Artificial food colours and children

Why we want to limit and label foods containing the 'Southampton Six' food colours on the UK market post-Brexit

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FIRST STEPS NUTRITION TRUST

Artificial food colours and children: Why we want to limit and label foods containing the 'Southampton Six' food colours on the UK market post-Brexit November 2020

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Executive summary

Artificial food colours have been historically used in ultra-processed foods to affect perception of flavour and quality and enhance appeal, often to children. They serve no dietary purpose but are cheaper and more stable than natural alternatives (Kanarek, 2011).

Links between the consumption of some artificial food colours and childhood behaviour have been made for nearly 50 years. A global body of evidence has associated the consumption of specific artificial food colours with symptoms of hyperactivity in children (Feingold, 1975a; Feingold, 1976; Bateman et al, 2004; Schab and Trinh, 2004; McCann et al, 2007). Most recently, a systematic review concluded with 'high confidence' that some artificial food colours adversely affect behaviour in children, both with and without pre-existing behavioural disorders. Animal studies also demonstrated a wide range of effects on activity, learning and memory as well as brain histomorphology. (OEHHA, 2020).

The effects of hyperactivity or attention deficit hyperactive disorder (ADHD) in children include over activity, inattention and impulsiveness (Arnold, 2012) as well as the inability to process information accurately (Kanarek, 2011). As such, frequent albeit small exposures to artificial food colours may present a significant long-term risk to educational attainment (Stevenson, 2009; Kanarek, 2011; Chorozoglou et al, 2015). The impact may be greater in pre-school children, whose immature organ systems and relatively higher intake of artificial food colours for their bodyweight make them more vulnerable to potential adverse effects (Martyn et al, 2013; Trasande et al, 2018).

In the UK two landmark studies examined the effect of six artificial food dyes and one preservative (sodium benzoate) on the health of children in the general population. Although the effects were small in clinical terms, results from these trials reframed historical concern regarding the behavioural effects of artificial food dyes from an issue affecting only those with symptoms of ADHD, to a more significant public health issue. These studies led the Food Standards Agency to bring in a 'voluntary ban' on the use of six colours (called 'The Southampton Six') Sunset Yellow (E110), Quinoline Yellow (E104), Carmoisine (E122), Allura Red (E129), Tartrazine (E102) and Ponceau 4R (E124) in foods and drinks in 2008. A change in European legislation in 2008 required any food product containing these food colours to carry a warning label that consuming the product '*May have an adverse effect on activity and attention in children*' (EC 1333/2008).

The UK voluntary ban was widely supported by food manufacturers and retailers and the use of these particular artificial dyes in the UK food supply significantly decreased (Stevenson, 2009; Saltmarsh, 2015). Foods and drinks sold by larger UK food retailers and produced by the major food brands have nearly all replaced these artificial colours with naturally sourced colours, but some manufacturers have not yet reformulated their products. While there is a lack of evidence on dietary exposure to these six food colours in children within the UK, there is some epidemiological evidence to suggest that daily intake is low, relative to the dose tested in the Southampton studies (Connolly et al, 2010), and that in a sample of European countries, intake among toddlers and children does not exceed acceptable daily intake established by the European Food Safety Authority (EFSA) (EFSA, 2009a-e; Huybrechts et al, 2010; EFSA, 2014; EFSA, 2015a-e).

There are however concerns about the use of any azo dye as a food colour, and the impact of cocktails of dyes, and whilst studies have not been conducted on all azo dyes, some of which are used less frequently in foods consumed by children, a precautionary approach would remove all of these unnecessary artificial food colours from the food supply.

In the context of establishing new trading arrangements following the UK departure from the EU, it is important to prevent an influx of food into the UK that challenges both voluntary and mandatory food policy. This is particularly important with regard to safeguarding the diet of young children, '*the very foundation stone of equality of opportunity*' (National Food Strategy, 2020).

A key concern, particularly regarding trade with the US and other countries where they have a different regulatory regime for additives, is that cheaper foods and drinks containing colourings we voluntarily restrict in the UK could come on to the UK food market. This could lead to wide-scale market availability of products, from the US containing Tartrazine (E102), Sunset Yellow (E110), and Allura Red (E129) and from other countries containing all of the 'Southampton Six' colours. A recent exposure estimate for artificial colour additives (Doell et al, 2016) demonstrated that a broad range of products marketed at children in the US, including confectionery, juice drinks and cereals, contain significant amounts of Allura Red (E129), Sunset Yellow (E110) and Tartrazine (E102).

More than 50% of dietary energy in the UK population (for those aged one and a half years or over) is derived from ultra-processed foods (Adams and White, 2015; Rauber et al, 2018). Evidence shows that household availability of ultra-processed foods internationally, many of which may have a high concentration of artificial food colours, is inversely related to their cost (Moubarac et al, 2013). The Food Foundation reported that the mean cost of healthy foods in 2019 per 1000 kilocalories was more than 3 times the cost of less healthy foods (Food Foundation, 2020). Logically, as lower income limits the purchase of more expensive foods, the effects of consuming cheaper ultra-processed foods and drinks with artificial colourings coming on to the UK market may disproportionately affect the most vulnerable children.

Any forthcoming trade deals should require the continuation of a warning label on food and drinks that contain the 'Southampton Six' colours, but one which is far more prominent than that currently present on products. In a wider context artificial food dyes are associated with ultra-processed food manufacture and stronger regulations limiting the amount of these foods on the UK market should be considered as there is convincing evidence these foods damage both health and the environment (FAO, 2019).

Recommendations

1. The UK Government should make the removal of azo dye food colourings mandatory for UK food and drink producers.

2. Citizens should be made aware of the potential risks to children of consumption of foods and drinks that contain azo dyes with a clear public information campaign and encouragement to check the labels of products.

3. Where food or drink does contain the 'Southampton Six' food colours the current EU warning label should remain mandatory but regulation should require this to be in a format with a font no smaller than 11pt and for this to be in a prominent place on the packaging, with a warning symbol to alert consumers.

4. When new trade deals are discussed that involve the import of foods and drinks from countries outside the EU which do not have any restrictions on the use of the 'Southampton Six' food colours, then the need for warning labels must be made explicit as part of any agreement.

5. Those negotiating trade deals should consider the risks to UK children of allowing cheap, ultra-processed food and drink on to the market that contains azo dyes and consider how this can be limited in any agreements made.

6. The Food Standards Agency website should provide clear information to citizens about the presence of the 'Southampton Six' food colours in foods and drinks and monitor the prevalence and volume of these artificial food colours that the population may be exposed to.

7. Civil society organisations that lobby for reduced sugar products or reformulated food for children should be mindful that they do not inadvertently encourage the consumption of foods and drinks that contain artificial colours.

1.0 Use of food colours in foods and drinks

Food consumption is a multisensory experience combining interactions between sight, taste and aroma, and colour can influence all of these (Rodriguez-Bustamante and Sanchez, 2007). Colour provides an important visual cue to identify the nature of a food, what it may be composed of and how it is likely to taste. The colour of food impacts on our perception of the quality of food and its safety (Burrows, 2009). As such, the colour of food is an important determinant of consumer choice and manufacturers have recognised the importance of the visual attractiveness of food in consumer preferences. One example of this is the failure of Crystal Pepsi, marketed in 1993 as a colourless alternative to cola. The product failed to drive consumer demand because the taste did not correspond with consumer expectations (Burrows, 2009).

Colour can be used to influence taste perception (Spence and Zampini, 2010). Colour provides visual information about what a food is likely to taste of, for example, in the UK, a red jelly would not be expected to taste of pineapple or lime but would be expected to taste of strawberry as this is what experience tells us red may taste of. Perception of colour varies across cultures and geographically, for example brown being associated with cola in the UK but with grapes in Taiwan (Shankar et al, 2010; Levitan et al, 2014).

Historically, food colouring additives have been used to perform specific functions in food. Colouring agents may be used to enhance natural colours, decrease colour loss due to processing treatments, to correct natural variations in colours and to make food more attractive to the consumer, and to provide colour to colourless, ultra-processed foods (FDA, 2011). Both natural and synthetic products have been used as food colours. Natural colourings are derived from vegetables, animals or minerals. They are typically more expensive than synthetic colours (FDA, 2011). Examples include annatto extract (yellow), dehydrated beets (bluish-red to brown), caramel (yellow to tan), beta-carotene (yellow to orange) and grape skin extract (red, green).

Artificial food colours have been preferred by manufacturers because they provide greater intensity and uniformity of colour, are cheaper and more stable than natural colourings and blend more easily with food to produce different colours (Kanarek, 2011).

2.0 Artificial food colours

Food colours are a food additive. Food additives are defined by the World Health Organisation as,

> *'substances added to food to maintain or improve its safety, freshness, taste, texture, or appearance' (WHO, 2018)*

and in the EU food additives are commonly defined as,

> *'any substance not normally consumed as a food in itself and not normally used as a characteristic ingredient of food, whether or not it has nutritive value, the intentional addition of which to food for a technological purpose in the manufacture, processing, preparation, treatment, packaging, transport or storage of such food results, or may be reasonably expected to result, in it or its by-products becoming directly or indirectly a component of such foods' (EC 1333/2008).*

Food colour additives both extracted from nature or wholly synthetic are both given E numbers in the EU. For example, Lycopene (E160d), a red coloured carotenoid which acts as an antioxidant is found abundantly in tomatoes but Brilliant Blue (E133) is created wholly synthetically from laboratory materials.

2.1 Azo dye artificial food colours

Azo dyes are a group of food colours which are wholly synthetic compounds originally derived from coal tar and now petroleum. Historically azo dyes could be manufactured at low cost as their raw materials are cheap and readily available. They are known for producing bright, high intensity colours in foods, drinks and medicines which have been more stable than natural alternatives (Yamjala et al, 2016). Azo dyes represent about 65% of all synthetic food dyes used in foods (Yamjala et al, 2016). In the US, where batch certification enables production of dyes to be measured, daily per capita intake of these dyes has increased fivefold over the last 50 years in parallel with increasing consumption of ultra-processed foods including breakfast cereals, snack foods, and soft drinks (Kanarek, 2011).

Azo dyes refer to any of a large class of synthetic dyes whose molecules contain two adjacent nitrogen atoms between carbon atoms. Most azo dyes contain one azo group and are known as monoazo dyes, but they can contain more (i.e. they can be diazo, triazo etc.) Specific colours belonging to this class of dyes, and their metabolites (in particular benzidine) have been associated with neurotoxicity, genotoxicity and carcinogenicity, (Chung, 2016) and many have been rendered illegal within the EU (European Parliament, 2002) or elsewhere.

Some azo dyes with specific structural similarities (Sudan I, Sudan II, Sudan III, Sudan IV, Para Red, Rhodamine B and Orange II, (Larsen, 2008)) are banned for use in the food supply due to genotoxicity, mutagenicity and/or carcinogenicity. In some cases, the precautionary principle has been used to ban some colours where evidence is equivocal.

There are currently 11 azo dyes that are typically used in foods: Tartrazine (E102), Yellow 2G (E107), Sunset Yellow (E110), Azorubine (E122), Amaranth (E123), Ponceau 4R (E124), Allura Red (E129), Brilliant Blue (E151), Brown FK (E154), Brown HT (E155) and Lithol Rubine BK (E180).

Five of these azo dyes, and one other colour, are known as 'the Southampton Six' food colours, named after research, conducted on them by a research team from Southampton University in the UK. These were selected for study as they were the most prevalent azo dyes used in foods and drinks consumed by children.

The 'Southampton Six' food colours

Six artificial food colours, commonly known as the 'Southampton Six' are all azo dyes with the exception of Quinoline Yellow which is a quinophlthalone dye.

Table 1 – The 'Southampton Six' food colours

EU name	E number	Chemical name
Tartrazine	E102	Trisodium 5-hydroxy-1-(4-sulphonatophenyl)-4-(4-sulphonatophenylazo)-H-pyrazol-3-carboxylate
Quinoline Yellow*	E104	Disodium 2-(1,3-dioxo-2-indanyl)-6,8-quinolinesulpfates; Disodium 2-(2-quinolyl)-indan-1,3-dionesolfonates
Sunset Yellow	E110	Disodium 6-hydroxy-5-(4-sulfonatophenylazo)-2-naphthalene-sulfonate
Azorubine/ Carmoisine	E122	Disodium 4-hydroxy-3(4-sulfonato-1-naphthylazo)-1-naphthalenesulfonate
Ponceau 4R	E124	Trisodium-2-hydroxy-1-(4-sulfonato-1-naphthylazo)-6,8-naphthalenedisulfonate
Allura Red AC	E129	Disodium 6-hydroxy-5-(2-methoxy-5-methyl-4-sulfonato-phenylazo)-2-naphthalenesulfonate

* quinophthalone dye; all of the other dyes are azo dyes

2.2 Artificial food colours and ultra-processed foods

The use of artificial food colours in ultra-processed food has been highlighted:

> *'.... colours either disguise unpleasant sensory properties created by ingredients, processes or packaging used in the manufacture of ultra-processed foods or give the final product intense sensory properties especially attractive to see, taste, smell and/or touch, or both.' (FAO, 2019)*

The NOVA food classification system is an epidemiological tool that classifies all foods and food products into 4 groups, based on the extent to which that food has been processed. The precise definition of each of these groups, superimposed on national dietary consumption data, allows the scientific assessment of the effects of food processing on human health and use of this information to inform public health policy (FAO, 2019).

The fourth group, in this classification system is 'ultra-processed foods'. This group consists of snacks, drinks, ready meals and many other product types '*formulated mostly or entirely from substances extracted from foods or derived from food constituents'* (FAO, 2019). Ultra-processed foods are created using many types of additive, including food colours, that render them convenient and hyperpalatable for consumers and highly profitable for manufacturers.

Examples of ultra-processed food groups that typically contain artificial food colourings include soft drinks; sweet or savoury packaged snacks and confectionery, (Connolly et al, 2010; Monteiro et al, 2017). These products are typically energy-dense and nutrient-poor and they may offer no nutritional benefit or may contain excessive amounts of energy, fat, sugar, or sodium and lower quantities of dietary fibre and essential nutrients (Monteiro et al, 2017). Bright colours have been historically used in these food groups to appeal to children alongside child-oriented 'fun' packaging, cartoon logos and marketing material.

2.3 Consumption of artificial food colours may disproportionately affect children from low income groups

Dietary intake and eating behaviours in England are related to socio-economic position (PHE, 2013). People from lower socio-economic groups (as measured by equivalised income and material deprivation) tend to have diets that are less healthy than people from higher socio-economic groups. Socio-economic differences in diet are a potential contributor to health inequalities (Maguire and Monsivais, 2015).

While consumption of ultra-processed foods in the UK is ubiquitous across the social spectrum, with no statistically significant differences by occupational social class (Adams and White, 2015), there is evidence to suggest that consumption of free sugars (a nutrient highly associated with ultra-processed foods and artificial food colourings (Stevens, 2015b)) is negatively associated with income and education (Maguire and Monsivais, 2015). Most importantly, evidence shows that household availability of ultra-processed foods is inversely related to their relative cost (Moubarac et al, 2013). Logically, lower income limits the purchase of more expensive, healthier foods (Food Foundation, 2020). Ultra-processed foods, which are energy dense but nutrient poor are the lowest cost providers of dietary energy (Monsivais and Drewnowski, 2007).

It follows that frequent exposure to, and the resulting effects of artificial colourings within these foods may disproportionately affect the most vulnerable children.

2.4 Food colouring regulation

The global Codex Alimentarius General Standards for Food Additives (Codex STAN 192-1995) outlines the conditions under which permitted food additives may be used in foods, whether or not they have previously been standardized by Codex.

According to Codex the labelling of all food additives must not be '*false, misleading, deceptive or likely to create an erroneous impression regarding their character'* (Codex Standard 107, 1981, revision 2001). Globally, Codex lists all food additives, but the EU uses a different system whereby only additives with a proposed use that have been evaluated to be safe are listed. This means that although the list of E numbers runs from E100 to E1599, there are gaps which indicate an additive not permitted for use (EC 1333/2008).

2.5 EU food colouring regulations

A comprehensive framework of legislation is in place within the European Union to control the use of additives to specify the conditions of use and foods to which they can be added, and the maximum amounts that can be used in the food supply to ensure they pose no risk to human health.

Approved additives are given an E number, which indicates that they have been approved for use within European Union member states. The evaluation, performed by the European Food Safety Authority (EFSA), assigns a maximum permitted level, based on scientific evidence of safe usage, which must reflect '*exposure to the food additive by special groups of consumers*.' Additionally, exposure assessments are performed to measure population intakes versus acceptable daily intakes (ADI).

Measuring intakes of artificial food colours

Maximum Permitted Levels (MPL) (mg/kg of food)

To control the volume of additives in the food supply, there are EU regulations in place that define which food groups may contain artificial colours and impose a maximum permitted level (MPL) in mg/kg of food, of each additive that those foods may contain. In the EU, unlike some other trading blocks, the 'Southampton Six' are subject to individual and combined maximum permitted limits within specific food groups. (Directive No. 94/36/EC – European Union 1994; and Directive No. 95/2/EC – European Union 1995).

In contrast, some countries such as Japan and the United States, permit the use of colours at '*good manufacturing practice*' (GMP) levels. GMP implies that the use of a colour is self-limiting in food for technological, organoleptic or other reasons.

Acceptable Daily Intake (ADI) (mg/kg body weight/day)

To ensure that colours are consumed without adverse effects, an Acceptable Daily Intake (ADI) value for each additive is calculated. The ADI is defined as an estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (WHO, 1987).

To establish the ADI for an additive, a minimum level of exposure is calculated, above which adverse health effects may manifest. This level is the no observed adverse effects level (NOAEL), mostly determined using animal studies (WHO, 1987). Safety factors are then applied to NOAEL, to account for differences between test animals and humans, and account for any sensitive subgroups, such as children. The ADI is expressed in a range, from 0 to an upper limit, which is considered to be the zone of acceptability for the substance.

ADIs are policed through regular exposure assessments carried out in the EU by The European Food Safety Authority Panel on Food Additives and Nutrient Sources Added to Food. These assessments monitor patterns of dietary chemical exposure among the general public and determine if population intakes of chemicals exceed the ADI (Scientific Committee on Food, 2001). Once these assessments have been completed, any potential risks to health can be assessed and analysed.

Historically, a key concern relating to the methodology of setting of ADIs is that they may not adequately protect young children and that a test animal may not accurately reflect the potential for harm in immature and developing organ systems (Martyn et al, 2013).

The Additive Regulation of 2008 (EC 1333/2008) describes a common authorisation procedure for food additives, enzymes and flavourings with numerous amendments since.

The EU regulations on food additives contain what is known as a positive list which refers to food additives which have been approved for use. The EU Food Additives database provides more detail on the status of food colours and is available online at: https://webgate.ec.europa.eu/foods_system/main/?sector=FAD&auth=SANCAS

There are three conditions which determine whether a colour is allowed to be included in the community list of food additives as set out in EC Regulation 1333/2008 Annex II.

These are:

- restoring the original appearance of food of which the colour has been affected by processing, storage, packaging and distribution, whereby visual acceptability may have been impaired;
- making food more visually appealing;
- giving colour to food otherwise colourless.

For those colours that are permitted for use, inherent in the risk assessment is balancing the weight of available scientific evidence and consumer safety with commercial liberties. As new scientific data becomes available, the understanding of risk associated with consumption is refined and ADIs are adjusted. Generally, as the body of literature examining the effects of azo dyes (human and animal studies) has grown, tighter restrictions have been imposed. Between 2009 and 2016, the ANS Panel of EFSA re-evaluated the safety of all previously authorised food colours as part of the re-evaluation of all food additives in use before January 2009, taking in to account any new evidence. As a result of this process EFSA lowered the ADI for several food colours including E104, E110 and E124. In 2012, the European Commission also lowered the maximum permitted levels of these colours for food uses. In addition, Red 2G (E128) was withdrawn from use in the EU in 2007 as new scientific evidence indicated that use could not be regarded as safe for human consumption.

One important area of research that has contributed to changes in the risk assessment of certain azo dyes is the study of how azo dyes are metabolised by intestinal bacteria. The intestinal microbiota plays a key role in the enzymatic reduction of azo dyes (Feng et al, 2012). Some of the metabolites of this process are carcinogenic while others are not, but further studies are needed to fully characterise the impact of azo dyes on the microbiome: mechanisms of reduction, the intermediates and the potential to produce genotoxic compounds (Feng et al, 2012).

2.6 UK regulation

In the UK, current regulations for the use of food additives have been applied since 1 June 2013. The EU food additives regulations are enforced by the Food Additives, Flavourings, Enzymes and Extraction Solvents Regulations 2013 with parallel measures in each of the four nations.

A compliance guide to assist UK based manufacturers, processors, retailers, caterers and enforcement officers in meeting the requirements of EU additive legislation is available from the Food Standards Agency here: https://www.food.gov.uk/sites/default/files/media/document/food-additives-legislation-guidance-to-compliance.pdf.

2.7 Naming and certification of 'Southampton Six' food colours in other countries

The US operates a different system where colours are categorised as '*certified*' or '*exempt from certification*' where certified colours generally include artificial colours and these are required to be tested for purity and composition at batch level (McAvoy, 2014). Colours exempt from certification are generally plant, animal or mineral additives or synthetic variations of naturally occurring additives and are labelled as either '*artificial colour*', '*artificial colour added*', '*colour added*' or '*coloured with*'. In the US, only 3 of the 'Southampton Six' are permitted to be used in foods. E102 or Tartrazine is known as FD&C Yellow No. 5; E110 or Sunset Yellow is known as FD&C Yellow No. 6, and E129 or Allura Red is known as FD&C Red No. 40. A benefit of the US batch system means that it is possible to quantify the total weight of synthetic dyes certified and therefore make a calculation of average individual intake (mg/person) which is not possible in the EU.

The US FDA website has further information on colour additives available online: https://www.fda.gov/ForIndustry/ColorAdditives/default.htm

Canada permits the same colourings as the US.

Japan permits the following:

218 Food Yellow No.4 (Tartrazine) and its Aluminum Lake
219 Food Yellow No.5 (Sunset Yellow FCF) and its Aluminum Lake
211 Food Red No.102 (New Coccine) [Ponceau 4R]
213 Food Red No.40 (Allura Red AC) and its Aluminum Lake

https://www.ffcr.or.jp/en/tenka/list-of-designated-additives/list-of-designated-additives.html

Australia has the same numbering system as the EU and permits the use of all the 'Southampton Six' colours: https://www.foodstandards.gov.au/publications/Documents/Additives%20alpha.pdf

Table 2. Naming and regulations relating to the 'Southampton Six' food colours in different regions.

Colours							
	EU name	Tartrazine	Quinoline Yellow	Sunset Yellow	Azorubin, Carmoisine	Ponceau 4R	Allura Red AC
	E Number	E102	E104	E110	E122	E124	E129
	US Name	FD&C Yellow No. 5		FD&C Yellow No. 6			FD&C Red No. 40
	JECFA ADI (mg/kg bw)	0-7.5	0-3	0-4	0-4	0-4	0-7
	EU ADI (mg/kg bw)	0-7.5	0-3	0-4	0-4	0-0.7	0-7
	US FDA ADI (mg/kg bw)	0-5		0-3.75			0-7
UK/EU		Permitted with a warning label					
Canada			Not permitted		Not permitted	Not permitted	
USA			Not permitted		Not permitted	Not permitted	
Japan			Not permitted		Not permitted		
Australia							

2.8 The regulation and consumption of artificial food colours in the US

After reviewing evidence from the Southampton study, the US Food and Drug Administration (FDA) declined to restrict the use of Tartrazine, Sunset Yellow and Allura Red in their food supply. Unlike the EU the FDA have not imposed any requirement on manufacturers to label products containing these artificial colours with a consumer warning regarding hyperactivity in children. Specific differences between the EU and US food colour regulatory systems are outlined in detail in a review by Lehto et al (2017), with a recommendation that greater harmonisation using a precautionary principle/public health approach would assist international trade and benefit population health. Ultimately the US continues to employ '*good manufacturing practice*' (GMP) levels which results in far wider market availability of products containing artificial food colours in their own food supply and in products exported to other markets. For example one study examining the amount of artificial food colours in the American diet reported that dependent on diet, a child could easily consume in excess of 100mg of artificial food colours just by consuming two or three servings of drinks, cereal and sweets, (Stevens et al, 2015b). This is significantly in excess of the challenge doses used in the Southampton research studies that triggered behavioural reactions in some 3 year old children.

Doell et al (2016) reviewed the exposure of children aged 2-5 years to seven azo dye colour additives allowed in the US and reported mean intakes in mg/kg body weight/day among those with low, average and high consumption of foods containing the colours based on food consumption data. Reported intakes are shown below for the three colours that are included in the 'Southampton Six' definition.

Table 3: Intake of FD&C Red No.40 (Allura Red), FD&C No.5 (Tartrazine) and FD&C No.6 (Sunset Yellow) in 2-5 year old children in the US

Colour	% of children eating foods with this colour	Low exposure Mean intake mg/kg bw/day	Average exposure mg/kg bw/day	High exposure mg/kg bw/day
FD&C Red No. 40	97%	2.6	6.8	38.8
FD&C Yellow No. 5	98%	2.2	3.4	5.5
FD&C Yellow No. 6	97%	2.5	4.2	14.2

The major food groups related to intakes of these colours for 2-5 year olds were:

FD&C Red No. 40 – soft drinks, juice drinks, frozen dairy desserts, breakfast cereals, cookies, cakes and cupcakes, ice cream cones, ice pops and frozen fruit bars and fruit leathers.
FD&C Yellow No. 5 – juice drinks, soft drinks, snack foods, cakes and cupcakes, pasta-based meals from a mix, frozen dairy desserts, breakfast cereals, yoghurts and cookies.
FD&C Yellow No. 6 – soft drinks, snack foods, sports drinks, juice drinks, breakfast cereal, crackers, fruit-based desserts (jellies), pasta-based meal mixes, ice cream cones and yoghurt.

Batada et al (2018) reviewed the products containing food colours in the US and reported that the most common artificial food colours were the azo dyes Red 40 (29.8% of products), Yellow 5 (20.5%), and Yellow 6 (19.5%). The highest percentage of products with artificial colours was found in confectionery (96.3%), fruit-flavoured snacks (94%) and drink mixes/powders (89.7%).

This can be compared with research from The Netherlands, which reported a low market availability of products containing artificial colours (only 13% of all products reviewed), with those with colours found predominantly in small groceries where food was imported (Kist-van Holthe et al, 2015). In a survey of school children, the authors also reported that only 15% consumed foods with artificial food colours, and none of the colours found were the 'Southampton Six.'

The high number of children exposed to artificial colours, the common use of these colours in the food supply and the intakes among those with higher consumption of foods that are common contributors suggest potentially high levels of exposure to artificial food colours amongst children in the US.

3.0 Artificial food colours and their association with adverse behaviour in children

Artificial food colours have been linked with adverse health effects since the 1970s when Peter Feingold, an American paediatrician specialising in allergy, hypothesised that artificial food colourings and flavours as well as foods rich in salicylates might be implicated in what he called hyperkinesis and learning disabilities which would now be known as attention deficit hyperactivity disorder (ADHD) (Feingold 1975b).

Hyperactivity and attention deficit hyperactivity disorder (ADHD)

Hyperactivity is a broad term used to describe behavioural difficulties that affect learning, memory, language, emotional responses and sleep patterns. Attention deficit hyperactivity disorder (ADHD) is a behavioural disorder stemming from both biological and environmental influences, and is characterised as a spectrum of neurodevelopmental behaviours which show marked individual differences in the general population, particularly in the areas of inattention, impulsivity and over activity. ADHD is associated with other co-morbid mental and physical health conditions and is widely known to affect quality of life, productivity and life expectancy (Chorozoglou et al, 2015; Franke et al, 2018). In children it can present a significant risk to educational attainment (Kanarek, 2011; Franke et al, 2018).

The effects of hyperactivity can lead to substantially increased costs in welfare: a study of 3 year old children in England, estimated that those with high levels of hyperactivity had 17 times higher mental health, education, social and criminal justice costs compared with their non-hyperactive peers (Chorozoglou et al, 2015). According to the US Center for Disease Control (CDC) approximately 9.4% of children aged between 2-17 years had been diagnosed with ADHD in the US in 2016 (CDC, 2018). In 2016 the prevalence of ADHD in the UK was reported by Public Health England to be 1.5% of children between 5-16 years (PHE, 2016). It has been hypothesised that the lower rates of ADHD in the UK are related to both lower intakes of azo food dyes as well as lower intakes of high-fructose corn syrup (Dufault, 2018).

One of the first trials that Feingold undertook in 1973 was of 22 children based in the community with 'behavioural disorders' who had already received, and not responded positively to, some degree of behavioural or psychological therapy. His study found that eliminating foods containing artificial food colours, flavours and salicylates for a few weeks led to rapid improvements in both academic performance and behaviour. These findings were presented at the American Medical Association's annual meeting. A congressional record detailing this work is available online: www.talkingaboutthescience.com/studies/FeingoldCongressionalRecord1973.pdf/

Feingold reported improvements in approximately 40-50% of children he treated with his diet therapy and noted greater success with younger children as they appeared to respond more rapidly (3-5 days in 2-5 year olds) and had a more profound response. Reintroduction of the additives were found to reinstate symptom onset within 24-36 hours, similar to delayed reactions noted in food hypersensitivity and showed a dose-response effect, more pronounced in those with greater hypersensitivity.

Although the work of Feingold was not widely used clinically in the UK, the Feingold diet was suggested as a possible therapeutic approach by charities such as the Hyperactive Children's Support Group (HACSG) who have supported families with hyperactive conditions since 1977. The focus of HACSG's work stems from concerns that the long-term safety of food additives is not known and that food additives acting in concert, over a lifetime may have adverse effects on health and behaviour. Information on the HACSG is available at: www.hacsg.org.uk/active-or-hyperactive/what-is-the-feingold-programme

In 1978 the use of synthetic colourings in food in general was banned in Norway due to the possible effect of synthetic azo dyes on children. This was however changed in 2001 when Norway implemented the EU directives (despite not being an EU member) for trade purposes. https://www.mattilsynet.no/language/english/food_and_water/food_additives_enzymes_and_flavouringsfood_additives_enzymes_and_flavourings.10704

In 1982, Feingold authored a review on diet and behaviour which was completed only days before his death , where he set out the theories supporting the direction of his work on what he described as the biological drivers affecting behavioural disorders (Feingold, 1982). Feingold acknowledged that the presentation of learning disorders was very individual affecting behaviour, the musculoskeletal (gross and fine motor control) and cognitive systems (e.g. what we would today define as sensory processing difficulties). Feingold's rationale for removing food colours and flavours to manage hyperactivity was that they composed around 80% of all food additives used and thus could result in high dietary intakes.

In the same year that Feingold died, the National Institutes of Health (NIH, 1982) reviewed the strength of the evidence for the Feingold diet and produced a consensus summary on diet and child hyperactivity (NIH, 1982). The NIH found evidence for its effectiveness inconclusive but suggested that it may be worth pursuing the Feingold diet in some cases, with close clinical supervision to ensure that it met individual needs in a small number of children. The panel did, however, recommend changes in the law to label all food ingredients so that individuals could choose to avoid components if they chose to.

Several years after the Feingold era a meta-analysis of 23 studies which adopted the Feingold diet concluded that there was a weak and not significant effect of diet on hyperactivity (Kavale et al, 1983). A very small double blind placebo controlled study in 1990 which gave an artificial food colour free diet and challenge to 19 children noted that at the time of the trial over 3000 food additives were in use and suggested the likelihood of any single mechanism being responsible for changes in children's behaviour was very unlikely (Pollock and Warner, 1990). Despite this evidence there remained interest in whether food additives were implicated in ADHD with many anecdotal reports of improvements when food colours were eliminated from the diet. In the first decade of the new millennium food additives come under scrutiny again with further UK studies (the Isle of Wight and the Southampton studies). Until this point the research had focussed on children with diagnosed ADHD. Whilst it was already acknowledged that hyperactivity had very individual presentation, it was not known how the general population might respond to artificial food colourings. To this end two landmark studies were undertaken to investigate food additive consumption in a sample of children in the community.

3.1 The Isle of Wight study

In 2002 a research group based in Southampton, funded by the Food Standards Agency (FSA), carried out a double-blind placebo-controlled crossover food challenge study investigating the effects of artificial food colourings on 277 three year old children from the general population. The main aim of the study was to determine whether the level of hyperactivity demonstrated by the children or their hypersensitivity status (how allergic they were) influenced the effects of food additives on behaviour. The study investigators did not use the term ADHD as diagnoses were not relevant to the study methodology.

After taking a baseline measurement to screen for hyperactivity (HA) and a skin prick test for atopy (AT) the children were grouped into one of four groups: HA/AT, non-HA/AT, HA, non-AT and non-HA/non-HT. For the first week the child consumed an additive free diet, having received guidance on removing four artificial food colours, Tartrazine (E102), Sunset Yellow (E110), Carmoisine (E122), and Ponceau 4R (E124) and one preservative, sodium benzoate (E211); additives commonly found in children's food. The child's hyperactivity was measured each week for four weeks. At weeks 2 and 4, the child was given a fruit juice drink of 300mls every day that week which either contained the additives or was a placebo but was taste, smell and colour identical. Week 3 was a wash out period with no challenge drinks. The drink itself contained 5mg of each artificial food colour (totalling 20mg) and 45mg of preservative. This particular dose was chosen as it represented the amount of food colouring that would be found in two 56g bags of sweets, typical of the pack size of confectionery marketed and sold to children.

Whilst not all of the children responded to the additives and no significant difference in child behaviour was noted, the study did show that the observed effect of food additives and colourings on parent reported hyperactivity was significant and substantial and that, '…*significant changes in children's hyperactive behaviour could be produced by the removal of artificial colourings and sodium benzoate from their diet'.* The effect was found to be independent of any previous hyperactivity or atopic status and lead the researchers to conclude that there may be a benefit to removing all artificial food colours and benzoate preservatives from children's diets.

The Committee on Toxicity (COT) reviewed the Isle of Wight findings and in 2001 released a statement in which they acknowledged the findings but felt that the effect was too small to have significance. COT concluded:

> *'We acknowledge that the study is consistent with published reports of behavioural changes occurring in some children following consumption of particular food additives. We also note that the authors suggest that this may apply to children who are not considered to be hyperactive. However, we consider that it is not possible to reach firm conclusions about the clinical significance of the observed effects'*
> *https://cot.food.gov.uk/sites/default/files/cot/COTFoodAdditivesStatement.pdf*
> *[accessed 190920]*

In 2004, Schab and Trinh performed a meta-analysis of 15 double blind cross-over trials conducted between 1977 and 1994, to evaluate whether artificial food colours affected symptoms of hyperactivity in children diagnosed with hyperactive syndromes. Among subjects whose baseline diagnosis had been graded, they found a statistically significant increase or '*effect size*' of 0.28 (observed by parents, not by clinical measures) when the subjects consumed the food colours, versus the placebo. The authors noted that the magnitude of this effect size represented '*a shift from the 50th to 61st percentile of hyperactivity for the average hyperactive child in the population of trials*' when consuming artificial food colours (Schab and Trinh, 2004).

3.2 The Southampton study

The Southampton University team that had conducted the Isle of Wight study were given funding by the FSA to do further work on artificial food colours and hyperactivity. This study sought to investigate whether mixtures of certain artificial food colours and the preservative sodium benzoate would increase hyperactive behaviour of children from the general population when compared with a placebo. It also aimed to investigate relationships with age, genetic variation, and two baseline hyperactivity scores. The Southampton study involved 297 children in a double-blind, placebo-controlled trial in 3 year olds (*n*=153) and 8-9 year olds (*n*=144). The primary outcome measure was a score of 'Global Hyperactivity Aggregate' (GHA), which included a range of assessments by parents, teachers and independent observers in the classroom.

Two challenge mixes were tested. Mix A (for 3 year olds) was identical to the challenge mix from the Isle of Wight study, allowing a direct comparison of results. For 8-9 year olds, the dose of colours in mix A was increased by 25% to reflect greater food intake by older children.

Mix B included two additional artificial colours, Quinoline Yellow (E104) and Allura Red (E124), in addition to Tartrazine (E102) and Sunset Yellow (E110), and the preservative, sodium benzoate (E211). The dose of colours in mix B (8-9 year olds) was based on an estimation of average consumption of foods containing colours, assuming those foods contained colours at their maximum permitted level. For the 3 year olds to consume equivalent amounts of mix B without exceeding regulatory limits on concentration of additives, they would need to consume 500mls of drink on a daily basis. Researchers felt this would likely result in a lack of compliance, so reduced the volume of the challenge drink to 300mls, with a consequential reduction in the colour dose.

Doses were designed to be relevant to dietary consumption of these additives in these age groups in the general population, and below the existing ADIs. For comparison with the ADI, doses were expressed on a mg/kg body weight basis, calculated using average body weight data taken from the UK National Diet and Nutrition Survey. On a mg/kg bodyweight basis, 3 year olds received higher doses of mix A, where for mix B, doses were comparable.

The challenge mixes and doses are outlined in Table 4.

Table 4: Additives used in the challenge mixes in the Southampton study

Age of subject	3 year olds		8-9 year olds	
Name of mix	Mix A	Mix B	Mix A	Mix B
Additives in mix	5mg Sunset Yellow 2.5mg Carmoisine 7.5mg Tartrazine 5mg Ponceau 4R 45mg Sodium benzoate	7.5mg Sunset Yellow 7.5mg Carmoisine 7.5mg Quinoline Yellow 7.5mg Allura Red AC 45mg Sodium benzoate	6.25mg Sunset Yellow 3.12mg Carmoisine 9.36mg Tartrazine 6.25mg Ponceau 4R 45mg Sodium benzoate	15.6mg Sunset Yellow 15.6mg Carmoisine 15.6mg Quinoline Yellow 15.6mg Allura Red AC 45mg Sodium benzoate
Total dose	20mg colour 45mg preservative	30mg colour 45mg preservative	24.98mg colour 45mg preservative	62.4mg colour 45mg preservative

The challenge mix was delivered as either a 300ml or 625ml mixed fruit juice drink for the 3 year olds and 8-9 year old groups respectively and this could be drunk from a sealed bottle freely over a 24 hour period each day for the challenge week (active or placebo). As in the Isle of Wight study, the drink was colour, taste and aroma identical between the active and placebo drinks. Three commonly used measures of behaviour and attention were used to assess the children. These ratings scales were completed by parents or in the classroom. One was based on eight minutes of observation three times a week. The 8-9 year olds also took a computerised test of attention.

The findings from this study were presented as a final technical report to the Food Standards Agency before being published in The Lancet (FSA, 2007; McCann et al, 2007).

The outcomes from this study were consistent with the findings from the Isle of Wight study. For mix A, researchers found a statistically significant adverse effect (0.2 95% CI: 0.01-0.39, $p<0.05$) on the average hyperactive behaviour of 3 year old children. The size effect was greater (0.32 95% CI: 0.05-0.6, $p<0.05$) when considering only those children who had consumed at least 85% of the challenge drinks. Among the 8-9 year olds, a statistically significant difference in hyperactivity was not found among the whole sample, though a small effect was found in the cohort that consumed at least 85% of the challenge drinks, (0.12 95% CI: 0.02-0.23, $p<0.05$).

With regards to mix B, no statistically significant difference in hyperactive behaviour was found in the 3 year old group. In contrast, mix B had statistically significant adverse effects on hyperactivity in the 8-9 year old group, both in the whole sample (0.12 95% CI: 0.03-0.22 $p<0.05$) and among the cohort that consumed 85% of the challenge drinks (0.17 95% CI: 0.07-0.28 $p<0.05$).

The authors concluded that:

> *'The present findings…lend strong support for the case that food additives exacerbate hyperactive behaviours (inattention, impulsivity and over-activity) in children at least up to middle childhood'.*

In a press release which accompanied the publication of the trial data Professor Jim Stevenson, who headed the Southampton study, said:

> *'We now have clear evidence that mixtures of certain food colours and benzoate preservative can adversely influence the behaviour of children. There is some previous evidence that some children with behavioural disorders could benefit from the removal of certain food colours from their diet.' (Stevenson, Southampton University website press release, 2007).*

Sodium benzoate

The preservative sodium benzoate was included in the additive mix in the Southampton study but no voluntary guidance was made to restrict the use of this additive and no warning label is required on drinks which use this preservative. Whilst NGO supporting families with children with ADHD encouraged this additive be avoided, the Food Standards Agency did not include this additive in their voluntary guidance after the Southampton study. Sodium benzoate is used in fruit flavoured and carbonated drinks as well as energy drinks, and the removal of benzoates from soft drinks was also triggered by potential lawsuits related to the potential carcinogenic nature of this additive. In 2008 the Food Standards Agency monitored the use of preservatives in soft drinks and 166 of 250 products sampled contained sodium benzoate. Of twenty-six own brand products that contained sodium benzoate in 2008, only two still contained sodium benzoate when the study was repeated in 2013. Of the 290 supermarket own brand soft drinks listed for internet sales from four major UK supermarkets in 2013, only six contained sodium benzoate. Of the twenty-eight major international brands which were found to contain sodium benzoate in 2008, fifteen continued to contain sodium benzoate in 2013 (Saltmarsh, 2013).

Whilst some soft drink brands and supermarket own brands have replaced sodium benzoate with potassium sorbate, many products still include sodium benzoate, and this additive is also common in drinks imported to the UK (see Appendix 1). Drinks that contain benzoates can contain small amounts of the carcinogen benzene, which is thought to be the result of a reaction between benzoate and vitamin C (Piper, 2018). While sodium benzoate has been associated with asthma, allergy and ADHD, benzoate has been associated with cognitive functioning and with potential impacts on brain neurochemistry (Piper, 2018).

A study in the US looking at sodium benzoate consumption among college students in the USA reported that a high intake of sodium benzoate rich beverages may contribute to ADHD-related symptoms and called for further investigation (Beezhold et al, 2012). A review of the safety of sodium benzoate intake found associations with ADHD and allergic reactions and recommended that further studies should be undertaken to examine the health impacts of this preservative (Linke et al, 2018). Professor Peter Piper at the University of Sheffield highlighed the risks associated with the consumption of sodium benzoate but was also clear that the safety of potassium sorbate is not fully known and that benzoate and sorbate are both disruptive to the structure of biological membranes (Piper, 2018). Encouraging limited consumption of soft drinks by children in particular therefore remains prudent.

3.3 What mechanisms might explain how food colours affect behaviour?

Scientists are unclear exactly how azo dyes may act to alter behaviour. As with other studies in nutrition, psychology and psychiatry, an individual's diet and determinants of their behaviour are complex with thousands of potential confounding factors. In the 1980s it was suggested that there might be an allergic reaction explanation for ADHD (Egger et al, 1985) but scientists were unable to determine an allergic mechanism (Pelsser et al, 2009). Histamine or other mediators which might cross the blood brain barrier were variously suggested as a possible pharmacological mechanism in 1990 (Pollack and Warner, 1990) and this theme of histamine was re-examined by the Southampton team at a genetic level which found that a polymorphism in the histamine N-methyltransferase (HMNT) gene could be responsible (Stevenson et al, 2010). The debate continues to be broad and a review on mechanisms proposed three possible ways in which artificial food colours may be responsible for changes in the behaviour of children with or without ADHD: toxicological, antinutritional, and hypersensitivity mechanisms (Stevens et al, 2013).

Most recently, a report published by the Californian Office of Environmental Health Hazzard Assessment in August 2020, (OEHHA, 2020), which reviewed a number of animal toxicology studies, suggested these dyes may bind to enzymes involved in neurotransmitter pathways, effectively inhibiting their function.

It has also been suggested that there is a link between lead and mercury as contaminants in food colours, and these heavy metals have been suggested as contributory to the development of ADHD (Dufault, 2018). Zinc is required to transport lead and mercury out of the body and there is also a hypothesis that high intakes of high fructose corn syrup (HFCS) can lead to reductions in zinc intake, and as many foods contain both artificial food colours and HFCS in the US this could also be a potential mechanism for ADHD development (Dufault, 2018).

3.4 Response to the Southampton study in the UK

The Committee on Toxicity (COT) reviewed the findings and released a statement in September 2007:

> *'We consider that this study has provided supporting evidence suggesting that certain mixtures of artificial food colours together with the preservative sodium benzoate are **associated with an increase in hyperactivity in children from the general population**. If causal, this observation may be of significance for some individual children across the range of hyperactive behaviours but could be of more relevance for children towards the more hyperactive end of the scale'.*

The statement is available here: https://cot.food.gov.uk/sites/default/files/cot/colpreschil.pdf.

In an FSA web page now archived, Dr Andrew Wadge, the then FSA Chief Scientist, said:

> *'This study is a helpful additional contribution to our knowledge of the possible effects of artificial food colours on children's behaviour. After considering the COT's opinion on the research findings we have revised our advice to consumers: if a child shows signs of hyperactivity or Attention Deficit Hyperactivity Disorder (ADHD) then eliminating the colours used in the Southampton study from their diet might have some beneficial effects. However, we need to remember that there are many factors associated with hyperactive behaviour in children. These are thought to include genetic factors, being born prematurely, or environment and upbringing.*
>
> *The Agency has shared these research findings with the European Food Safety Authority (EFSA), which is currently conducting a review of the safety of all European Union permitted food colours at the request of the European Commission. This review is being undertaken because of the amount of time that has elapsed since these colours were first evaluated.*
>
> *Finally, if parents are concerned about any additives, they should remember that, by law, food additives must be listed on the label so they can make the choice to avoid the product if they want to.'*

In April 2008 the FSA issued new advice:

> *'If your child shows signs of hyperactivity....you might choose to avoid giving your child food and drinks containing the following artificial colours: Sunset Yellow (E110), Quinoline Yellow (E104), Carmoisine (E122), Allura Red (E129), Tartrazine (E102) and Ponceau 4R (E124). Parents may wish to check the labels of brightly coloured foods if they want to avoid certain colours'*

In 2008 the UK Government also instituted a voluntary ban on the 'Southampton Six' colours, encouraging food manufacturers and retailers to reformulate foods (Food Commission, 2008).

In 2011, the FSA published guidelines outlining alternative approaches available to industry in the light of voluntary removal in order to assist reformulation (FSA, 2011). These included naturally derived colours and colouring foodstuffs which could replicate the intensity of the reds, yellow and orange colours associated with the 'Southampton Six' colours.

The FSA committed to sharing information about how to find foods free of the 'Southampton Six' colours in a continuously updated list of manufacturers, retailers, caterers and restaurants who had committed to remove the colours from their ranges to assist parents. The FSA stopped doing this in 2014 and no information is currently available.

3.5 The European response

In 2008 the EFSA panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials set up a working party to evaluate the Southampton findings. In their response: (http://www.efsa.europa.eu/press/news/080314) they concluded there was a small, but not consistent, effect, with large variation. Based on this EFSA determined that there was not sufficient evidence at that time to change the ADIs for the 'Southampton Six' food colours or sodium benzoate.

It was concluded that the Southampton data could not be used as a basis for altering the acceptable daily intake (ADI) of the respective food colours or sodium benzoate because the additives had been administered in combinations so that the effect could not be ascribed to individual colours.

> *'The Panel concludes that the McCann et al. study provides limited evidence that the two different mixtures of synthetic colours and sodium benzoate tested had a small and statistically significant effect on activity and attention in children selected from the general population excluding children medicated for ADHD…..' (EFSA, 2008)*

In July 2008 however MEP's within the European Parliament voted in favour of labelling changes. Regulation 1333/2008 required that from the 20th July 2010 all pre-packaged food and drink containing one or more of the following six food colours, Sunset Yellow (E 110), Quinoline Yellow (E 104), Carmoisine (E 122), Allura Red (E 129), Tartrazine (E 102) or Ponceau 4R (E 124) are required to be labelled with the following additional information: Name or E-number of the colour(s) (e.g. Sunset Yellow): '*may have an adverse effect on activity and attention in children*'.

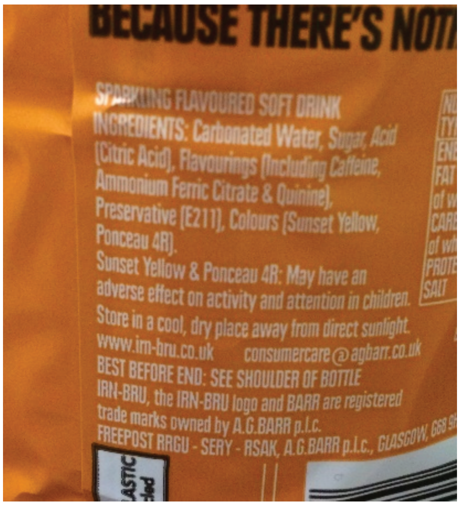
It was hoped that a warning label would assist consumer choice and discourage sales of these products to further incentivise manufacturers to stop adding them to foods. This move was in part due to extensive lobbying by child health and public health NGOs across Europe.

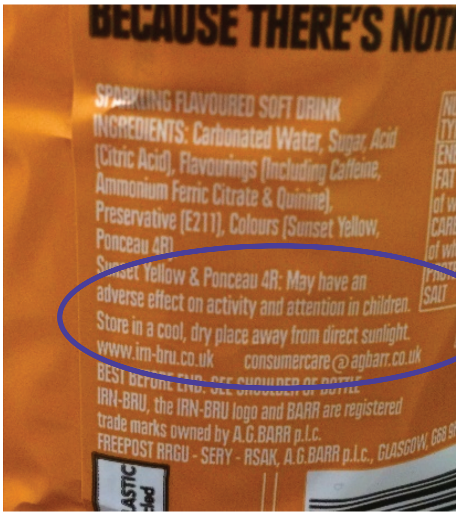
The warning message applies to all pre-packaged food and drink products, with the exception of foods where the colour(s) has been used for the purposes of health or other marking on meat products or for stamping or decorative colouring on eggshells. In addition, alcoholic drinks containing alcohol above 1.2% by volume do not need to carry the warning. The information provided must comply with Article 13(1) of Regulation 1169/2011, i.e. it must be easy to understand and marked in a conspicuous place in such a way as to be easily visible, clearly legible and where appropriate indelible. It could be argued however that this aspect of the labelling has not been successfully introduced.

The problem with the warning label

Despite the requirement for a warning on food labels that are easily visible and clearly legible, these are often hard to read as they are in small font and tend to be found on the back of food packaging. Whilst some manufacturers choose to highlight the presence of no artificial colours, there was no commonly adopted logo which would have made it clear whether a food contained artificial colours or not. A simple warning symbol would also make it easier for citizens to avoid products.

Current example of a warning label on a soft drink





Warning label we would like to see on packaging:

⚠ **E102, E104, E110, E122, E124, E129** MAY HAVE AN ADVERSE EFFECT ON ACTIVITY AND ATTENTION IN CHILDREN

Notes: minimum 11pt font. E numbers linked to hyperactivity in bold. Warning must be clearly visible on the packaging and in a different colour type to the ingredients list. A warning symbol should be used.

3.6 The UK civil society response

The Southampton studies were a catalyst for campaigning action both in Europe and the US. Parent groups such as the Hyperactive Children's Support Group (HASCG) who had historically supported the Feingold diet and were open to the concept of additive free diets were joined in the UK by a campaigning group '*Action on Additives*' and these groups pushed for a mandatory ban on the 'Southampton Six' food colours. Campaign groups believed that there was no risk or cost to remove these colours from a child's diet, given that they were of no nutritional value, and that the benefit of removal, even if small, was a worthwhile venture.

'*Action on Additives*' was established by The Food Commission in April 2008 with the aim of raising awareness of the health risks of food additives to children and helping to engage parents and schools to spot artificial food colours, flavourings and sweeteners in foods, drinks and medicines. In a survey of UK products at that time the Food Commission found over 1,000 products containing artificial food colours.

Anna Glayzer, who was co-ordinator of the Food Commission's Action on Additives Campaign commented:

> *'From the point of view of the consumer however, it remains impossible to measure what quantity of any of these additives one is consuming as levels are not indicated on labels. These colours are totally unnecessary in foods. We continue to call for a mandatory ban.' (Food Commission, 2008)*

The Food Commission ceased activities in 2011.

3.7 The response of other countries to the Southampton study

Prompted by the results of the 2007 Southampton study, the Center for Science in the Public Interest (CSPI) petitioned the US FDA to reconsider the evidence linking approved azo dyes (for use within the US food, drug and cosmetics industries) to adverse behavioural effects in children (CSPI, 2008). The CSPI argued that based on the UK evidence, the use of some artificial colourings in foods contributed to behavioural issues in children and should be banned.

In 2011, the FDA responded with a public hearing to examine whether a causal relationship existed between the consumption of US certified colour additives in food and hyperactivity in children in the general population. The FDA concluded that there was not enough evidence to demonstrate causality between consumption of dyes and hyperactivity and as such, warning labels would not be required. This decision was however criticized in a review by an academic working in environmental health. Weiss argued that the scope of the FDA review was too narrowly defined, focussing solely on whether artificial food colours caused ADHD, as opposed to adverse behavioural issues among the general population of children. In his opinion this framing and consequent inaction failed to consider the response of vulnerable subgroups (including those with enhanced sensitivity) and indeed the general population itself which the Southampton study had shown could be adversely affected by consuming certain artificial colour additives (Weiss, 2012).

Food Standards Australia and New Zealand used the US response to come to its conclusion that there should be no mandatory warning label on foods containing the 'Southampton Six' artificial food colours, stating that the food colours have been used safely for decades and that intakes are low: https://www.foodstandards.gov.au/consumer/additives/foodcolour/Pages/default.aspx

In 2019[1] however the FDA requested the Science Board to look again at colour additives and their effects on children asking them to review:

1 Whether the latest science establishes a link between the consumption of the permissible azo food dyes in foods by children in the general population and adverse effects on their behaviour.
2 Whether the latest science establishes that the use of artificial food colour exclusions is an efficacious dietary treatment in the non-pharmacological treatment of children with ADHD and
3 Whether since 2011 there has been any new considerations in terms of a study or tool intended to test the hypothesis that there is a causal link between individual color additives and ADHD in children.

This request coincided with a risk assessment on the potential of impacts of synthetic food dyes in children, commissioned by the California Legislature in 2018. The review considered seven out of nine FDA batch certified dyes, including Yellow 5, Yellow 6 and Red 40. This report was published in August 2020 (OEHHA, 2020). The report considers additional clinical trials using synthetic dyes with neurobehavioral outcomes in children, and also laboratory studies of neurotoxic effects in developing animals, that were published after the FDA's review in 2011.

In contrast to the position of the FDA, the report concludes with 'high confidence' that epidemiologic evidence shows some synthetic dyes impact neurobehavior in children. Moreover, this is supported by biologically plausible mechanisms of action for neurotoxicity, based on recent animal studies. Crucially, although their exposure assessment found that child intake estimates of synthetic dyes did not exceed the US FDA ADIs, a number of mature animal studies and animal developmental toxicology studies showed evidence of adverse behavioural effects at doses lower than the NOAEL, used by the FDA to establish those ADIs.

Specifically, this review concludes:

- In human studies, there is evidence of a relationship between synthetic food dye exposure and adverse behavioural outcomes in children, ***both with and without pre-existing behavioural disorders.***
- In animal studies (despite varying methodologies with different exposure regimens) a wide range of effects on activity, learning and memory, neurotransmitter pathways, brain histomorphology and stereology, provides evidence of changes in behaviour, and these changes suggest that the synthetic food dyes may contribute to adverse behavioural effects in children.
- For several dyes, notably FD&C Red No. 40, the existing ADIs should be considerably lower.

[1] https://www.fda.gov/media/131378/download

- At a minimum, in the short-term, the neurobehavioral effects of synthetic food dyes in children should be acknowledged and steps taken to reduce exposure to these dyes in children

'Although the effects are transient or short-term in nature, for the child who is affected and their family, their teachers, and the school system, a short-term increase in inattentiveness or restlessness and anxiety that is repeated routinely when food dye is consumed is adverse'.

3.8 Studies since the Southampton study

Since the UK voluntary ban work has continued in this area. A further double blind placebo controlled crossover study investigating the role of genetic polymorphisms in the varying responses to giving food colours and preservatives to 3 and 8-9 year old children was conducted by the team that did the Southampton study, and it was reported that a histamine polymorphism may in part explain variation in behaviour response to food colours and sodium benzoate (Stevenson et al, 2010).

A meta-analysis of 24 trials, in part funded by the National Confectioners Association, determined that approximately 8% of children with ADHD may experience symptoms of ADHD because of artificial food colours (Nigg et al, 2012). They concluded that although evidence of an effect was '*too substantial to dismiss*' as there was a notable effect it was also *'too weak to justify a strong precautionary stance'*. This review however included small trials, with some publication bias, and it is common for industry to justify inaction. Whilst it found only a small average effect size at a clinical level, it conceded that the effect size could be '*quite substantial from the perspective of population wide preventative efforts.*'

As part of a wider investigation into non-pharmacological treatments for ADHD, Sonuga-Barke et al (2013) considered whether dietary exclusion of artificial colours in participants with a diagnosis of ADHD is an effective treatment to reduce the severity of symptoms. The meta-analysis reviewed 8 studies and concluded that exclusion of artificial food colours had modest but statistically significant effects on ADHD symptoms.

Some studies continue to show no adverse effects of artificial food colours in children however. A placebo controlled trial of 137 children from Hong Kong who took one of two capsules containing either artificial food colours or sodium benzoate found no adverse effect compared with placebo on two behaviour scores (an ADHD strengths and weaknesses and normal behaviour score and a child behaviour checklist teacher report form) (Lok et al, 2013). Most recently artificial food colours have been one of the subjects of a systematic review of 14 meta analyses of double blind placebo controlled trials evaluating the efficacy of diet interventions on the behaviour of children with ADHD (Pelsser et al, 2017). These authors concluded that the evidence does not warrant the removal of artificial food colours as an intervention, but consensus appears to be moving towards treating the removal of artificial food colours as a public health rather than a treatment issue.

3.9 What we don't know about potential for harm from food colours in the food supply

Despite a growing body of literature associating the consumption of some azo dyes with genotoxic and carcinogenic effects and more specifically the 'Southampton Six' azo dyes with hyperactivity, there are limitations on what is known regarding the effect of artificial food colours on children in the general population. As such, there may be potential for harm at exposure levels below the current ADIs.

Although evaluated for safe use, there is a lack of available evidence on some azo dyes that have not been the subject of clinical trials with neurobehavioral end points in children. In addition, the largest trials that have associated the 'Southampton Six' dyes with adverse behavioural effects used a mix of dyes, and sodium benzoate in the challenge doses, so the effects of individual dyes have not been elicited. As such, the synergistic action of a mixture of artificial colours versus individual colours has not been characterised. Further, although there is evidence of a dose-response relationship with regard to consumption of tartrazine and adverse behavioural effects (Rowe and Rowe, 1984) the exact nature of this relationship, with regard to individual and mixtures of dyes requires more systematic exploration (Arnold et al, 2012). Under the existing UK regulatory framework where these colours are permitted for use, given some colours are more prevalent in the food supply (Doell et al, 2016), this would be useful information in future risk assessments.

A key concern relates to the lack of data on long term or chronic consumption of azo dyes. Studies to date have examined the effects of acute exposure to dyes over a short period. It is unknown whether there is a different cumulative risk of chronic, repeated and long-term exposure to colours (Schab and Trinh 2004; Stevenson, 2009; Weiss, 2012).

The pharmacokinetics of azo dyes in children's bodies is not understood. As the distribution and absorption of chemicals can differ in children's bodies, there is concern that artificial colours may penetrate more easily into tissues and organs from the blood stream (Martyn et al, 2013). Given that key organ systems are developing in young bodies, developmental processes may be disrupted by exposure to these chemicals (Trasande et al, 2018).

4.0 Artificial food colours in the UK food supply chain

> *'From an initial use of E numbers in ingredient lists, manufacturers are increasingly using the names of additives. This trend is being extended to avoid the use of anything the consumer might consider an additive, particularly in connection with colours and preservatives. Specifically, the colours used in the Southampton study on the impact of food colours on hyperactivity in children have largely been replaced by colouring foodstuffs, and the preservative used in the study, sodium benzoate, has been replaced by potassium sorbate in the majority of soft drinks'*
> *(Saltmarsh, 2015)*

As a result of the Southampton study, the FSA asked manufacturers to stop using the six colours used in the study, and continued to encourage the food industry to use natural alternatives. Consequently, these colours are now much harder to find on the supermarket shelves and credit goes to the supermarkets and manufacturers who found alternative natural sources of colour for food and drink products. A 2013 survey of the products most likely to contain food colourings, soft drinks and sugar-based confectionery, showed that of 290 supermarket own brand soft drinks, there were no products containing the 'Southampton Six' food colours (Saltmarsh, 2013).

4.1 Where can the 'Southampton Six' colours still be found in the UK food supply?

One way in which food colours can slip into the food system is because manufacturers, aware of the consumer fear of E numbers, have tended to label artificial food colours by their name, rather than their E number as it sounds less alarming (Saltmarsh, 2015).

For example Irn-Bru, a popular soft drink in Scotland still contains azo dyes and sodium benzoate and labels its products as containing: Carbonated Water, Sugar, Acid (Citric Acid), Flavourings (Including Caffeine, Ammonium Ferric Citrate & Quinine), Sweeteners (Aspartame, Acesulfame K), Preservative (**E211**), Colours (**Sunset Yellow FCF, Ponceau 4R**).

Another main brand drink in the UK which still contains azo dyes is Lucozade original – which also names colours on its label: Carbonated Water, Glucose Syrup (13%), Acids (Citric Acid, Lactic Acid), Acidity Regulator (Sodium Citrate), Preservative (Potassium Sorbate), Caffeine, Sweeteners (Aspartame, Acesulfame-K), Antioxidant (Ascorbic Acid), Colours (**Sunset Yellow, Ponceau 4R**), Flavourings

Within the UK some smaller food manufacturers and suppliers continue to produce foods and drinks with artificial food colours, and many of these continue to be manufactured directly for, and marketed directly to, children. Some confectionery wholesalers still sell a variety of sweets with azo dye colouring, and many of these may be sold in a way that a warning label cannot be easily seen. Whilst smaller manufacturers may lack the scale of the large retailers to reformulate, the reality is that it is possible to remove azo dyes with virtually no economic or public health cost. The lack of any incentive or drive from the FSA in recent years, and limited public discussion of the issue means that many of the smaller manufacturers have not felt an incentive to remove colours, and newer families may be less aware of the need to avoid the 'Southampton Six' colours. Table 5 shows some products found in UK supermarkets that contain the 'Southampton Six' colours.

Table 5: Examples of products containing the 'Southampton Six' azo dyes for sale in the UK

Type of Food	Product Name		'Southampton Six' colours as listed on the ingredients list
Confectionery	Mike & Ike Mega Mix		Tartrazine Allura Red Sunset Yellow
	Crazy Candy Factory Strawberry Lances		E122 E129
	Jolly Rancher Chews		Red 40 Yellow 5 Yellow 6
	Wonka Rainbow Nerds		Allura Red (E129) Tartrazine (E102) Sunset Yellow (E110)
Baked Goods	Pearl's Cafe Iced Bakewell Tarts		Sunset Yellow Ponceau 4R
Baking Decoration	Baked With Love 10 Pack Unicorn Decorations		E102 E122 E129

Type of Food	Product Name		'Southampton Six' colours as listed on the ingredients list
Baking Decoration cont'd	Cake Decor Cake Pens 16G		E102 E110 E120 E129
Breakfast Cereals	Lucky Charms		Tartrazine Sunset Yellow Allura Red
	Malt-O-Meal Marshmallow Mateys		Tartrazine (E102) Sunset Yellow (E110) Allura Red (E129)
Soft Drinks	Irn Bru		Sunset Yellow Ponceau 4R
	Nashs Red Lemonade		E110
	Bigga Fruit Punch		Allura Red Sunset Yellow

5.0 Brexit and future risks of changes to the UK food supply

Regulations on the use of food colours, permitted levels and product labelling vary between countries and trading blocks. The international guidelines established by the Joint Expert Committee on Food Additives (JECFA) (administered by FAO and WHO) sets standards globally. The WHO International Programme on Chemical Safety (IPCS) also assesses the health impact of chemicals in food. Although these international guidelines are recognised, they are not necessarily translated into national and regional frameworks of regulations, standards and procedures designed to ensure food safety. It follows that as trade agreements are structured in the wake of Brexit, there will be an additional challenge around compliance to the existing EU regulatory framework and the precautionary approach to artificial food colours, if these standards are not met by trading partners.

Artificial colours are commonplace within the global food supply. However, as a result of the UK voluntary ban and the EU regulation on the labelling of foods that contain the 'Southampton Six', market availability of foods and drinks containing these colours in the UK is low (Saltmarsh, 2015). This is supported by evidence of exposure in children in Ireland, (a market likely to be representative of the UK) (Connolly et al, 2010) and The Netherlands (Kist-van Holthe et al, 2015), where estimated intakes of food colour additives in children were in the majority of cases, below the doses used in the Southampton study and foods containing the colours were not commonly found.

Exposure studies, using similar methodologies, conducted in multiple markets, including the US (Doell et al, 2016) and Australia and New Zealand (FSANZ, 2008) have also concluded that exposure in children is below the established ADIs, even in high use scenarios. However, inherent in the conclusions of these studies is that the ADIs set by the FDA and the JECFA, are adequate to protect young children. This notion has been challenged on the basis that both the methodology and the scale of acceptable daily intake are flawed (Martyn et al, 2013; Lefferts and Stevenson, 2017; Trasande et al, 2018). The ADIs are based on chronic toxicity tests performed in animals; they do not assess neurobehavioral outcomes (Lefferts and Stevenson, 2017; Trasande et al, 2018). Additionally, a test animal may not accurately reflect the potential for harm in immature and developing organ systems (Martyn et al, 2013; Trasande et al, 2018). It is also not known whether there is a different cumulative risk of repeated and long-term exposure to colours (Stevenson, 2009).

The ADIs also establish permitted exposures far greater than doses shown in randomised trials to have an adverse effect: the JECFA ADI would permit a cumulative intake of 355.5mg day (based on a 15kg child) of artificial colours. Conversely, challenge doses of 20 and 30mg produced statistically significant adverse behavioural outcomes in children in studies including the landmark Southampton studies. One study has shown evidence of a dose response relationship, with adverse behavioural effects observed over a range of doses of tartrazine from 1 to 50mg/kg (Rowe and Rowe, 1994).

Over and above these unsettled issues with the ADI, there is evidence of wide scale availability of artificial colours in the food supply outside the EU, specifically in ultra-processed foods marketed to children. In the US the prevalence of child-oriented products containing artificial colours in a grocery store in North Carolina reported that 43% of products marketed to children contained Allura Red, Sunset Yellow and Tartrazine, with these colourings accounting for 90% of all colours used (Batada and Jacobsen, 2016). Categories with the highest proportions of artificial food colourings were confectionery, fruit flavoured snacks and drink mixes/powders.

5.1 Products containing azo dyes in the US which don't in the EU

Many international food companies reformulated foods without the 'Southampton Six' colours for sale in the EU but did not do the same for foods marketed elsewhere. Many have made claims that they will remove these dyes but have been slow and inconsistent in doing so. Table 6 shows the same or closely related products marketed in the US and UK and how their colourings vary.

Table 6. Examples of foods and drinks marketed in the US with azo dyes that have been removed for products sold in the UK

	US	'Southampton Six' colours	UK	Colours used instead of 'Southampton Six'
Kellogg's Pop Tarts Frosted Strawberry Sensation		Yellow 6 Red 40		Beetroot Red Annatto Paprika Extract
Kellogg's froot Loops		Yellow 5 Yellow 6 Red 40		Carotenoids
Fanta Orange		Yellow 6 Red 40		Carrot Pumpkin
Sunny D Tangy Original & Sunny D Citrus Fusion		Yellow 5 Yellow 6		Beta Carotene
Haribo Goldbears		Yellow 5 Red 40		Fruit and plant concentrates
Milk Chocolate M&Ms		Yellow 5 Yellow 5 Lake Yellow 6 Yellow 6 Lake Red 40 Lake		Carotenoids Cochineal

5.2 Foods marketed for children in the US that contain azo dyes

Many foods sold to children on the US market contain 'Southampton Six' azo dyes and some examples are given below.

Table 7: Examples of food and drink made in the US that contain 'Southampton Six' colours

Type of Food	Product Name		'Southampton Six' colours
Confectionery	Starburst		Yellow 5 Red 40
	Original Skittles		Yellow 5 Yellow 6 Red 40
Cereals	Lucky Charms		Yellow 5 Yellow 6 Red 40
	Quaker Cap'n Crunch Crunch Berries		Yellow 5 Yellow 6 Red 40
Powdered Drinks	Kool-Aid on the Go		Yellow 5 Yellow 6 Red 40
	Sunkist Orange		Yellow 5 Red 40
	Welch's Strawberry Peach juice Low calorie drink mix		Yellow 6 Red 40

Type of Food	Product Name		'Southampton Six' colours
Fruit Snacks	Kellogg's Fruity Snacks		Red 40
	Kellogg's Paw Patrol Fruit snacks		Yellow 5 Red 40
	Welch's Fruit Snacks		Red 40
Cake mixes, biscuits and desserts	The Original Circus Animal Cookies		Yellow 5 Yellow 6 Red 40
	Stauffer's Animal Cookies Iced		Red 40
	Betty Crocker Super Moist Strawberry cake mix		Red 40
	Great Value Deluxe Moist Confetti cake mix		Yellow 5 Yellow 6 Red 40
	Jell-O strawberry		Red 40

How much colour do these products contain?

20 mg of artificial food colours (Mix A) in the Southampton study produced an adverse effect in the behaviour of 3 year olds. For comparison, one serving of Skittles (61.5g) sold in the US contains more than 1.5 times the challenge dose, containing 33.3mg of artificial food colours (Stevens et al, 2015b). One serving of Kellogg's Froot loops (27g) or Cap'n Crunch's Crunch Berries (26g) would be almost equivalent to the challenge dose of Mix A, providing 14.6mg and 17mg artificial food colours per serving, respectively. Given the amounts of artificial food colours in these foods, the total amounts consumed on a daily basis 'could easily exceed 100mg depending on the child and particular diet' (Stevens et al, 2015b).

6.0 Conclusion

A body of research evidence suggests that the use of some azo dyes in food and drink may have an adverse effect on the health and development of children. These dyes are not needed and can be easily replaced in foods, and their removal should be a matter of urgency for all food and drink manufacturers globally.

Children, particularly pre-school children, may be particularly susceptible to the effects of azo dyes, and have higher relative exposures compared with adults. Metabolic systems and key organ systems are still developing, and undergoing substantial changes, during childhood and are vulnerable to disruptions. The long term impact on children and any cumulative risk of repeated and long term exposure remains unknown. Children who consume larger amounts of ultra-processed foods and children in poorer households may be at greater risk of frequent exposure to azo dyes in foods. In addition to evidence showing that the artificial colours known as the 'Southampton Six' can cause adverse behaviour in some children, artificial food colours disguise the absence of nutritious ingredients and make ultra-processed foods (and frequently sweet foods) more appealing.

There are simply too many unknowns about the impact of all azo dyes on child health to allow the food chain to contain unnecessary artificial colours. Consumers cannot measure consumption levels and warning labels offer limited protection. The precautionary principle needs to be used in all decision making on the safety of unnecessary food additives.

Appendix 1

Examples of soft drinks containing the preservative sodium benzoate (E211) commonly available in UK retail outlets

Brand	Products
Vimto	Vimto sparkling, Vimto fizzy, Vim2O, Vimto original squash, Vimto remix squash
R Whites	Lemonade
7-Up	7-Up free cherry flavour
Oasis	Summer fruits, Summer fruits zero, Citrus punch, Citrus punch zero. Blackcurrant apple,
Irn Bru	Irn Bru, Irn Bru Extra, Irn Bru sugar free, Irn Bru no sugar energy,
Rubicon	Sparkling mango, Sparkling passion fruit, Sparkling guava, Sparkling lychee
Old Jamaica	Ginger beer, Ginger beer light, Ginger beer extra fiery, Grape soda, Sparkling pineapple soda, Cream soda
Ben Shaw's	Root beer, Cloudy lemonade, Dandelion and burdock, Cream soda,
Ka	Sparkling fruit punch, Karibbean Kola, Sparkling pineapple, Sparkling black grape, Sparkling strawberry

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