‘Southampton six’ and attention deficit hyperactivity disorder (ADHD) - safety of food additives analyzed with ToxWiz expert report database

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Introduction
Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood disorders and can continue through adolescence and adulthood. While the biological pathways leading to ADHD are not clearly delineated, a number of genetic and environmental risk factors for the disorder are recognized, among them artificial food dyes and preservatives. In 2010, following research that suggested a link between certain food colors and ADHD in children, it was decided that EU-wide, health warnings, stating that the food ‘may have an adverse effect on activity and attention in children’, would be put on the food containing six artificial food colors - Tartrazine (E102), Quinoline Yellow (E104), Sunset Yellow (E110), Carmoisine (E122), Ponceau 4R (E124) and Allura Red (E129), which were used in the experimental study, known as ‘Southampton six’. In US, after public petitions and reviewing process, FDA rejects calls for putting the warning labels on link between food dyes and hyperactivity. This decision still brings lot of attention and private initiatives, as US manufacturers are now using natural colourings in food products for EU market but the same products contain artificial food dyes in the United States. In regards to safety of food dyes, European Commission asked EFSA (European Food Safety Authority) in 2010 to re-evaluate the safety of all previously authorized food additives by 2020, taking into account the latest science. In this study, ToxWiz expert report database is used to investigate the connection between food dyes and ADHD. ToxWiz is a fast report system that provides users with extensive information on chemicals and their biological effects on organisms. Using previously collected data on chemicals from the public domain and proprietary datasets and associations annotated in 150 years of expert curation effort, this software enables researchers to get fast and reliable information on chemical safety, interacting proteins, pathways, and biological effects.

Food dyes: Effects on biological system – Attention Deficit Hyperactivity Disorder (ADHD)
Direct link with ADHD was seen for Quinophthalone (Quinoline Yellow), reported to has implication in the induction and severity of behavioural disorders such as attention deficit hyperactivity disorder (ADHD) when combined with Aspartam. It was also reported that behavioural changes in irritability, restlessness, and sleep disturbance are associated with the ingestion of tartrazine in some children. A ToxWiz search for target molecules of six food dyes, resulted in molecules such as signal transducer and activator of transcription 3 isoform 1 (STAT3) which plays a key role in cellular processes such as cell growth and apoptosis, ATP-binding cassette ABCC1, peroxisomal biogenesis factor 5 and 12 (PEX 5 and 12), proopiomelanocortin preproprotein (POMC) with the role in steroidogenesis and immune modulation, and trefoil factor 3 and 2 precursor (TFF2 and 3), expressed in gastrointestinal mucosa. Analysis of pre-annotated pathologies and scientific literature (PubMed) with ToxWiz expert report database software identified indirect connections of food dyes to molecules, known to contribute to the development of ADHD (Figure 1).
Those include solute carrier family 6 member 4 (SLC6A4 or 5-HTT), an integral membrane protein that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons, reported to be involved in susceptibility to ADHD⁵; solute carrier family 6 member 3 (SLC6A3 or DAT) and dopamine receptor D4 (DRD4) also contributing to ADHD susceptibility⁶. Monoamine oxidase A (MAOA), an enzyme that degrades amine neurotransmitters, such as dopamine, norepinephrine, and serotonin⁷, and therefore a strong candidate gene for ADHD is also present as well as AKT1, serine-threonine protein kinase, described to be down-regulated in stroke-prone spontaneously hypertensive rats (SHRSP)⁸, rat model for ADHD.

**Summary**

Analysis using ToxWiz expert report database, in just few hours, gave the safety profile of food dyes in relation to ADHD. We identified common protein targets for five food dyes and indirect connection to proteins known to be associated with ADHD (SLC6A3 or DAT, DRD4, MAOA, AKT1 and SLC6A4 or 5-HTT). This indirect relationship between food dyes and ADHD, became apparent after just a few hours of searching, thus demonstrating the power of molecular network analysis from the reported data.

**References**