use of mixtures of food dyes.

JECFA (WHO, 2017) gathered studies on the exposure to food with tartrazine carried out in the European Union (EFSA, 2009); United States (DOELL *et al*., 2015; IACM, 2015); Australia (FSANZ, 2012); France (ELHKIM *et al*., 2007); Ireland (CONNOLLY *et al*., 2010); Hong Kong (LOK *et al*., 2010); India (DIXIT *et al*., 2011); Indonesia (FIRDAUS; ANDARWULAN; HARIYADI, 2011), and South Korea (SUH; CHOI, 2012; HA *et al*., 2013). These studies were performed using various concentrations and followed the dietary culture of each country. EFSA concluded that the maximum exposure for children aged 1 to 10 years should be 0.4 to 7.3 mg/kg/day, and exposure to tartrazine by the population, in general, does not present a health concern.

Evaluation of tartrazine ecotoxicity

Dyes have a high organic load that, in many cases, depletes dissolved oxygen and causes changes in the biological community. Its presence in water bodies affects from microalgae, which are the base of the aquatic food chain, to the top trophic level, humans. The accumulation of algae can cause eutrophication, a phenomenon that occurs when the environment receives higher concentrations of nutrients, mainly nitrogen (present in the chemical constitution of azo dyes such as nitrogen, nitrites, and nitrates), and excessive increases in algae and cyanobacteria may release toxins (MATSUZAKI; MUCCI; ROCHA, 2004).

There is little ecotoxicological research with the tartrazine yellow dye, except for those by Joshi and Katti (2017) that present values of CENO and CL50, and Jiang *et al*. (2020) that present LC50 values for the species *D. rerio*. In this context, Silva and Fracácio (2020) studied the development of *D. rerio* embryos and larvae in concentrations of 0.05 and 0.5 $g.L^{-1}$ of analytican tartrazine (100%), and commercial standard of 86% and at a concentration of 0.05 $mg.L^{-1}$. They observed loss of viability of the eggs after 24 hours of fertilization, and from 48 to 72 hpf there were no hatching and deformities, such as edema of the yolk sac, cardiac edema, distortion of the tail, lack of pigmentation and decreased heart rate, indicating ecotoxicity at the said concentrations. This paper shows ecotoxicological effects in concentrations below those presented by other papers available in the literature.

Results

Analyses of toxicological literature

After the application of the manuscript selection criteria, 29 articles were considered, in which four of them were on ecotoxicology.

The biggest concern regarding the use of tartrazine azo dye is its reduction to aromatic amines (DEMIRKOL; ZHANG; ERCAL, 2012). This mechanism is responsible for several disorders, such as anemia, pathological lesions in the brain, liver, kidney and spleen, in addition to allergic reactions, tumors, and cancer. Changes in serum albumin in humans also compromise biological functions (PAN *et al*., 2011). In molecular toxicology studies, tartrazine has bound to the central hemoglobin cavity (BASU; KUMAR, 2016a).

Liver enzymes increased in rats administered with tartrazine, suggesting lesions and impairment of liver cells, cytoplasm, and mitochondrial organelles (AMIN; HAMEID II; ELSTTAR, 2010; HIMRI *et al*., 2011; KHAYYAT *et al*., 2017).

In reproductions, tartrazine induced a marked deficiency in antioxidant biomarkers (SOD, catalase and GSH) in groups of young male rats (MOHAMED; GALAL; ELEWA, 2015). Tartrazine also induced adverse effects on the memory and learning of rats (GAO *et al*., 2011), hyperactivity, antisocial behavior, and anxiety in male rats (KAMEL; EL-LETHEY, 2011).

The largest number of studies regarding dye toxicity was carried out with rats (13 papers); cellular components or blood of human beings (four papers); mice (three papers); hamster (one paper) and others such as *Allium cepa*, calves, and horses (four papers covering these groups), as seen in Table 1.

Ecotoxicological analyses

In the bibliographic survey we found papers with the fish *D. rerio* exposed in different phases to varied concentrations of the tartrazine yellow dye. Joshi and Katti (2017) found a value of the unobserved effect concentration (CENO) and lethal concentration (CL (I) 50, 96 h) of 5 ($2.67\ gL^{-1}$) and 29.4 mM, respectively ($15.7\ gL^{-1}$). Jiang *et al*. (2020) found the CL (I) 50, 96 h value of 47.10 mM ($25.1\ g.L^{-1}$). Of these papers, those of Gupta *et al*. (2019) and Silva and Fracácio (2020) described deformities that were found in the embryonic and larval development of *D. rerio*, suggesting that the tartrazine dye, once released into the aquatic environment, compromises aquatic life (Table 2).

Discussion

According to the literature, the tartrazine yellow dye can cause toxicity to humans in dosages considered safe, in periods of prolonged exposure. Dosages below that recommended for IDA demonstrated the ability to damage liver and kidney tissues in fetuses, in addition to other changes described (Table 1), depending on the time of exposure.

The reduction of dye into aromatic amines and benzene compounds in the digestive system of rats can trigger anemia, pathological lesions in the brain, liver, kidney and spleen, in addition to aller-

Table 1 – Research carried out in the last ten years with the tartrazine yellow dye that resulted in toxicity.

Author (s)	Objectives	Dose	Conclusions
Amin, Hameid II and Elsttar (2010)	To evaluate the toxic effects of tartrazine dye, using biomarkers of oxidative stress in the kidney and liver of rats.	15 and 500 mg/ kg/pc/day, in rats (*Rattus norvegicus*) for 30 days.	• Blood and enzymatic changes • Significant weight loss • Reduction of liver antioxidants • Increased oxidative stress • Decreased activity of superoxide dismutase (a cellular antioxidant enzyme).
Morais (2010)	To evaluate the toxic effects of tartrazine dye in people with respiratory problems and sensitivity to non-steroidal anti-inflammatory drugs.	Doses of 5, 10, and 20 mg of the additive in 77 subjects for seven days.	• Reduction in peak expiratory flow; itchy skin and hives; • Immune system reactions affecting the skin and airways.
Mpountoukas *et al.* (2010)	To evaluate the toxic effects of tartrazine dye in human peripheral blood cells with the dye.	0.02 to 8.0 mM (0.01 and 4.27 g.L-1) in vitro peripheral blood cells (for 72 hours).	• The dye changed the rates of mitotic division at high concentrations (4.0 and 8.0 mM); • High cytotoxicity (that can cause cell death); • The dye also demonstrated its ability to bind to DNA.
Gao *et al.* (2011)	To evaluate the toxic effect of tartrazine on learning and memory functions in mice and rats.	Kun ming mice and Sprague dawley 175, 350 and rats 700 mg/kg of tartrazine by body weight once daily for 30 days per gavage.	• Oxidative damage to the brain; • Decline in catalase, glutathione activities; peroxidase (GSH-Px) and superoxide dismutase (SOD); • Increase in the level of malonaldehyde (MDA), which resulted in adverse effects on learning and memory functions that can be attributed to the increase in lipid peroxidation products and reactive oxygen species, inhibiting antioxidant defense enzymes.
Kamel and El-Lethey (2011)	To address the influence of different doses of tartrazine exposure to levels of hyperactivity, anxiety, depression, and antisocial behaviors in rats.	0, 1 and 2.5% administered to male Wistar rats for 16 weeks.	• Tartrazine-treated rats showed hyperactivity; • The anxiogenic effect of tartrazine was evident; • Ingestion of tartrazine promoted significant depression, expressed by prolonged immobilization during forced swim test; • Compromised social interaction.
Kashanian and Zeidali (2011)	To address DNA interactions of the cells of a calf's thymus and its interaction with tartrazine.	10 nM of the dye	• The DNA – tartrazine interaction affected the helical structure of the DNA, in addition to showing an easier connection between tartrazine and denatured DNA. The DNA bound to the dye underwent changes.
Pan *et al.* (2011)	To test the molecular link between plasma albumin and tartrazine.	Human albumin and bovine albumin at concentrations of 5.0 x 10^{-5} mol.L^{-1} and tartrazine at concentrations of 1.0 x 10^{-5} mol.L^{-1}.	• Tartrazine can bind to albumin spontaneously and form a complex, with Van der Walls bonds and hydrogen bonds; • Tartrazine alters the conformation of the protein.
Himri *et al.* (2011)	To address oral toxicity in Wistar rats.	7.5; 10 mg /kg/pc/day with 3.75 mg/kg/pc/ day of sulphanilic acid.	• Liver increased by 10 mg/kg/pc/day; • Changes in the kidneys; • In high doses, tartrazine can induce oxidative stress through the formation of free radicals.
Demirkol, Zhang and Ercal (2012)	To evaluate changes in oxidative stress parameters, such as glutathione (GSH), malondialdehyde (MDA), glutathione peroxidase. Activity (GPx) and catalase (CAT) in hamster ovary cells.	Chinese hamster cells (CHO) (10 x 10^3 cells) exposed in tartrazine concentrations of 10, 100, 500, 1,000, 2,000 µM (5.34; 53, 43; 267.15; 534.3; 1068 g.L^{-1} – 3, 8, 12 and 24 h).	• Depletion of GSH (one of the main antioxidant cells), causing oxidative stress (that plays an important role in sclerosis, chronic lung disorders, paralysis, rheumatoid arthritis, age-related degenerations, and Alzheimer's disease).
Gomes *et al.* (2013)	To address cytotoxic effect of tartrazine on the cell cycle of *Allium cepa L.*	0.4 and 4.0 mL in Allium cepa L roots, in 24- and 48-hour exposures.	• Mitotic analyzes of the doses and exposure times evaluated were cytotoxic to the cells.

Continue...

Table 1 – Continuation

Author (s)	Objectives	Dose	Conclusions
Ghonimi and Elbaz (2015)	To evaluate histological changes in selected tissues of Wistar rats after ingestion of tartrazine with a protective effect of royal jelly and cod liver oil.	Adult Wistar rats administered at doses of 500 and 300 mg/kg/pc/day + royal jelly of 0.4 mg/kg/pc/day + cod liver.	• At 500 mg/kg/pc/day, necrosis of liver tissues; hyperplasia of interstitial connective tissue; vacuolations in brain tissues; degenerative changes in the stomach mucosa; degeneration in the renal tubules; • The curative protective effect of royal jelly and cod liver was not significant against the toxicity of tartrazine.
Mohamed, Galal and Elewa (2015)	To evaluate the possible neurotoxic effect of tartrazine, as well as to determine the potential modulating role of cod liver oil and royal jelly in protecting against dye.	Evaluate rat pups in five different groups: a) 300 mg/kg/pc/day + royal jelly; b) 0.4 mL/kg/pc/day + cod liver oil; c) 500 mg/kg/pc/day of tartrazine; d) 500 mg/ kg/pc/day + royal jelly; e) 500 mg/kg/pc /day + cod liver oil.	• Significant decrease in the concentration of brain neurotransmitters, • Marked scarcity in the level of antioxidant biomarkers; • These parameters were more recovered in the tartrazine groups with royal jelly and tartrazine with cod liver oil, which provided sufficient protection against the effects of tartrazine on function and structure of the puppies' brain tissue.
Soares et al. (2015)	To evaluate the potential effects of cytotoxicity, genotoxicity on DNA.	Human lymphocytes exposed to 0.25 – 64.0 mM dye (0.13 – 34.19 $g.L^{-1}$).	• Tartrazine did not show cytotoxicity; however it showed genotoxicity.
Basu and Kumar (2016)	To test interaction of tartrazine with human hemoglobin.	Hemoglobin concentration determined through a molar absorption coefficient of 1.79.000 $M\text{-}1cm^{-1}$ at 405 nm, where the tartrazine solution was injected.	• The dye significantly interfered with the helical stability of hemoglobin and probably the absorption of tartrazine and its metabolites in the blood plasma affected the function of hemoglobin, compromising its activity.
El Golli *et al.* (2016)	To evaluate the toxic potential of food tartrazine in different tissues of adult rats: blood, liver, kidneys, and spleen.	Tartrazine was administered orally at a dose of 300 mg/kg/pc/day in adult male Wistar rats over a period of 30 days.	• Increase in platelets, reduction in peripheral lymphocytes and TCD8 lymphocytes of the spleen; • Increased activities of hepatocellular enzymes that promoted changes in renal biomarkers; • Critical oxidative changes in all organs; • Enzymatic changes.
Al-Shabib *et al.* (2017)	To study of the interaction of tartrazine with myoglobin protein at two different pH levels.	Equine myoglobin was prepared in 20 mM and tartrazine in concentrations of 0.0 to 10.0 mM. (5.34 $g.L^{-1}$).	• The anionic sulfate group of tartrazine electrostatically interacted with myoglobin cationic amino acid residues leading to aggregation.
Khayyat *et al.* (2017)	To address the effects on hepatic-renal function, also genotoxicity in white blood cells, through the comet assay.	7.5 mg/kg/pc/day in Wistar rats for 30 days.	• Increased level of ALT, AST, ALP, urea, uric acid, creatinine; • Decrease in the total antioxidant level; • Damage to DNA in leukocytes.
Meyer *et al.* (2017)	To study the transcriptional function of the human estrogen alpha receptor in an in vitro cell model.	Transgenic mice administered at doses 50 mg/kg/pc/day.	• Increased serum alkaline phosphatase activity and mild periportal fibrosis; • Sulphotransferase in the excretion of bile acids caused periportal inflammation and liver pathology.
Abo-El-Sooud et al. (2018)	To evaluate the daily administration of dye in hepato-renal and DNA changes in rats.	Administered orally to rats, 10 times the acceptable daily dose (IDA) for 60 days.	• Significant increases in the DNA nucleus; • Histopathology of the liver and kidneys showed destructive and degenerative changes that can cause genotoxicity and hepato-nephropathy.
Bhatt *et al.* (2018)	To test the effect of the dye on the neuro-biochemistry network of Wistar rats.	7.5 mg/kg by body weight through gavage for 40 consecutive days.	• Decreased activity of Superoxide Dismutase (SOD), Catalase (CAT), considering that there was a decline in Glutathione-Stransferase (GST) Glutathione Reductase (GR); • Levels of ADI in the dye affect and alter biochemical markers of brain tissues and cause oxidative damage.

Continue...

Table 1 – Continuation

Author (s)	Objectives	Dose	Conclusions
Floriano *et al.* (2018)	To evaluate the cytotoxicity and genotoxicity of tartrazine in human leukocyte culture.	Concentrations of 5, 17.5, 35, 70, 100, 200, 300, 400, and 500 μg mL^{-1} in leukocyte cultures.	• At a concentration of 70 μg mL^{-1}, the dye induced DNA damage.
Abd-Elhakim *et al.* (2019)	To study the fibrogenic fibers of rats triggered by tartrazine, through tests with dye and chlorophyll.	The rats were administered ten times the acceptable daily intake of tartrazine or chlorophyll for 90 consecutive days.	• Increase in mRNA and immunohistochemical localization of renal fibrotic markers and liver collagen; • Differences in AST, ALP, creatinine, and urea levels; • Decline in SOD, CAT and GSH enzymes in kidney and liver.
Hashem *et al.* (2019)	To determine the effect of tartrazine dye on fetal development.	Daily administration of 0.45 and 4.5 mg/kg/pc/ day tartrazine, in the fetal development of Wistar rats from the 6^{th} to the 15^{th} day of gestation.	• Liver damage; • Destroyed and necrotic renal tubules; • Absent coccygeal vertebrae; • Absence of hind limbs; • Irregular ribs.
El-Sakhawy, Mohamed and Ahmed (2019)	To evaluate the histological and immunohistochemical evaluation of tartrazine in the cerebellum, submandibular glands, and kidneys in rats.	Adult male albino rats received doses of 7.5; 15 and 100 mg/kg/pc/ day.	• Kidneys with interstitial hemorrhage and dilation of the glomerular capillaries; • Collecting tubules in the medulla with flattened epithelial cells; • Severities were higher with increasing doses.
Albasher *et al.* (2020)	To evaluate perinatal exposure of the dye in doses within the IDA range in mice, with an emphasis on neuro behavioral changes and redox imbalance.	Pregnant female mice received tartrazine; after birth, at 21 and 35 days, the mice were sacrificed and histological analyzes were performed.	• Lipid peroxidation and decreased antioxidants in different regions of the newborn's brain; • Increased hemoglobin, erythrocytes, leukocytes, and platelets; • Altered locomotor behavior as a reflex of anxiety; • Oxidative stress.

gic reactions, tumor, and cancer. Changes in serum albumin cause decreased production and malabsorption of proteins, cirrhosis, and higher liver enzymes, which compromise cells and the work of mitochondria, leading to an imbalance of oxidative stress and presence of free radicals that cause cytogenicity. The dye was able to interact with DNA, triggering mutations.

Ingestion of the dye also worsens symptoms in patients with allergic reactions, bronchial asthma, hives, and behavioral changes such as attention deficit and hyperactivity in children. Tartrazine also induced adverse effects on memory, learning and behavioral changes in rats and fish.

Research with *D. rerio* has shown that the additive alters physiological functions, not only by ingestion, but also at constant exposures, as is the case in aquatic environments. Regarding the ecotoxicity of the tartrazine yellow dye, data from Joshi and Katti (2017) indicated a CENO value of 5 mM, equivalent to a concentration of 2.67 g/L-1, in seven-day tests with *D. rerio* embryos. However, it is worth mentioning that the eggs of this species present the chorion, an acellular membrane that surrounds the embryo until the moment of its hatching, which occurs at 72 hpf (hours after fertilization). This structure has pores between 0.5 and 0.7 mm in diameter and, in this way, partially isolates the embryo from the environment (MEDEIROS *et al.*, 2017). Therefore, for this value to be considered safe, other stages of the species' development must be tested. The literature also reports that the chorion can be impervious to a good number of pollutants; however, studies have proven that the tartrazine yellow dye has overcome this protective barrier (JOSHI; KATTI, 2017; GUPTA *et al.*, 2019; SILVA; FRACÁCIO, 2020), and the dye also accelerated the embryo hatch rates (from 72 hpf to 48 hpf).

In the absence of CENO, literature recommends using the lethal concentration value to 50% of the exposed population, at a given exposure time, and dividing it by 10, as estimated safety values. Thus, the estimated CENO values would be 2.94 and 4.71 mM, corresponding to 1.57 and 2.51 $g.L^{-1}$ respectively, which is close to the reported CENO values. However, data obtained by Silva and Fracácio (2020) show that in low concentrations, compared to the values reported, there was toxicity to larvae in 48 hours after hatching at a concentration of 0.05 $g.L^{-1}$.

The concern with aquatic life protection lies in the fact that the dye can reach surface waters through large-scale production, with an

Table 2 – Ecotoxicological research carried out in the last ten years with the tartrazine yellow dye that resulted in toxicity.

Author (s)	Objectives	Concentrations	Conclusions
Joshi and Katti (2017)	To evaluate embryological development of *Danio rerio*, exposed to the tartrazine dye.	Concentrations of 0.1, 2, 3, 4, 5, 10, 20, 30, 40, 50, 75 and 100 mM (0.053; 0.53; 1.06; 1.60; 2.13; 2.67; 5.34; 10.68; 16.03; 21.37; 26.71; 40.07 and 53.43 $g.L^{-1}$) in the gastrulation stage (5.25 hours after fertilization (hpf). Observation until the seventh day. SCENE = 5 mM (2.67 $g.L^{-1}$) CL (I) 50, 96h = 29.4 mM (15.7 $g.L^{-1}$)	• 20 to 30 mM caused tail flexion, and edema of the cardiac sac in 50% of the larvae; • At 30 to 50 mM, heartbeat declined along with tail flexion deformities, edema of the cardiac sac, causing mortality within 96 to 144 hpf; • Development has completely stopped at 75 to 100 mM concentration.
Linskens (2018)	To evaluate learning, cognitive flexibility, and the memory of adults of *D. rerio*, exposed to the dye in labyrinth tests, with different exposure times.	Concentration of 22 µM (11.75 $g.L^{-1}$) of the dye throughout its life stage (eggs to adulthood) and *D. rerio* eggs subjected to the dye and removed from the dye after 24 hours after fertilization.	• Lack of understanding and cognitive flexibility; • Exposed for 24 hpf, problems in completing the memory tasks; • Constant exposure to dye will affect the ability to learn, remember and reduce the body's cognitive flexibility, even if only exposed to an embryonic level.
Gupta *et al.* (2019)	To compare oxidative stress in embryonic phases of *D. rerio*	96 hpf embryos exposed to 0.1% tartrazine in 100 µL with the superoxide dismutase enzyme (SOD).	• Accelerated the hatch rate; • During the initial development it induces the expression of superoxide dismutase 1, inducing oxidative stress pathways; • The embryo's sensitivity to exposure resulted in significant mortality in a concentration-dependent manner, especially at higher concentrations.
Jiang *et al.* (2020)	Evaluation of *D. rerio* embrio-larval toxicity when exposed tartrazine dye	*D. rerio* subjected to a concentration of 5 to 50 mM. (2.67 $g.L^{-1}$ to 26.71 $g.L^{-1}$) LC50 = 47.10 mM (25.16 $g.L^{-1}$)	• Difficulty in hatching and developmental abnormalities, such as cardiac edema, decreased heart rate, yolk sac and spinal edema; • Scoliosis and tail distortion.
Silva and Fracácio (2020)	Evaluation of toxicity in embryos and larvae of *D. rerio* when exposed tartrazine dye	*D. rerio* subjected to concentrations of 0.05 $g.L^{-1}$ in two dye patterns (Commercial and Pure) and in concentration of 0.5 $g.L^{-1}$ of pure standard	• Coagulation in the embryos; • Deformities in the larvae such as edema (cardiac and yolk sac); • Scoliosis and tail distortion

interaction between the consumption of these industrialized foods and the quality of aquatic ecosystems – a challenge for the coming years (TEIXEIRA; PORTO, 2008). Conventional effluent treatment systems cannot effectively degrade this type of dye due to its high stability, resistance to light, and moderate oxidizing agents. Many companies, due to the peculiar characteristics of their products, dilute the dyes to cause less color impact on the environment. The dye use should be limited to the smallest amount as possible to achieve the desired effect and only when there is no other alternative, considering the lack of adequate legislation and impacts they cause to the environment and human health.

Conclusions

- Tartrazine yellow food dye is toxic even at the dose indicated for acceptable daily intake for humans. In this sense, the laws that regulate the use of the additive in food should consider the new research on the molecular interactions of the dye with animal cells to review the doses considered safe;
- There is a direct relationship between the production and use of these dyes and aquatic ecotoxicity, through the release of effluents generated in water bodies. Without adequate treatments, these chemical compounds and their by-products cause risks to biota;
- The tartrazine yellow dye crosses the protective barrier of the chorion in *D. rerio* embryos and accelerates reproduction. However, studies with other stages of the life cycle of the referred species and with other species of different trophic levels are recommended;
- The Regulation 333/2012 of the state of São Paulo should serve as a model for other areas of the national territory, and greater attention should be given to the launch of food dyes, since the azocores are freely purchased and used commercially in the food industry. This economic sector is still in need of effective regulation and implies in environmental damage and risks to human health.

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Silva, J.: conceptualization, methodology, validation, formal analysis, investigation, writing — original draft. Fracácio, R.: resources, data curation, writing — review & editing, funding acquisition.

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