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Perspective
Naturally safe?

A recent advertising campaign for a frozen food company in the UK suggested that their meals contain no nasty artificial additives. This is presumably a reference to two recalls of foods manufactured with spices that were contaminated with illegal dyes. In February 2005 more than 600 products were recalled because they had been made with a batch of chilli powder that was contaminated with Sudan I,[1] and in May 2005 a further 69 products were recalled because they had been manufactured with cayenne pepper contaminated with Para Red.[2] It is difficult to see how two dyes that have industrial uses (Sudan dyes are used for colouring solvents, oils, waxes, petrol and shoe and floor polishes, and Para Red in printing), but no legal uses in foods, can *accidentally* contaminate spices. Indeed, although the UK Foods Standards Agency website talks mainly about 'contaminated' spices, it does also state that 'Sudan I was first discovered in adulterated chilli products in May 2003'.[1] Since July 2003, all cargoes of dried and crushed or ground chilli and curry powders coming into any EU Member State have to be accompanied by a certificate showing they have been tested and found to be free of Sudan I. In addition, FSA and local authorities randomly sample more than 1000 consignments of imported chilli products.

An alternative interpretation of the advertising campaign claim that their foods are free of nasty artificial surprises might be that they contain real, or natural, nasty surprises instead. The pungent compound in chillies is capsaicin (8-methyl-*N*-vanillyl-6-nonenamide). It is a natural secondary metabolite of *Capsicum* spp., which protects the fruit from consumption by herbivores. Birds are insensitive to capsaicin—presumably consumption of the fruits by birds will ensure wide dispersal of the seeds, while consumption by herbivores will not. At least one company markets seed for feeding wild birds that has been treated with capsicum oleoresin and ground cayenne pepper, under the trade name Pepper Treat, to deter squirrels.[3] Their website warns that you should wear rubber gloves when handling the products, and wash the gloves and your hands afterwards—anyone who has cut fresh chillies and inadvertently touched a sensitive area of the skin will know that capsaicin stimulates pain receptors; indeed it has long been used by pharmacologists as a nociceptive (pain-causing) agent for testing analgesics. However, having stimulated pain receptors in sensory nerve endings, capsaicin depletes the peptide neurotransmitter substance P, leading to (temporary) desensitisation to pain. There is evidence that topically applied capsaicin is effective in treating persistent pain, associated with a variety of conditions, that is not responsive to conventional analgesics.[4,5]

In the same way that many people have developed a liking for foods containing (often quite large amounts of) the nociceptive agent capsaicin, many Japanese people enjoy 'dicing with death' and consider fugu (the porcupine or puffer fish, *Diodon holacanthus*) to be a delicacy. The gonads and viscera of fugu contain tetrodotoxin, and the fish must be prepared by specially trained and licensed chefs to avoid contamination of the flesh with the toxin, which has a median lethal dose (LD_{50}) of the order of 8–10 $\mu g\,kg^{-1}$ body weight.[6,7] Tetrodotoxin selectively blocks sodium channels in nerves, leading initially to numbness and a (possibly pleasurable) tingling sensation, followed by increasing paralysis, and death within 4–6 h if a sufficient quantity has been consumed. Between 1974 and 1983 there were 646 reported cases of fugu poisoning in Japan, with 179 fatalities, and it is a continuing problem affecting 30–100 people annually, mainly from home preparation of the fish.[6] It is not clear whether tetrodotoxin is produced by the fish itself or is the result of bacterial or algal synthesis.

When a population of dinoflagellate algae (*Gonyaulax* spp.) develops rapidly, to concentrations above 10^4 cells L^{-1} sea water, it is termed a bloom. At 10^6 cells L^{-1}, the water can become discoloured—so-called 'red tide'. The dinoflagellates produce saxitoxin and other neurotoxins, which accumulate in molluscs feeding on the algae. Human beings eating the molluscs are at risk of paralytic shellfish poisoning, and toxic amounts of saxitoxin can accumulate in shellfish even when the total algal population is below the threshold for bloom formation if there is a relatively large proportion of *Gonyaulax* spp.—the LD_{50} of saxitoxin is 9 $\mu g\,kg^{-1}$ body weight.[7,8] Another dinoflagellate, *Gambierdiscus toxicus*, occurring around coral reefs, is the source of ciguatoxin, which accumulates in the fish that feed on the reef. Consumption of the fish leads to ciguatera, characterized by neurological and gastrointestinal symptoms. It is rarely fatal, and most people recover within a few days.[7,8] Red tides involving the dinoflagellate *Gymnodinium breve* can result in neurotoxic shellfish poisoning (a milder disease than paralytic shellfish poisoning), either by eating shellfish containing the alga and its toxins, or by inhaling aerosols containing the alga, when the

symptoms are mainly respiratory. Diarrhoeic shellfish poisoning can be due to either bacterial contamination (e.g. when there is sewage contamination of the water) or the presence of *Dinophysis* spp. Unlike other dinoflagellates, *Dinophysis* rarely form red tides; however, *D. fortii* at as little as 200 cells L^{-1} can lead to mussels and scallops being toxic to human beings.[7,8]

Infection with tapeworms (*Taenia* spp.) is a well-known hazard of undercooked meat, but is nowadays rare in developed countries as a result of both rigorous meat inspection and sewage systems that break the cycle between excretion of eggs in human faeces and infection of the animal alternate host. The fish tapeworm, *Diphyllobothrium latum*, occurs in freshwater fish worldwide, and was historically a major problem in the Baltic region; both human beings and bears provide a land-based host for the mature worm. Although infestation is no more severe than with any other tapeworm, and can be eliminated with a variety of antihelminthic drugs, *Diphyllobothrium* absorbs a very large amount of vitamin B_{12} (up to 80–100% of a test oral dose) and can lead to the development of megaloblastic anaemia and the neurological damage of vitamin B_{12} deficiency.[9] There are fears that the increasing popularity of sushi and other raw fish dishes may lead to an increase in infestation.

A variety of toxins occur naturally in plant foods; like capsaicin, they are secondary plant metabolites that have, presumably, evolved as protection against pests and predators. A previous *Perspective* in this journal[10] discussed the celery cultivar that was bred for resistance to pests and wilting (and so had a longer shelf life), but contained high concentrations of psoralens, which cause a photosensitive dermatitis on contact with the skin; its introduction was associated with photodermatitis among grocery employees. It is well known that exposing potatoes to light leads to greening and the accumulation of potentially hazardous amounts of the bitter-tasting glycoalkaloids solanine and chaconine, both of which are glycosides of solanidine. (I note that the packaging on trays of loose potatoes on display in my local supermarket states that they must be covered at night, although I would have thought there was more light exposure during the day than at night.) Exposure to light is only one of the stress factors that lead to increased synthesis of glycoalkaloids: sprouting, mechanical damage and improper storage conditions, either of the tuber or after partial processing, are also important. The symptoms of mild solanine poisoning are acute gastrointestinal upset with diarrhoea, vomiting and severe abdominal pain. In more severe cases, neurological symptoms, followed by unconsciousness and, in some cases, death has also been reported. There is also some evidence that solanidine alkaloids may be teratogenic, and there is a higher incidence of neural tube defects in areas where potatoes are eaten in large amounts.[11]

Broccoli and other *Brassica* spp. have been regarded as protective foods in recent years because of their high content of glucosinolates, which may protect against cancer by reducing the activity of cytochromes P_{450} and so reducing the activation of dietary procarcinogens to active carcinogens, and also by increasing the metabolic clearance of potential carcinogens and their metabolites by increasing the activity of glutathione *S*-transferases and quinone reductases.[12,13] However, the glucosinolate progoitrin is a substrate for myrosinase, forming goitrin, which inhibits the iodination of mono-iodotyrosine to di-iodotyrosine, and so has a goitrogenic effect. In addition, the thiocyanate released by myrosinase action competes with iodide for uptake into the thyroid gland, and so may be goitrogenic when iodine status is low. There is no evidence that normal consumption of *Brassica* spp. has any significant effect on thyroid hormone status in human beings, but goitre can be a problem when cattle are fed large amounts of brassicas. In the long seafaring voyages of discovery in the 14th and 15th centuries, half or more of the crew often died from scurvy, but this was considerably less of a problem for Dutch explorers, apparently as a result of their consumption of large amounts of sauerkraut—fermented cabbage in which vitamin C is well preserved. The corollary of this was that iodine-deficiency goitre, a condition traditionally associated with inland upland areas on thin limestone soil, was surprisingly common, partly as a result of poor absorption of iodide from the acid water-logged soil of the Rhine delta, and partly as a result of the high intake of glucosinolates. Because of this, iodization of salt was introduced in the Netherlands in the 1920s, second only to Switzerland's introduction of iodized chocolate to prevent deficiency in children.

Soya beans and other legumes have long been known to contain trypsin inhibitors which, being proteins, are denatured by cooking, and hence of little relevance in human nutrition, although they may be problematic when oil-seed cake is used to feed livestock. During the late 1970s, slow cookers, in which the ingredients for a casserole could be left to cook at a low temperature throughout the day, became (briefly) fashionable. There were a number of reports of acute and severe gastrointestinal disturbance that was eventually traced not to bacterial growth in foods kept below boiling point for several hours, but to lectins in red kidney (and other) beans—proteins that are resistant to moderate heating, and require boiling for at least 10 min to ensure denaturation.[14,15]

In a debate about a definition of the term 'natural' in relation to foods and food safety, someone once commented cynically that 'cyanide is natural too'. Indeed it is, and a large number of foods contain significant amounts of glycosides that yield cyanide when exposed to β-glucosidase released when plant cells are disrupted. These cyanogenic glycosides include dhurrin in cassava, linamarin and lotaustralin in cassava and lima beans, and taxiphyllin in bamboo shoots. Probably more important than acute cyanide poisoning is the condition of tropical ataxia neuropathy, due to chronic cyanide intoxication

in areas where bitter varieties of cassava that are high in cyanogenic glycosides are consumed.[16] Amygdalin, the cyanogenic glycoside in bitter almonds and apricot kernels, has been marketed as 'laetrile' or (misleadingly) 'vitamin B_{17}', as a cure for cancer. The US National Cancer Institute notes that 'laboratory and animal studies have shown little evidence that laetrile is effective against cancer',[17] but it is associated with signs of chronic cyanide intoxication. Despite the lack of evidence of efficacy, the obvious hazards, and the fact that it is not approved by the US Food and Drug Administration (FDA), laetrile is manufactured in, and sold from, Mexico.

Many consumers choose organic produce on the grounds of safety, but there is little evidence that organically produced food is either more or less safe than conventionally produced food. By definition, organic produce will contain much lower levels of agrochemical residues than conventionally produced food, but there is no evidence that permitted levels of agrochemical residues are harmful. In contrast, it can be argued that organically produced food may be *less* safe than conventional produce. Use of manure rather than chemical fertilisers may cause contamination with pathogenic organisms. The varieties of plants that are most suitable for cultivation without the use of agrochemicals are those that produce large amounts of natural pesticides and other toxins, many of which have been shown to have carcinogenic or mutagenic potential.[18] The message to consumers is that neither 'natural' nor 'organic' means 'safe'.

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