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Health safety issues of synthetic food colorants

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ABSTRACT

Increasing attention has been recently paid to the toxicity of additives used in food. The European Parliament and the Council published the REGULATION (EC) No. 1333/2008 on food additives establishing that the toxicity of food additives evaluated before 20th January 2009 must be re-evaluated by European Food Safety Authority (EFSA). The aim of this review is to survey current knowledge specifically on the toxicity issues of synthetic food colorants using official reports published by the EFSA and other available studies published since the respective report. Synthetic colorants described are Tartrazine, Quinoline Yellow, Sunset Yellow, Azorubine, Ponceau 4R, Erythrosine, Allura Red, Patent Blue, Indigo Carmine, Brilliant Blue FCF, Green S, Brilliant Black and Brown HT. Moreover, a summary of evidence on possible detrimental effects of colorant mixes on children's behaviour is provided and future research directions are outlined.

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1. Introduction: food colorants

A colour additive, or food colorant, is any dye, pigment, or other substance that imparts colour added to food, drink or any non-food applications including pharmaceuticals. In addition, a colour additive is also any chemical that reacts with another substance and causes formation of a colour (de Boer, 2014; Newsome et al., 2014). The main reasons to use the colour additives in food are:

1) Compensation of colour loss due to exposure to light, air, temperature and storage conditions;
2) Enhancement of natural colours to make the food more attractive and appetizing;
3) Provision of colour to colourless foodstuff; or
4) To allow consumers to identify products on sight, especially drugs (Barrows et al., 2003).

Food colorants can be classified according to several criteria: origin (natural, identical to natural or synthetic; organic and inorganic), solubility (soluble and insoluble) and covering ability (transparent and opaque). However, these categories often overlap. The most widely used classification is the distinction between soluble and insoluble substances.

Soluble colorants can be subdivided into natural, semisynthetic and synthetic ones. Natural dyes are obtained from various food material or other natural materials. They include e.g. riboflavin (E 101), chlorophylls (E140), carotenes (E160a), betalain (E 162) or anthocyans (E 163). The dyes of natural origin are not very stable and can be characterized by their own physiological activity. Colorants are like natural dyes, with the only difference between the two being attributed to the fact that colorants are produced by chemical synthesis. Synthetic dyes are produced also by chemical synthesis but cannot be found naturally. They were originally manufactured from coal tar and now they are obtained from highly purified oil products. The group of synthetic organic colorants consists of azo-dyes, xanthan, chinilin and antrachinon dyes, which have generally more intensive and permanent colour than natural substances, do not impart any flavour to products and they are generally more stable.

Insoluble dyes are called pigments. They are very stable colours exhibiting good cover properties and are also insoluble in common solvents. Pigments can be inorganic with a limited variety of colours available, e.g. white titanium dioxide, calcium carbonate, red iron oxide and black adsorbent carbon, or organic. Organic pigments are usually in the form of lacquers which are insoluble complex salts of water-soluble azo-dyes in a wide colour palette (Golka et al., 2004; Moller and Wallin, 2000).

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1.1. Regulatory measures concerning food dyes in the European Union

The first international collection of food standards and guidelines, called Codex Alimentarius (CA, website: http://www.codexalimentarius.org/), was established early in 1962 by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO). In the framework of the CA operates the Codex Committee on Food Additives and Contaminants (CCFAC). The CCFAC specifically focuses on food additives and contaminants and releases recommendations for the permitted maximum levels of use for individual food additives. Codex Alimentarius and WHO/FAO have developed a database, which collects available evidence for biological activity of food additives, so called General Standards for Food Additives (GSFA, Available online: http://www.codexalimentarius.net/gsfaonline/docs/CXS_192e.pdf). The purpose of these standards is to harmonize international rules concerning additives, which are useful in the context of the food world trade.

All member states of the European Union (EU) follow the REGULATION (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002, laying down the general principles and requirements of food law, establishing the European Food Safety Authority and defining procedures in matters of food safety. These conditions are reflected in all national laws and decrees. In accordance with this regulation, additives used in the EU must be first reviewed by the European Food Safety Authority (EFSA), belonging to the European Commission. EFSA conclusions are based on the recommendations of CCFAC. EFSA publishes, on request from the European Commission, in the EFSA Journal, officially known as "Scientific Opinion." Topics that are covered and discussed include toxicity of food colorants and the method of its application, which is developed by a standard process (detailed information is available on the EFSA website: http://www.efsa.europa.eu). The content of the EFSA Scientific Opinion comprises technical and chemical specifications of the colorant, description of the manufacturing process, analytical methods used for the determination, chemical reactivity with food, summary of the current authorization for use, dose range, toxicokinetic information (absorption, distribution, metabolism and excretion), toxicological data such as acute oral toxicity, sub-chronic and chronic toxicity, carcinogenicity, genotoxicity, developmental and reproductive toxicity and hypersensitivity to the substance.

Approval of food additives depends on the level of scientific knowledge at a given time; therefore, it is necessary to regularly revise the recommendations and to take into account new scientific information in evaluating the conditions of a specific additive use. For this reason, the monitoring of consumption and use of food additives takes place in each member state. The European Commission prepares a summary report for the EU member states and suggests implications for the next period of monitoring.

1.2. Indicators of food additives' toxicity

Permission to use colorants in the food industry is subjected to a wide range of toxicity tests (such as detection of the acute, sub-chronic and chronic toxicity, carcinogenicity, mutagenicity, teratogenicity, reproductive toxicity, accumulation in the body, bioenergy effects and immune effects) and strict legislative provisions in all developed countries. The available toxicological data shall be assessed and subsequently confirmed in more species. Toxicity is monitored in six species and at least three of them must be mammalian. Most of the tests use small rodents (mouse, rat, guinea-pig, etc.) as well as special breeds of rabbits, dogs, cats or pigs which are particularly close to the human body physiology (Hallagan et al., 1995; Kumar and Madan, 2014; Magnuson et al., 2013). The non-mammalian species used for toxicology studies comprise usually nematodes (e.g. *Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*) or zebrafish (*Danio rerio*) (van Vliet, 2011).

In order to evaluate potential toxicity of food additives, preclinical studies are done in order to determine the **NOAEL (No-Observed-Adverse-Effect Level)**, i.e. "the greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure" (Duffus et al., 2009). For clinical recommendations this value is divided by a safety factor that is usually a value of 100 (in the case of toxic substances with serious effects the safety factor can be increased a thousandfold). Due to this factor, the differences in extrapolating animal models to human and individual differences in human populations in response to the additive are considered. This value is called **Acceptable Daily Intake (ADI)**, expressed as mg per kg of body weight (Duffus et al., 2009). This value indicates the amount of food additive that can be consumed daily throughout life without posing an appreciable risk to consumer health. The specific eating habits of certain groups of consumers (e.g. children, vegetarians, etc.) are also considered to ensure that the ADI will not be exceeded.

The values set by regulatory authorities obviously cannot completely eliminate the risk of possible adverse reactions to a particular substance, especially with regard to vulnerable populations or hypersensitive individuals. However, even in such cases there should be no threat to life, besides perhaps rare anaphylactic reactions unlikely to occur after ingestion of the colorant in food.

Based on provision for food labelling determined by the Codex Alimentarius committee, there was a need to unambiguously identify food additives. CCFAC created an International Numbering System (INS), which allows the identification of food additives on the list of ingredients by a three-digit number. This number replaces the specific name of the additive, which is often long, because it describes a complex chemical structure. Within the European Union, a system of **E numbers** was implemented in order to identify all food additives. E numbers are composed of the letter E (for Europe) followed by the INS three-digit number. Colorants with numeric code E are substances that have proved to have no detrimental effects on human health at expectable exposures.

2. Toxicity evaluation of synthetic food dyes

Increasing attention has been recently paid to the toxicity of additives used in food, namely to azo-dyes. This group of colorants typically consists of bright colours. However, the main concern often limiting their use is potential carcinogenicity occurring after their azoreduction to carcinogenic metabolites by intestinal microbiota (Feng et al., 2012). These metabolites are known to be produced in the human body; however, the clinical importance of this phenomena depends on the ingested amount of the colorant (Golka et al., 2004). Furthermore, given the low rate of absorption, harm to human health is unlikely (see Table 1). However, in light of new findings, is it necessary to regularly assess potential toxicity of food colorants by regulatory authorities and consequently revise guidelines for their use.

The European Parliament and the Council published in 2008 the REGULATION (EC) No. 1333/2008 on food additives (available on the official EU website: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32008R1333). This document established that the toxicity of food additives which were evaluated before 20th January 2009 must be re-evaluated by EFSA. The program was initiated in 25th March 2010 by REGULATION (EC) No. 257/2010 setting up a

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