Food additives and preschool children

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Food additives have been used throughout history to perform specific functions in foods. A comprehensive framework of legislation is in place within Europe to control the use of additives in the food supply and ensure they pose no risk to human health. Further to this, exposure assessments are regularly carried out to monitor population intakes and verify that intakes are not above acceptable levels (acceptable daily intakes). Young children may have a higher dietary exposure to chemicals than adults due to a combination of rapid growth rates and distinct food intake patterns. For this reason, exposure assessments are particularly important in this age group. The paper will review the use of additives and exposure assessment methods and examine factors that affect dietary exposure by young children. One of the most widely investigated unfavourable health effects associated with food additive intake in preschool-aged children are suggested adverse behavioural effects. Research that has examined this relationship has reported a variety of responses, with many noting an increase in hyperactivity as reported by parents but not when assessed using objective examiners. This review has examined the experimental approaches used in such studies and suggests that efforts are needed to standardise objective methods of measuring behaviour in preschool children. Further to this, a more holistic approach to examining food additive intakes by preschool children is advisable, where overall exposure is considered rather than focusing solely on behavioural effects and possibly examining intakes of food additives other than food colours.

Historically, there is a strong tradition of adding ingredients or substances to foods to perform a specific function. The first records of these ‘additives’ can be traced back to Ancient Egyptian papyri circa 1500 bc, which illustrate the use of spices in foods to flavour and make them more appealing1; the Egyptians were also responsible for improving the bread-making process by adding yeast from brewing beer to allow the bread to rise2. In the nineteenth century, the first modern baking powder was developed in the UK3. Used to replace yeast in baking, this leavening substance which contains bicarbonate of soda (E500), allowed the production of more predictable and consistent manufactured goods3. This consistency of products was a key development of food production during the Industrial Revolution that saw a shift from household food production to large-scale factory manufacturing4. In recent decades, there have been rapid developments in food science and technology, leading to an increase in the number and variety of substances used to perform functions in food or ‘food additives’5. Currently 322 food additives are approved for use in the European Union6.

Definitions and uses
Under European regulation (EC) No. 1333/2008, food additives are defined as any substances ‘not normally consumed as food itself’ which are added to a food to perform a technological purpose e.g. preservation7. There are twenty-six categories of food additives outlined in this regulation, which fall broadly into two main categories depending on their purpose (i) safety and prevention of

Abbreviations: ADI, acceptable daily intake.
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degradation of food by bacteria, oxidation or chemical reactions or (ii) improvement of the taste, appearance or mouth-feel of the product(8). The main aim of the food industry is to produce a variety of consistently safe, appealing and nutritious products; the use of additives is a key factor in achieving this5,8. Apart from the basic functions of additives, there are additional benefits of their use e.g. the use of non-nutritive sweeteners to reduce the sugar content of food, thereby potentially reducing the occurrence of dental caries and the energy content of foods9,10.

Legislation

Throughout history, in order to ensure the safety of substances that are added intentionally to foods, e.g. additives, legislation regarding their use has been required. The first record of legislation relating to the ingredients that could be added to foods or beverages was the German Reinheitsgebot law, dating from 1516, which governed the purity of beer ingredients11. Since then, the use of legislation has been enforced to regulate the action of food producers and safeguard the health of the general public.

Currently in Europe, there is a complex framework of guidelines regulating the use of additives, their purity12–14, the foods to which they can be added6,7, the maximum amounts to be used (maximum permitted levels)6,7 and labelling of such products15. E numbers are a standard coding system used to indicate that these food chemicals have been evaluated and approved for use8,16. Within Europe, this is completed by the European Food Safety Authority’s Panel on Food Additives and Nutrient Sources Added to Food17. Each E number is assigned a maximum permitted level based on scientific evidence relating to safe usage levels, which must account for ‘the intake of the food additive from other sources and the exposure to the food additive by special groups of consumers’17. Globally, there are a number of bodies which carry out similar roles, e.g. the Joint Expert Committee on Food Additives and the WHO33,34. Nevertheless, controversy and consumer debate regarding the use of food additives have recently led to the phenomenon known as ‘clean label’ products whereby food manufacturers alter the formulation of foodstuffs to produce products that are free from artificial food additives8. While these products are not clearly defined in legislation, they have been described as products that are ‘free from artificial ingredients’ or ‘use ingredients which are familiar to the consumer’35. This has led to a search for ‘natural’ alternatives to artificial additives36. However, often more complex processing of ingredients and higher quantities of alternative ingredients are needed to obtain a ‘clean’ label35. Efforts are needed to educate consumers about what clean labels are and to reaffirm safety concerns regarding the use of additives.

Food chemical exposure

Additives are just one type of food chemical found in the food supply37. They are added intentionally during manufacture to fulfil a function; however, chemicals may also be added unintentionally, e.g. pesticides, or they may be present naturally, e.g. phytochemicals38. All chemicals are potentially toxic39; in order to determine the levels that should be used in foods, the minimum level of exposure above which unfavourable health effects may occur is calculated. This level is known as the No Observed Adverse Effect Level (NOAEL) and is determined primarily using animal-based studies39,40. Safety factors are applied to the NOAEL (100-fold) which account for interspecies differences between the test animal and human subjects (10-fold) and intraspecies variability among human subjects, considering sensitive populations (10-fold)39,40. This yields the acceptable daily intake (ADI) value for the chemical. The ADI is defined as ‘the amount of a substance that people can consume on a daily basis during their whole life without any appreciable risk to health. ADIs are usually expressed in mg per kg of body weight per day (mg/kg body weight/day)41. The European Food Safety Authority Panel on Food Additives and Nutrient Sources Added to Food regularly carry out exposure assessments to either determine if population intakes of chemicals exceed the ADI or to monitor patterns of dietary chemical exposure among the general public8,21. Once these assessments have been completed, any potential risks to health can be assessed and analysed.

Controversy and clean labels

Despite this complex framework of regulation and the ongoing safety assessments regarding the use of additives in food, there remains a high level of interest in the use of these chemicals in foods and in some cases concern and confusion about their use. The main concerns are related to intolerances and carcinogenicity. Food additive intolerances can be defined as adverse reactions to additives which are not mediated through the immune system21; whereas associations with cancer relate to proposed genotoxic effects. Two examples of additives that have been widely investigated are aspartame (E951), a sugar replacer22, and monosodium glutamate (E621), a flavour enhancer23. Over the past number of decades, both of these additives have been subject to in-depth investigations regarding their intakes and effects on health24–31. However, recent reviews have confirmed that there are no safety concerns regarding the use of either additive22,32, and monosodium glutamate was placed on the safest list of food additives by the Joint Expert Committee on Food Additives and the WHO33,34. Nevertheless, controversy and consumer debate regarding the use of food additives have recently led to the phenomenon known as ‘clean label’ products whereby food manufacturers alter the formulation of foodstuffs to produce products that are free from artificial food additives8. While these products are not clearly defined in legislation, they have been described as products that are ‘free from artificial ingredients’ or ‘use ingredients which are familiar to the consumer’35. This has led to a search for ‘natural’ alternatives to artificial additives36. However, often more complex processing of ingredients and higher quantities of alternative ingredients are needed to obtain a ‘clean’ label35. Efforts are needed to educate consumers about what clean labels are and to reaffirm safety concerns regarding the use of additives.

Risk analysis

Risk analysis is the structured approach of assessing risks to human health and safety42. With regard to food
Safe and adequate nutrition is crucial for the proper development of children. As outlined earlier, the safety of additive-containing foods is ensured via legislation and safety assessments. However, some studies have suggested that children may have increased exposure and consumption of certain food additives, in comparison with adults, and are therefore an important subgroup that should be addressed by exposure assessments.

In addition to the standard factors that are considered regarding these assessments for the general population, there are additional factors that need to be accounted for with analysing exposure by children, as outlined below.

**Rapid growth and development**

Childhood, particularly the preschool years, is a time of rapid growth and development. It is a period when many key organ and tissue systems in the body grow and mature. Thus, the potential exists for these developmental processes to be disrupted by exposure to chemicals in high doses. Young children may be more vulnerable than adults to chemical exposures as a result of their immature organ systems, rapid physical development and higher metabolic rates. Furthermore, metabolic processes may differ between children and adults, as, per kilogram body weight, smaller organs usually need more oxygen and nutrients than adult organs. Finally, the distribution and absorption of chemicals throughout the body can differ, e.g. water-soluble substances are distributed over a relatively greater volume within the body of a child in comparison with that of an adult and can penetrate more easily into tissues and organs from the bloodstream.

**Higher intakes of foods/beverages**

This rapid growth and development increases a child’s energy and nutrient requirements per kilogram body weight compared with those of adults (up to 5-fold), which results in higher food intakes on a body weight basis. The preschool age is also associated with a change in dietary habits with the introduction of ‘table’ foods in place of a milk-based diet. Therefore preschoolers consume a greater number of foods and are exposed to a wider range of food chemicals, in comparison with infants. Further to this, the more limited range of foodstuffs consumed during childhood may lead to higher intakes of additives which are present in specific, highly consumed foods. The combination of these factors means that preschool children are likely to be the population group with the highest exposure to chemicals in the diet.

**Toxicokinetic and toxicodynamic factors**

As discussed earlier, the ADI is established based on animal studies. When considering intakes of chemicals by young children, it is important to account for the fact that developmental changes in human infants and children may not be reflective of changes observed in the test animal.
species(39). In addition, there may be differences in the magnitude of the toxic response to chemicals between adults and children due to variations in the way that substances are absorbed, distributed, metabolised and excreted by the body (toxicokinetics) and target organ sensitivity, cytoprotective mechanisms, and homeostatic control (toxicodynamics)(39,56,58). It is for this reason that uncertainty or safety factors are applied to the NOAEL when establishing the ADI value for a chemical(58).

While each of these factors emphasises the reasons why children may be at increased risk of chemical exposure than adults, it is important to note that the differences in metabolism and excretion of chemicals may not always increase exposure. Compounds may be metabolised and eliminated more quickly from the body given the larger liver mass in relation to body mass and increased blood flow through the liver(54). A report by the International Life Sciences Institute Europe Acceptable Daily Intake Task Force concluded that special safety ADI are not required for children; however, due to the higher intakes of foods, as described earlier, exposure should be monitored for this age group(56).

### Exposure assessments in preschool children

Prior to 2008, there was a low number of dietary exposure assessment studies among children, which led to the establishment of the 'Individual food consumption data and exposure assessment studies for Children' (EXPOCHI) project within Europe(50). This European Food Safety Authority-funded project developed a network of databases from various countries in Europe which could be linked to carry out long term exposure assessments for children aged 1–14 years(50). To date, four different risk assessments have been carried out (Pb, Cr, Se and food colours). Their report on food colours(59) utilised food consumption data from eleven countries to examine long-term exposure to forty different food colourings. This report illustrated that different countries had different levels of exposure and emphasised the need for a harmonised approach in food consumption data collection within Europe.

Detailed exposure assessments are also conducted at a national level as in the UK. Lawrie(56) examined intakes of saccharin, a sweetener, using food consumption data from the National Diet and Nutrition Survey(56) and chemical information from manufacturers. At the 97.5th percentile, intakes of saccharin were 6-5 mg/kg body weight/d, exceeding the ADI of 5 mg/kg body weight/d. The main dietary source was soft drinks, primarily dilutable drinks. Following on from this study, saccharin-containing dilutable drinks were labelled with instructions to add extra water when preparing them for young children. This example illustrates how information from exposure assessments can be used practically to reduce the exposure in the diet.

### Behavioural effects

One of the most frequently investigated potential hazards associated with young children and food additives, particularly food colours, surrounds their suggested effects on behaviour. In 1973, Dr Ben Feingold postulated that the consumption of food additives and natural salicylates (present in fruits) were an important factor in the development and maintenance of hyperkinesis and hyperactivity in children(61). Since this time, these effects have been widely investigated(62–69). In order to examine this association, a literature search was carried out to identify double-blind placebo controlled trials, which examined the effects of food additives on behaviour in preschool children. Five suitable studies were identified, the key findings and study designs of which are presented in Table 2. Where possible, the results presented are limited to children within the sample cohorts who were aged from 1 to 6 years, thereby limiting the sample size; only one included study had results outside this age group(64), in which findings were not split by age. For two studies, only the results for children aged from 1 to 6 years are shown here, however, outcomes were replicated in older children(65,66) with behavioural effects being stronger among the younger age group than the older cohort in one case(68).

### Additives used

As stated earlier, artificial food colours are the additive category most widely associated with behavioural effects in children. This is evident in Table 2 where four of the five studies examined the effects of various colours on hyperactivity and behaviour(64,66–68); all of these studies included tartrazine, the colour most strongly associated with this effect, with many food manufacturers still hesitant to use it in their products(59). Three studies included a blend of colours and two also included a preservative, sodium benzoate(67,68). Each of these four studies noted some changes to behaviour in varying responses. Only one study investigated aspartame, a sweetener, and did not find any effects on hyperactivity(65).

### Dosage used

The dose of additives administered should reflect actual intake in the population sample in order to assess risks to health by the population. The levels of additives used in two studies(64,65) were greater than the levels that children would normally consume. In both cases no effects were seen on behaviour. McCann et al.(68) compared the effects of two combinations of food additives, and found that Mix A (Sunset Yellow 5 mg; Tartrazine 7.5 mg; Carmoisine 2.5 mg; Ponceau 4R 5 mg; sodium benzoate 45 mg) had significant adverse effects on hyperactivity in comparison with the placebo; this food additive mix is similar to that of Bateman et al. (Sunset Yellow 5 mg; Tartrazine 5 mg; Carmoisine 5 mg; Ponceau 4R 5 mg; sodium benzoate 45 mg), who found a similar response(57). Mix B used by McCann et al. (Sunset Yellow 7.5 mg; Quinoline Yellow 7.5 mg; Carmoisine 7.5 mg; Allura Red AC 7.5 mg; sodium benzoate 45 mg), however, did not have a similar effect(68). Connolly et al.(70) have identified that the combination of food chemicals used in the food additive blends outlined hardly ever occurred in a single food or meal among Irish children and teenagers; thus suggesting that these effects on hyperactivity are unlikely to occur in this age group.
Table 2. Summary of double-blind placebo controlled studies investigating the relationship between food additive intake and behavioural effects in pre school-aged children

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Age (years)</th>
<th>Additives investigated (daily dose)</th>
<th>Length of trial (weeks)</th>
<th>Participant involvement</th>
<th>Behaviour measurement (recorded by)</th>
<th>Measured outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>39</td>
<td>2–15</td>
<td>Tartrazine (50 mg) Sunset Yellow (25 mg) Carmoisine (25 mg) Amaranth (25 mg)</td>
<td>7</td>
<td>Daily somatic and BQ Weekly BQ</td>
<td>Conner’s hyperactivity index (parents) Behaviour changes noted (parents)</td>
<td>Adverse effects recorded by CHI but not by weekly behaviour change questionnaire Parents could not detect changes in behaviour observed by CHI No significant effect of aspartame on behaviour</td>
</tr>
<tr>
<td>64*</td>
<td>25</td>
<td>3–5</td>
<td>Aspartame (38 mg/kg bw)</td>
<td>9</td>
<td>All family food provided Dietary intake recorded Weekly BQ</td>
<td>Paediatric behaviour scale (parents) ADDH comprehensive teachers’ rating scale (pre-school teacher) Behaviour symptom checklist (examiner) Paediatric assessment of mood (child) Static steadiness test (examiner) Motor-activity test (examiner) Behavioural observations (examiner)</td>
<td>Forty-eight percent of participants had adverse reactions Parents were reliable at observing and rating behaviour at varying doses Above 10 mg an increased duration of behavioural effect was noted suggesting a possible dose–response relationship</td>
</tr>
<tr>
<td>66†</td>
<td>23</td>
<td>2–6</td>
<td>Tartrazine (1, 2, 5, 10, 20 and 50 mg)</td>
<td>3</td>
<td>Minimum 6-week run-in additive-free diet before baseline Twice daily BQ</td>
<td>Thirty-item behavioural rating Inventory (parents) Conner’s ten-item APTQ (parents)</td>
<td>No differences in behaviour detected by psychologist-administered tests</td>
</tr>
<tr>
<td>66‡</td>
<td>277</td>
<td>3–4</td>
<td>Sunset Yellow (5 mg) Tartrazine (5 mg) Carmoisine (5 g) Ponceau 4R (5 mg) Sodium benzoate (45 mg)</td>
<td>4</td>
<td>Daily dietary record Daily BQ</td>
<td>WWP (parents) Validated behavioural assessment and observations (psychologists) Aggregate test hyperactivity index (psychologist)</td>
<td>Mix A caused significant adverse effects on GHA in comparison with the placebo Mix B did not have significant adverse effects on GHA in comparison with the placebo Changes to hyperactivity occurred within 1 h</td>
</tr>
<tr>
<td>68†‡</td>
<td>137</td>
<td>3–4</td>
<td>Mix A Sunset Yellow (5 mg) Tartrazine (7.5 mg) Carmoisine (7.5 mg) Ponceau 4R (5 mg) Sodium benzoate (45 mg) Mix B Sunset Yellow (7.5 mg) Carmoisine (7.5 mg) Quinoline Yellow (7.5 mg) Allura Red AC (7.5 mg) Sodium benzoate (45 mg)</td>
<td>6</td>
<td>Daily food diary Daily juice diary Weekly behaviour records</td>
<td>ADHD Rating Scale IV – Teacher Version (teacher) Weekly hyperactivity scale (parents) Activity observation (psychologists) Three measures – weight equally: GHA</td>
<td>Mix B did not have significant adverse effects on GHA in comparison with the placebo Changes to hyperactivity occurred within 1 h</td>
</tr>
</tbody>
</table>

n, Number of participants; BQ, behavioural questionnaire; CHI, Conner’s hyperactivity index; kg bw, kilogram body weight; ADDH, attention-deficit disorder with hyperactivity; APTQ, abbreviated parent–teacher questionnaire; WWP, Weiss–Werry–Peters activity scale; ADHD, attention hyperactivity disorder; GHA, global hyperactivity aggregate.

*Data shown relates only to children aged 3–5 years.
†Data shown relates only to double-blind placebo controlled trial for children aged 2–6 years.
‡Data shown relates only to children aged 3–4 years.
Dietary restrictions

In each of the studies, parents were asked to control the foods that their child consumed during the experimental trial. Two studies required total elimination of food additives from the diet(64,65). Wolraich et al.(65) also required the entire family to maintain this diet and supplied all family foods on a weekly basis during the 9-week trial. The other three studies requested the removal of food colourings(66) and sodium benzoate(67,68). In three studies, parents were asked to record any dietary infarctions or deviations from this diet(65,67,68); however, parents may not have been aware of every food consumed over the several week trials, for example when the child was in childcare; or may have been unaware of ingredients in some foods. The other two studies(64,66) did not ask parents to record foods consumed or infarctions, this may be a limitation to the effects recorded. Wolraich et al.(65) was the only study to confirm dietary compliance by testing urinary samples for ascorbic acid; all foods supplied containing aspartame had been supplemented with equal amounts ascorbic acid. Subjects were eliminated based on poor compliance.

Length of trials

Each child served as their own control, i.e. effects on behaviour were observed using a placebo and a test substance, thus the study periods were several weeks in length, allowing for washout periods between additive administrations. Only one study did not allow for a washout period(65), which may have caused carryover between the trial periods. The shortest washout period was 2 d(66) and the longest was 3 weeks(64), in both cases no carryover effects were reported. The length of these trials required huge commitment by parents, who had to alter the foods being consumed by the child(64,66–68), or the entire family(65); administer a drink or tablet daily; record dietary infarctions on a daily basis(65,67,68); and complete daily(64,66,67) or weekly(65,68) assessments of the child’s behaviour. This high participant burden may explain the high dropout rates in two of the studies; 30 % (67) and 51 % (64).

Study sample

In general, the preschool children investigated were ‘normal’ with no behavioural problems; however, one trial had a sample with an average or above average intelligence quotient(65) and two trials included participants for whom the parents believed that their child had behavioural problems linked to the diet(64,66). Both of the latter studies found differing results regarding the reliability of parents in detecting alterations in behaviour; Pollock et al.(64) found that most parents could not detect changes in behaviour on different diets, whereas Rowe et al.(66) concluded that parents were reliable observers of their child’s behaviour. Another consideration is that three of the five studies had small sample sizes(64–66), which makes the results different to relate to the general population.

Behavioural observations

The study protocols in each of the studies outlined were well-controlled and designed to avoid bias by the observer (double-blind placebo controlled trials). Further to this, each of the studies used validated behavioural measures to examine the effects of the food additives, e.g. Conner’s hyperactivity index. However, the results reported in most studies are based primarily on the opinions of parents; two of the studies recorded only parents’ observations(64,66). Bateman et al.(67) concluded that there was a ‘general adverse effect’ of artificial food colours; however, these effects were only noted by parents rather than validated psychologist tests and McCann et al.(68) weighted the opinions of parents equally with those of teachers and psychologists. Only one study placed more emphasis on objective examinations(65). As noted earlier, conclusions differed regarding the reliability of parents as observers(64,66).

Arising from these studies, additives intakes in children have gained a lot of interest in the media and general population and have had far-reaching impacts as highlighted by Regulation (EC) No. 1333/2008, which stipulated that all foods on sale in the EU containing any one of six food colours used in the research by McCann et al.(68) (E110, E104, E122, E129, E102 and E124), must be labelled to indicate that these additives ‘may have an adverse effect on activity and attention in children’. It is important that limitations of such studies are accounted for when interpreting these results; a standardised approach of behavioural measurement which would reduce observer bias is one consideration for such trials.

Conclusions and future work

Children are not little adults(71); they have different dietary requirements and sensitivities as outlined earlier. Food additives are chemicals in the food supply which are closely regulated to ensure they do not provide any risk to human health(72); exposure assessments are fundamental to ensuring that there is no concern from the intakes of such chemicals in the diet, and can provide valuable information for risk assessors(59) and manufacturers(56). There is a high level of interest in the area of additives and young children, which is focused primarily on the behavioural effects of these food chemicals(62–69); however, it is important to consider the limitations of the available scientific studies when interpreting results. This review highlights the need for a more holistic investigation of exposure patterns and intake levels of food additives by preschool children, rather than focusing on specific hazards. Future assessments should, where possible, examine a range of food additive types rather than food colours exclusively.

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