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Peter Williams
University of Wollongong, peterw@uow.edu.au

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Abstract
Key Points

• Despite the many potential health risks associated with foods, in practice the degree of risk associated with the modern food supply is extremely low.

• By far the most important hazards of significance are those from biological agents: pathogenic bacteria, viruses, fungi and a few toxic seafoods.

• Trends to larger-scale production, longer distribution chains in the food supply, increased eating away from the home and the emergence of new pathogens means foodborne illness continues to be a significant public health issue.

• The assessment of the safety of food additives is led internationally by JECFA, but each individual country still develops and determines their own local regulations and food standards.

• The ADI is defined as the amount of a chemical that might be ingested daily, even over a lifetime, without appreciable risk to the consumer

• Genetically modified foods, novel foods and nano-materials pose new challenges for traditional safety assessment processes but, as the food supply becomes increasing global, food regulations about food safety are becoming more harmonized internationally.

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FOOD TOXICITY AND SAFETY

Peter Williams PhD FDAA
Associate Professor of Nutrition and Dietetics, University of Wollongong

Until recently, eating food in modern industrialised countries has usually been regarded as a low risk activity, but several highly publicised food safety scares have raised consumer concerns about the safety of our food supplies (Table 1).

Very few of the foods that we commonly eat have been subject to any toxicological testing and yet they are generally accepted as being safe to eat. However, all chemicals, including those naturally found in foods, are toxic at some dose. Laboratory animals can be killed by feeding them glucose or salt at very high doses and some nutrients such as vitamin A and selenium are hazardous at intakes only a few times greater than normal human requirements. Even very common foods such as pepper have demonstrated carcinogenic activity. Toxicity testing of a food or ingredient can tell us what the likely adverse effects are and at what level of consumption they may occur, but by itself this does not tell us whether it is safe to eat in normally consumed amounts.

'Risk' is the probability that the substance will produce injury under defined conditions of exposure. The concept of risk takes into account the dose and length of exposure as well as the toxicity of a particular chemical, and is a better guide to the safety of a food. Consequently, any attempt to examine the safety of the food supply should not be based on the question 'Is this food or ingredient toxic?' (the answer is always 'yes'), but rather by finding out if eating this substance in normal amounts is likely to increase the risk of illness significantly, ie 'Is it safe?'

1. HAZARDOUS SUBSTANCES IN FOOD

Three general classes of hazards are found in foods: (1) microbial or environmental

contaminants, (2) naturally occurring toxic *constituents*, and (3) those resulting from intentional food *additives* or *novel foods or ingredients*. The most dangerous contaminants are those produced by infestations of bacteria or moulds in food, which can produce toxins that remain in the food even after the biological source has been destroyed. Other contaminants, such as pesticide residues or heavy metals, are usually well controlled in modern food supplies but can be significant hazards in particular localities. Naturally occurring toxic constituents are usually present in doses that are too small to produce harmful effects when foods are eaten normally, except in the cases of atypical consumers who may be sensitive to individual ingredients. Food additives or novel foods are generally the least dangerous hazards because their toxicology is well studied and the conditions of use are tightly controlled. Table 2 summarises the types of hazardous substances that may be present in food.

The US Food and Drug Administration (FDA) has ranked the relative importance of health hazards associated with food in the following descending order of seriousness:

1. Microbiological contamination
2. Inappropriate eating habits
3. Environmental contamination
4. Natural toxic constituents
5. Pesticide residues
6. Food additives

This list is very different from that found in public opinion polls, which show that most people rate food additives as one of their major concerns about the safety of the food supply.

2. MICROBIAL CONTAMINATION

2.1 Pathogenic bacteria

Outbreaks of acute gastroenteritis caused by microbial pathogens are usually called food poisoning. They can be caused by foodborne *intoxication* (where microbes in food produce a toxin that produces the symptom) or foodborne *infection* (where the symptoms are caused by

the activity of live bacterial cells multiplying in the gastrointestinal system). Table 3 lists the most common bacterial causes of food poisoning, in order of the rapidity of onset of symptoms. In general the intoxications have a more rapid onset.

The most important pathogens are *Clostridium botulinum*, *Staphylococcus aureus*, *Salmonella* species and *Clostridium perfringens*. The last three organisms account for about 70-80% of all reported outbreaks of foodborne illness, but there are also many others as well as some viral and protozoan agents. The four most frequently identified factors contributing to food poisoning incidents are: improper cooling of food, lapses of 12 hours or more between preparing and eating, contamination by food handlers, and contaminated raw foods or ingredients.

The reported incidence and cost of foodborne illness in most countries is increasing, although it is difficult to measure this exactly. It is estimated that less than 1% of cases are captured in existing notification schemes. Some of the reasons for increasing rates of foodborne illness are: new and emerging pathogens, changes in the food supply (including more intensive animal husbandry and longer shelf life fresh chilled products), aging populations, and a greater proportion of food eaten away from home. Around 60-80% of foodborne illness arises from the food service industry.

2.2 Control of Food Poisoning

The trend in all countries today is to require more formal training of all food handlers and the development of food safety plans wherever food is prepared and served to the public, based on the principles of Hazard Analysis of Critical Control Points (HACCP). HACCP is a preventive approach to quality control, used worldwide in all segments of food production, from primary production, to food manufacture and food service settings. It is based on seven principles:

* identifying all potential *hazards* at each step in the food chain and possible preventative actions
* determining the *critical* points in the operation where the hazards must be controlled
* establishing *limits* at each critical control point. Examples of control procedures are washing hands, sanitising food preparation surfaces and tools, cooking food to specific temperature,

maximum food storage times.

* setting up procedures to *monitor* each critical control point.
* planning the *corrective actions* to be taken if a critical limit is exceeded
* establishing a *recording system* to document performance of the process
* *verifying* that the HACCP process is working.

Table 4 outlines an example of some parts of a HACCP plan for a commercial food product sold as ready-to-eat.

2.3 Mycotoxins

Moulds, or fungi, are capable of producing a wide variety of chemicals that are biologically active. Humans have used some of these as effective antibiotics, but there are also a number of diseases resulting from accidental exposure to fungal products that contaminate food. Some examples are as follows:

Aflatoxins These are a group of highly toxic and carcinogenic compounds from the common *Aspergillus* fungus species. They are stable to heat and survive most forms of food processing. Aflatoxin contamination can occur whenever environmental conditions are suitable for mould growth, but the problem is more common in tropical and semitropical regions. Aflatoxins were first recognised in the 1960s in peanuts. On a world-wide basis, maize is the most important food contaminated with aflatoxin.

Patulin is an antibiotic that is produced by the mould *Penicillium caviforme.* It has been implicated as a possible carcinogen from one study in rats although other studies have not confirmed this. Patulin in primarily associated with the apple rotting fungus and so apple juices and some baked goods with fruit can contain patulin.

Fumonisins are carcinogenic mycotoxins from the *Fusarium* fungus associated with corn. There were first characterised in 1988 and are known to be potent inhibitors of sphingolipid synthesis. Ingestion of fumonisin-affected corn has been shown to be carcinogenic in rats. In 1990 it was reported that use of mouldy corn with high levels of fumonisins to make beer in

the Transkei of South Africa was associated with a very high incidence of oesphageal cancer.

2.4 New foodborne diseases

Three of the most serious food pathogens today (Campylobacter, Listeria and enterohemorrhagic E. coli) were unrecognised as causes of illness 30 years ago. Some of the more important new organisms are:

Campylobacter jejuni was a well-known bacterium in veterinary medicine before it was identified as a human pathogen in 1973. It is now recognised as one of the most important causes of gastroenteritis in humans of similar importance to *Salmonella.* It is present in the flesh of cattle, sheep, pigs and poultry and can be introduced wherever raw meat is handled.

Listeria monocytogenes is a bacterium widely distributed in nature but is unusual in that it grows at refrigeration temperatures (down to 0°C). Listeriosis can cause abortions as well as death in the elderly and those with compromised immune systems, such as people with AIDS. Listeria has been linked to the consumption of contaminated pâtés, milk, soft cheese and undercooked chicken, and is often found in pre-prepared chilled food.

Escherichia coli 0157:H7 is a bacterium that can damage the cells of the colon, leading to bloody diarrhoea and abdominal cramps. Raw or undercooked hamburger meat was a major vehicle of transmission in a number of well publicised outbreaks in the USA in 1993 and contamined metwurst was responsible for a major outbreak of illness in Australia in 1995.

Salmonella typhimurium is a multi-drug resistant strain that has become a major pathogen in the UK in the 1990s. As well as being highly virulent it can survive at low pH and be infectious in very low numbers.

Norwalk virus is found in the faeces of humans and illness is caused by poor personal hygiene among infected food handlers. Symptoms include nausea, vomiting, diarrhoea, abdominal pain and fever. Because it is a virus, it does not reproduce in food, but remains active until the food is eaten.

'Mad cow disease' (or BSE -bovine spongiform encephalopathy) is a slowly progressive and ultimately fatal neurological disorder of adult cattle that results from infection by an unique transmission agent called a prion. Prions seem to be modified forms of normal cell surface proteins. BSE was first confirmed in Britain in 1986, but has now spread to cattle in other countries of Europe, Japan and North America. The same infective agent is also responsible for variant Creutzfeldt Jakob Disease (vCJD), a fatal disease of humans, mostly affecting young adults. By October 2009, it had killed 166 people in Britain and 44 elsewhere, with the number expected to rise because of the disease's long incubation period. Three principal controls have been put in place to keep infected meat out of the food chain: banning slaughter of beef aged over 30 months (before the age at which BSE typically develops), removal of parts of the body with the highest levels of infection (eg nervous and bone tissue), and a ban on feeding meat and bonemeal to any farmed livestock. Milk and gelatine products from beef do not appear to be affected.

3. ENVIRONMENTAL CONTAMINATION

3.1 Heavy metals and minerals

Selenium is one of the most toxic essential trace elements. The level of selenium in foods usually reflects the levels in the soil and in a few high-selenium areas, such as North Dakota and parts of China, excessive selenium intake has been associated with gastrointestinal disturbances and skin discolouration. In China in the early 1960s, selenium intoxication affected up to fifty per cent of the population in certain villages, with brittle hair, skin lesions and neurological disturbances the main symptoms.

Mercury. Fish can contain 10-1500mg/kg of organic mercury, and even higher levels when mercury wastes are released into lake waters. Serious poisonings from mercury in fish have occurred in Japan, the most famous being that in Minamata Bay (from 1953 to 1960). Another example of widespread mercury intoxication occurred in Iraq in 1971/72 as a result of bread made from wheat treated with mercury-based pesticides. Most countries have now established

maximum permitted levels on mercury in fish in the range of 0.4-1.0mg/kg.

Cadmium is a toxic element that accumulates in biological systems. Chronic exposure at excessive levels can lead to irreversible kidney failure. Plants readily take up cadmium from the soil, and there has been a slow increase in the cadmium levels in soils due to the use of phosphate fertilisers and the affect of air and water pollution. The average food-based cadmium intake is now approximately 10-50μg per day, which is approaching the provisional tolerable weekly intake. Measures to control cadmium contamination include controls on waste disposal, and developing new crops that accumulate less cadmium.

3.2 Criminal adulteration

Modern food regulations began in the nineteenth century when there widespread examples of adulteration of foods to increase profits. Milk was diluted with water, cocoa with sawdust, and butter with borax. Today standards in the food industry are much higher and risks from illegal adulteration are rare. However, there are still some notorious instances.

In Spain in 1981 there was an outbreak of an apparently new disease characterised by fever, rashes and respiratory problems. Many thousands were hospitalised and over 100 people died. The agent responsible was identified as cooking oil that had been fraudulently sold as pure olive oil but in fact was mostly rapeseed oil intended for industrial uses, which was contaminated with aniline. In China in 2008, at least six children died of acute kidney failure and nearly 300,000 fell ill after consuming tainted infant formula. Melamine, a synthetic nitrogenous product found in many industrial goods, was found to have been illegally added to milk-based foods to make them appear higher in protein than they really were.

3.3 Packaging migration

The materials used to package food can sometimes result in contamination of the food itself. At one time the lead used in the solder of metal cans was a significant source of contamination of infant formulae, but this problem has been eliminated by the introduction of non-soldered cans. Bisphenol A (BPA) is an industrial chemical used as the starting material for the production of

polycarbonate plastics and synthetic resins. BPA is found in containers that come into contact with foodstuffs such as drinking vessels, baby bottles, and the internal coating on cans for tinned food. BPA belongs to a group of substances that can act in a similar way to some hormones, and studies in laboratory animals suggest that low levels may have an effect on the reproductive system. In 2010, the FDA released a report on the safety of BPA, which raised concern about its potential effects on the brain, behavior, and prostate gland in fetuses, infants, and young children. Subsequently manufacturers of baby bottles around the world have agreed to move to BPA-free bottles as soon as possible.

3.4 Industrial pollution

Throughout the industrial era, many potentially hazardous substances have been released into the environment and are now widely distributed in the food chain. Among the most important are the polychlorinated biphenyls (PCBs). PCB is a generic term for a wide range of highly stable derivatives of biphenyl that have been used in a vast number of products, including plastics, paints, and lubricants. Although manufacture has now ceased, their stability and lipid solubility has meant that they accumulate in fatty tissue and they have become widespread, particularly in seafood. They can be found at low levels now even in human milk. The health effects of PCBs are not well established, although they are thought to be mild carcinogens. In one incident in Japan in 1978 when rice oil was contaminated with 2000-3000ppm PCB, growth retardation occurred in young children and the foetuses of exposed mothers.

3.5 Radioactive fallout

The most important dangerous radioisotopes in fall-out are strontium-90 and caesium-137, with half-lives of 28 and 30 years. Strontium is absorbed and metabolised like calcium and stored in bones. Because it is concentrated in milk it is particularly dangerous for infants and children. Since the Nuclear Test Ban Treaty of 1963, the level of radioactive contamination from atmospheric dust has markedly declined, but accidental exposure can still occur, such as that after the Chernobyl disaster, and lead to dangerous food contamination over widespread areas.

3.6 Changes during cooking or processing

Food is frequently exposed to high temperatures during cooking. In roasting and frying, localised areas of food may be subjected to temperatures that lead to carbonisation and under these circumstances any organic substance is likely to give rise to carcinogens. The major compounds are polycyclic aromatic hydrocarbons (PAH), produced mainly by burning of fats, and heterocyclic amines (HCA) produced from amino acids. Char-broiling or barbecuing is particularly likely to lead to carcinogen formation.

Acrylamide. In 2002 the Swedish National Food Authority announced that acrylamide could be found in starch-containing foods cooked at high temperatures, such as fried or roasted potato products, and cereal-based products including sweet biscuits and toasted bread. In 2010 a WHO expert committee determined that there is evidence that acrylamide can cause cancer in laboratory animals and, while there is currently no scientific evidence which links acrylamide with cancer risk in humans, all food regulatory agencies around the world are promoting a reduction in exposure to acrylamide in food by encouraging new technological strategies aimed at reducing its formation.

Irradiation can be used to sterilise foods, control microbial spoilage, eradicate insect infestations and inhibit undesired sprouting. Despite the great potential of the technology, there has been substantial opposition from consumer groups concerned about the process producing toxic chemicals in foods. Extensive studies have shown the products formed are no different from those produced in normal cooking and over 1300 studies have consistently found no adverse effects from feeding irradiated food to animals or humans. Food irradiation is approved by the WHO and currently more than 30 countries allow some form of use.

4. NATURAL TOXINS

Many plant species contain hazardous levels of toxic constituents. Intoxications from poisonous plants usually result from the misidentification of plants by individuals harvesting

their own foods, but many ordinary foods also contain potential toxicants at less harmful levels.

4.1 Inherent natural toxins

There are many examples of potentially dangerous toxins in natural food products: cyanogenic glycosides in plants such as almond kernels, cassava and sorghum, alkaloids in herbal teas and comfrey, lathyrus toxin in chick-peas. In Japan the puffer fish, which contains a potentially fatal neurotoxin, is considered a delicacy and is consumed to produce a tingling sensation. However, natural toxicants are a generally accepted hazard because the foods that contain them have been eaten in traditional diets for many generations. We are protected from their harmful effects in three ways: avoidance, removal and detoxification.

Firstly, traditional knowledge has been passed down about which foods are safe and which are not. Thus we know it is safe to eat certain mushrooms and not others. Secondly, traditional preparation methods have evolved to reduce harmful effects. Specialist chefs prepare puffer fish to remove the parts with the highest toxin concentration. People in South America and Africa use complex chopping and washing procedures in their preparation of cassava that removes much of the cyanide naturally found in the raw product. Thirdly, the body has numerous detoxification systems, mainly enzymes in the liver, to deal with any toxins we do ingest. So we can still happily eat nutmeg and sassafras, even though both contain the naturally occurring carcinogen safrole.

4.2 Abnormal conditions of the animal or plant used for food

Some foods only become hazardous during particular conditions of growth or storage.

Ciguatera poisoning. This is serious human intoxication, caused by eating contaminated fish, causing gastrointestinal disorders, neurological problems and, in severe cases, death. There are over 400 species of fish that may become ciguatoxic, but almost all of the fatal cases are attributable to barracuda. The poisoning is particularly insidious because it occurs in tropical and subtropical fish that are normally safe to eat, but only when they have been feeding on certain dinoflagellates that produce toxins that accumulate in the flesh.

Paralytic shellfish poisoning. It has been known for many centuries that shellfish can occasionally become toxic. Symptoms include numbness of the lips and fingertips and ascending paralysis, which can lead to death within 24 hours. The poisoning, which primarily affects mussels and clams, occurs when dinoflagellates undergo periods of rapid growth ("blooms", or "red tides") in areas where the shellfish grow. The toxin cannot be removed by washing or destroyed by heat.

Glycoalkaloids in Potatoes. Solanine is one of a range of heat stable glycoalkaloid compounds found in the green parts of the potato plant that are toxic above concentrations of 20mg/100g. In normal peeled potatoes there is about 7mg solanine/100g. Solanine synthesis can be induced by exposing the tubers to light and also by simple mechanical injury. In very green potatoes, the levels can reach up to 100mg/100g. These glycoalkaloids possess anticholinesterase activity which can produce gastrointestinal and neurological disorders, and deaths have occasionally been reported from consumption of excessive amounts of green potatoes.

4.3 Enzyme inhibitors

Protease Inhibitors. Substances that inhibit digestive enzymes are widespread in many legume species and trypsin inhibitors are found in oats and maize as well as Brussels sprouts, onion and beetroot. These inhibitors are proteins and therefore are denatured and inactivated by cooking. Thus for humans these substances are not a problem, although feeding raw legumes to animals can result in pancreatic enlargement.

4.4 Antivitamins

One of the best known antivitamins is the biotin-binding protein, avidin, in raw egg white. Biotin deficiency induced by eating raw egg white is rare because biotin is well provided in most human diets. The few cases that have been reported involved abnormally large amounts of raw egg white, so the occasional raw egg is perfectly safe. Avidin is inactivated when heated. Other antivitamins, such as the pyridoxine antagonist amino-*D*-proline in flax seeds and a tocopherol oxidase in raw soybeans, are only of importance in animal feeding.

4.5 Mineral-binding agents

Goitrogens. There are a number of glucosinolate and thiocyanate compounds in foods that interfere with normal utilisation of iodine by the thyroid gland and can result in goitres. Goitrogens are widely distributed in cruciferous vegetables such as cabbage, Brussels sprouts and broccoli. The average intake of glucosinolates from vegetables in Great Britain is 76mg per day and clinical studies have found that intakes of 100-400mg per day may reduce the uptake of iodine by the thyroid. There is no evidence that normal consumption of these foods by humans is harmful, but it is possible that eating large amounts of brassica plants might contribute to a higher incidence of goitre in areas where dietary iodine intake is low.

Phytate. In wholemeal cereals can bind minerals and make them less available for absorption. In leavened bread, phytases in the yeast break down the phytate, but in some parts of the Middle East, where unleavened bread is a dietary staple, phytate has been reported to be the cause of zinc deficiency.

Oxalate. Certain plants, including rhubarb, spinach, beetroot, and tea, contain relatively high levels of oxalate. Oxalate can combine with calcium to form an insoluble complex in the gut that is poorly absorbed and high intakes can lower plasma calcium levels. Kidney damage and convulsions can accompany oxalate poisoning. However, the average diet supplies only 70-150mg oxalate per day which could theoretically bind 30-70mg calcium. Since calcium intakes are usually ten times this amount, food oxalates do not normally have any detrimental effect on mineral balance.

Tannins (polyphenols). These are present in tea, coffee and cocoa as well as broad beans. Tannins inhibit the absorption of iron and in Egypt, in children with low iron intakes, regular consumption of stewed beans has been associated with anaemia. High levels of tea consumption may contribute to low iron status in people with marginal iron intakes.

5. AGRICULTURAL RESIDUES

5.1 Pesticides

The most common agricultural chemicals found in foods are pesticides, albeit at very low levels. The chlorinated organic pesticides (such as DDT and chlordane) were among the first modern pesticides to be used. In general they have low toxicity to mammals and are highly toxic to insects. However they are very stable compounds, which persist in soils, and they are stored in the fat tissue of animals. Because of concern about their effect on the reproduction of certain birds and possible carcinogenic activity, use of these compounds has been restricted. Surveys of foods show that the levels of organochlorine compounds have been in declining in recent years. Alternative insecticides now in use - such as organophosphates - do not accumulate in the environment. No food poisonings have ever been attributed to the proper use of insecticides on foods, but in 1997 there were 60 cases of food poisoning in India attributed to indiscriminate organophosphate spraying in a kitchen.

5.2 Fungicides and herbicides

Most fungicides and herbicides show very selective toxicity to their target plants and therefore present very little hazard to humans. In addition, most do not accumulate in the environment.

5.3 Hormones

The use of hormones, such as bovine somatotrophin (BST), to improve yields of meat and milk has been controversial in many countries. Although low levels of BST can be detected in the milk of treated cows, the hormones are inactive in humans and are digested and inactivated in the stomach when consumed in food. The FDA approved the commercial use of BST in 1993 and later reviews by Canadian authorities and Codex Alimentarius have agreed that there are no health risks to humans. However in several countries BST use is not permitted on animal welfare grounds.

6. INTENTIONAL FOOD ADDITIVES

6.1 Approval process for food additives

Each country has its own legislation to control the approval of additives in foods, but most follow the same general principles that are used by the two main international bodies of experts organised by WHO and the FAO: the Joint Expert Committee on Food Additives (JECFA) and the Codex Alimentarius Committee on Food Additives and Contaminants. The aim of the evaluation of a food additive is to establish an Acceptable Daily Intake (ADI). The ADI is usually expressed in mg/kg of body weight and is defined as the amount of a chemical that might be ingested daily, even over a lifetime, without appreciable risk to the consumer. The evaluation process consists of a number of steps, as follows:

1. Toxicity testing is carried out in experimental animals - usually mice and rats, but other species may also be employed. Three types of testing are performed: (a) acute toxicity studies at high doses to determine the range of possible toxic effects of the chemical, (b) short-term feeding trials at various doses, and (c) long-term studies of two years or more to examine the effect of exposures over several generations.

2. From the feeding trials, the level of additive at which observed health effects do not appear in the animals is determined. This is called the 'no observed effect level' (NOEL).

3. The lowest NOEL is divided by a safety factor to derive an exposure level that is regarded as acceptable for humans, the ADI. Most commonly a safety factor of 100 times is used, but for some substances factors of up to 1000 have been used. This safety factor allows for possible differences in susceptibility between experimental animals and humans and also the differences in sensitivity of individual people.

Not all additives have been evaluated for safety using modern testing procedures. Some have been used for many years without apparent harm and in the USA ingredients not evaluated by prescribed testing procedures can be classified as Generally Recognised As Safe (GRAS). This list includes common ingredients such as salt, sugar, seasonings and many food flavourings.

While the 100 fold safety factor is accepted for most additives, in the USA the Delaney Clause prohibits the use in *any* amount of substances known to cause cancer in animals or humans.

When the bill was introduced in 1958, chemicals could be detected down to 100 parts per billion; anything less was considered zero. Improved analytical techniques can now detect substances at parts per trillion and there might be only trivial risks from such minute quantities. The FDA has now changed the interpretation of the clause so that if a food additive increases the chance of developing cancer over a lifetime by less than one case per million of cancer, the threat is considered too small to be of concern.

Ames has ranked the level of carcinogenic risk associated with a variety of chemicals we may be commonly exposed to. The Human Exposure/ Rodent Potency Index (HERP) expresses the typical human intakes as a percentage of the dose required to produce tumours in fifty per cent of rodents. The values in Table 5 show that the risk from the alcohol in a glass of wine is almost 100 times higher than that from the saccharin in a can of diet cola, and more than 10 000 times the hazard from the residues of the pesticide EDB. That the risks from wine appear more acceptable to most consumers seems to relate to the fact that benefit is easily perceived, that wine is seen as 'natural', and because the risk is voluntary. Although the risks from other additives and contaminants may be far smaller, they arouse suspicion because they are risks that people generally cannot control.

6.2 Artificial sweeteners

Saccharin is one of the oldest artificial sweeteners, having been used in foods since the last century. Studies in rats have linked high doses (7.5 % of the diet by weight) of saccharin with bladder cancer and because of this there have been attempts to ban its use in human foods. However at lower doses, such as one per cent, no adverse effects are found and large epidemiological studies of diabetics who have had lifetime exposure to saccharin have found no increased incidence of cancer in humans.

Cyclamate. Dietary cyclamate appears to promote bladder cancer and induce testicular atrophy in rats although carcinogenicity testing in mice, dogs and primates have all been negative. The US FDA banned the food use of cyclamate in 1969, but in over 50 other countries it is still a permitted sweetener, and there is no good evidence from mutagenicity testing or epidemiological studies that it is a health risk to humans.

Aspartame is a dipeptide of two amino acids, phenylalanine and aspartic acid. Aspartame is metabolised to phenylalanine and therefore carries a risk for people with phenylketonuria, but for the normal population it is an extremely safe sweetener that is digested like any other protein.

6.3 Preservatives

Preservatives are used in foods as antioxidants and to prevent the growth of bacteria and fungi. Most pose no toxicological problems, but a few have generated some concerns.

Sodium nitrite is used as an antimicrobial preservative that is very effective in preventing the growth of *Clostridium botulinum,* as well as acting as a colour fixing agent (to preserve the red colour) in cured meat products such as bacon and ham. Nitrite reacts with primary amides in foods to produce N-nitroso derivatives, many of which are carcinogenic. However, the risk to human health from dietary nitrite is difficult to assess. While food additive nitrites are significant, a substantial amount is also produced by bacterial reduction from naturally occurring nitrate in vegetables. In recent years, manufacturers have worked to reduce the levels of nitrite used in cured meats, and have added agents such as ascorbic acid which help to prevent the formation of nitrosamines in the stomach.

Sulphur dioxide and its salts (sulphites) are commonly used as inhibitors of enzymic browning, dough conditioners, antimicrobials and antioxidants. Although sulphites have been used for many centuries, with no adverse effect for most consumers, one to two per cent of asthmatics are sensitive to sulphites, and in those individuals the reaction can be fatal.

6.4 Colours and flavours

All colours and flavours approved for use in foods are rigorously evaluated before being approved for use.

Red No 2 (Amaranth). In the early 1970s, data from Russian studies raised questions about Red No. 2's safety. The FDA Toxicology Advisory Committee evaluated numerous reports and decided there was no evidence of a hazard but concluded that feeding it at a high dosage results in a statistically significant increase in malignant tumors in female rats. The FDA ultimately decided to ban the color, but it is still found in foods in Canada and Europe.

Yellow No 4 (Tartrazine). Food sensitivity to tartrazine can be experienced by a small number of individuals, but claims related to clinical problems such as asthma and hyperactivity are not well supported by scientific studies. Tartrazine is still a permitted additive, but its presence has to be declared in ingredient lists so sensitive individuals can avoid it.

Monosodium Glutamate (MSG). The flavour enhancer MSG is a sodium salt of glutamic acid, one of the most common amino acids. It is present in virtually all foods and found in high levels in tomatoes, mushrooms, broccoli, peas, cheese and soy sauce. Chinese Restaurant Syndrome has been claimed to be caused by foods with a lot of added MSG, but most controlled studies have not demonstrated this effect.

Traditional methods for evaluating the safety of colours have not usually considered their potential behavioural effects. New research published in 2007 in the medical journal The Lancet, using a mixture of six permitted colours (sunset yellow, tartrazine, carmoisine, ponceau, quinoline yellow and allura red) at relatively high doses, concluded that there was limited evidence that these colours could effect the activity and attention of children in the general population. However the European Food Safety Authority concluded that uncertainties in the study meant there was insufficient evidence to change current permissions for use of these colours.

7. NOVEL FOODS

Technology now allows the development of many new ingredients or whole foods that do not have a history of traditional use in the human food supply. Many of these novel foods have been developed to have improved nutritional quality. Recent examples include genetically modified foods, artificial fat substitutes for energy-reduced foods, new algal sources of omega-

3 fatty acids, and phytosterols to reduce cholesterol.

7.1 Approval process for novel foods

There are significant practical difficulties in assessing the long term safety of modified whole foods or ingredients. Unlike additives, which can be fed at very high doses to assess their toxic effects, it is not possible to feed large amounts of one single food to animals without making their diet nutritionally unbalanced. Animals also prefer a mixture of foods and are likely to refuse to eat if offered a single food in large amounts. These difficulties, and welfare concerns about the use of animal studies that were unlikely to result in meaningful information, led to the development of the concept of 'substantial equivalence', particularly for the assessment of genetically modified (GM) foods. This type of assessment does not quantify the safety or risk of a food, but aims to determine whether novel foods are as safe as traditional counterparts. For GM foods the process involves assessment and comparison of a wide range of factors including:

- Source and nature of any new protein
- Stability of any genetic changes
- Potential toxicity of the new protein
- Levels of naturally occurring and newly introduced allergens
- Nutritional composition
- Levels of anti-nutrients
- Ability of the food to support normal growth and wellbeing
- Potential unintended environmental consequences.

7.2 Genetically modified foods

Modern biotechnology now allows specific individual genes to be identified, copied and transferred into other organisms in a much more direct and controlled way. For example, genes for the enzyme chymosin from beef have been inserted into yeast, and the GM chymosin from these organisms has now widely replaced natural rennet from animals in cheese making. Genetic modification can also allow individual genes to be switched on or off: the gene that controls fruit softening can be repressed to maintain a higher solids content in tomatoes designed for use in tomato paste.

In 2009, 134 million hectares of GM crops were planted worldwide and 77% of all soy is now grown from GM varieties. Most plants have been modified for agricultural purposes: herbicide-tolerant soy and canola and insect-resistant corn and cotton now make up the bulk of those crops in North America. There are many future uses planned that will bring more direct consumer benefits: oils with improved fatty acid profiles, rice with higher levels of vitamins, nuts with lower levels of allergens and potatoes that absorb less fat during frying. However, there has been concern expressed about the environmental impacts and safety of these novel foods, in particular related to the issues of allergenicity, toxicity of transgenic food and possible transfer of antibiotic resistance.

Genetic modification usually requires the introduction of the selected gene together with a marker gene. The marker genes are often antibiotic resistance genes that allow selection of the plants that have successfully integrated the new selected gene. Many have expressed concern that when the modified food is eaten the resistance gene might be transferred to bacteria in the gut and acquire resistance to clinically useful antibiotics. Although it has been estimated that the chances of this occurring are extremely small, the use of this method is now being phased out.

Most countries have now established stringent approval processes for GM foods including mandatory labelling to inform consumers when foods include GM modified ingredients. Assessments to date have usually found GM foods to be as safe as their normal counterparts and there are likely to be increasing numbers of GM foods in the marketplace in the future.

7.3 Fat substitutes

There are a number of fat substitutes now in use, including *Simplesse* (microcapsules of milk proteins or egg white), *Splendid* (derived from pectin), and *N-oil* (derived from tapioca). In the US *Olestra* - a mixture of heat stable sugar polyesters, that are not digested and yield no energy - has been controversial because it can reduce the absorption of fat soluble vitamins. The FDA approved use of Olestra in a limited range of foods in 1996, but required addition of vitamins A, D and K as well as further monitoring of the health impacts and warning labelling that it

may cause abdominal cramping and loose stools. In 2003, after a scientific review of several post-market studies, the FDA concluded that the warning statement was no longer warranted. Olestra is not yet approved in the UK, Europe or Australasia.

7.4 Phytosterols

In many countries, plant sterols are now approved to be added to a range of foods to help lower blood cholesterol. They work by reducing the absorption of cholesterol from the gut, but have a side effect of also lowering absorption of carotenoids. A typical daily dose of 2-3g per day can reduce serum beta-carotene levels by 20-25%. Safety reviews have concluded that since there is no evidence of reduction in serum retinol levels, this effect is not a significant health concern and that advice to maintain adequate fruit and vegetable intakes can ensure adequate carotene intakes.

7.5 Nanotechnology

Nanotechnologies are comprised of a range of technologies, processes and materials that involve manipulation of substances at sizes in the nanoscale range (from 1 nm to 100 nm). Food and drinking water naturally comprises particles in the nanometre scale. Humans ingest many millions of organic and inorganic nanoscale particles every day in their food and it is estimated that people inhale around 10 million nanometre scale particles in every breath. Generally, proteins in foods are globular structures 1-10 nm in size and the majority of polysaccharides and lipids are linear polymers with thicknesses in the nanometre range. Milk is an example of an emulsion of fine fat droplets of nanoscale proportions.

It has been claimed that some of the nanomaterials now being used in foods and agricultural products introduce new risks to human health because they may be absorbed more easily. For example, nanoparticles of silver, titanium dioxide, zinc and zinc oxide materials now used in nutritional supplements and food packaging. However reviews have concluded that safety cannot be determined from the size alone, and it is novelty and not size which raises concern

and which needs to be considered in undertaking risk assessments.

8. REGULATORY AGENCIES

Although all regulators use similar processes to evaluate scientific evidence and assess the safety of foods, the management of food safety legislation varies between countries.

The Codex Alimentarius Commission (Codex) was created in 1963 by the Food and Agriculture Organisation (FAO) and the World Health Organisation (WHO) to develop international standards, guidelines and codes of practice related to food composition and safety, with the aim of harmonising food regulations between countries. Over 165 countries are members of Codex. While not legally binding on individual countries, Codex standards are very influential and form benchmarks for key World Trade Organisation agreements such as those on the Application of Sanitary and Phytosanitary Measures and Technical Barriers to Trade which make it increasingly difficult for countries to adopt food standards that are significantly different from Codex.

In the US, the FDA develops standards for food composition, quality and safety as well as being responsible for approval of therapeutic drugs and cosmetics. It also has food inspection and monitoring responsibilities nationally. The work of the FDA, such as the GRAS listings, is influential internationally because of the high quality and resourcing of the many expert scientific staff.

In Australasia, the bi-national authority, Foods Standards Australia New Zealand, sets standards for all manufactured foods for both countries, including standards for additives and contaminants and assesses the safety of novel foods. Primary food production and food service safety standards are set separately in each country. In Australia compliance is the responsibility of individual State governments, not the national body standard setting agency.

In Britain, an independent food safety watchdog – the Food Standards Agency – was

established in 2000 to protect the public's health and consumer interests after concerns raised by the BSE outbreak. The FSA provides advice and information to the public and Government on food safety from farm to fork, nutrition and diet. It also protects consumers through effective food enforcement and monitoring.

In Europe, the European Food Safety Authority (EFSA) was created in 2002 to provide independent scientific advice on all matters linked to food and feed safety. EFSA principally deals with requests for risk assessments from the European Commission, Parliament and Council and plans to take on a wider brief from other European institutions in the near future.

One of the key roles of all regulatory agencies is risk assessment and management.
Risk assessment is a scientific process consisting of four steps:

1) Hazard identification (biological, chemical or physical agents capable of causing adverse health effects)
2) Hazard characterisation (qualitative and quantitative evaluation of the hazards – in including dose-response effects)
3) Exposure assessment (the likely intake of the risk factor from food, taking into account typical dietary patterns)
4) Risk characterisation (estimating the probability and severity of potential adverse effects).

Risk management is the process of weighing policy options in the light of the risk assessment results and selecting appropriate control measures. Control options can include prohibiting certain substances in foods entirely (some carcinogenic herbs, for example), setting maximum permitted levels in foods (eg, additives, or agricultural residues), through the development of codes of good manufacturing practice, labelling requirements (eg, warnings about allergens) or by public education about safe use of foods (eg, in relation to mercury in fish).
Risk communication is the process of making the risk management information comprehensible to food producers, policy makers and consumers.

9. KEY POINTS

- Despite the many potential health risks associated with foods, in practice the degree of risk associated with the modern food supply is extremely low.
- By far the most important hazards of significance are those from biological agents: pathogenic bacteria, viruses, fungi and a few toxic seafoods.
- Trends to larger-scale production, longer distribution chains in the food supply, increased eating away from the home and the emergence of new pathogens means foodborne illness continues to be a significant public health issue.
- The assessment of the safety of food additives is led internationally by JECFA, but each individual country still develops and determines their own local regulations and food standards.
- The ADI is defined as the amount of a chemical that might be ingested daily, even over a lifetime, without appreciable risk to the consumer
- Genetically modified foods, novel foods and nano-materials pose new challenges for traditional safety assessment processes but, as the food supply becomes increasing global, food regulations about food safety are becoming more harmonized internationally.

FURTHER READING

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Some key food safety websites

World Health Organisation. http://www.who.int/foodsafety/en/

US Food and Drug Administration: http://www.cfsan.fda.gov/list.html

European Food Safety Authority: http://www.efsa.europa.eu/

Food Standards Australia New Zealand: http://www.foodstandards.gov.au/

Codex Alimentarius Commission: http://www.codexalimentarius.net/web/index_en.jsp

Joint Expert Committee on Food Additives: http://www.who.int/ipcs/food/jecfa/en/index.html

Table 1. A chronology of recent food scares

1986	First cases of mad cow disease in Britain
1990	Benzene in Perrier mineral water in France
1996	Salmonella in peanut butter in Australia
1997	Contagious swine fever in The Netherlands`
1999	Contaminated Coca-Cola in Belgium
1999	Pollen from GM maize reported to kill Monarch butterflies
2001	Foot and mouth disease all over Europe
2002	Acrylamide found in starchy foods cooked at high temperature
2003	Outbreak of bird flu in Asian poultry
2004	Warnings about mercury in shark, mackerel and swordfish in the
2008	Melamine contamination of baby milk formula in China

Table 2. Potential Hazard in Foods

Hazards	Examples
Microbial contamination	
Pathogenic bacteria	Toxins from *Clostridium botulinum*
Mycotoxins	Aflatoxin from mould on peanuts
Environmental contamination	
Heavy metals and mineral	Arsenic and mercury in fish
Criminal Adulteration	Aniline in olive oil
Packaging Migration	BPA from plastics
Industrial Pollution	PCB, radioactive fallout
Changes during Cooking or Processing	Carcinogens produced in burnt meat
Natural toxins	
Inherent toxins	Cyanide in cassava
Produced by abnormal conditions	Ciguatera poisoning from fish
Enzyme Inhibitors	Protease inhibitors in legumes
Antivitamins	Avidin in raw egg white
Mineral-binding agents	Goitrogens in brassica vegetables
Agricultural residues	
Pesticides	DDT
Hormones	Bovine somatotrophin
Intentional food additives	
Artificial sweeteners	Cyclamate
Preservatives	Sodium nitrite

Table 3. Common Bacterial Food Poisoning Organisms

Organism	Symptoms	Time after food	Typical food sources
Toxins			
Staphylococcus aureus	Vomiting, diarrhoea, abdominal pain	1-6 hours (mean 2-3h)	Custard and cream-filled baked goods, cold meats
Clostridium perfringens	Diarrhoea and severe pain, nausea	8-24 hours (mean 8-15h)	Meat products incompletely cooked or reheated
Bacillus cereus	a) nausea, vomiting; b) abdominal pain, watery diarrhoea	a) 1-5 hours; b) 6-16 hours (mean 10-12h)	Rice dishes, vegetables, sauces, puddings
Clostridium botulinum	Dry mouth, difficulty swallowing and speaking, double vision, difficulty breathing. Often fatal	2h-8 days (mean 12-36h)	Home canned foods (usually meat and vegetables), and inadequately processed smoked meats
Infection			
Vibrio parahaemolyticus	Diarrhoea, abdominal cramp, nausea, headache, vomiting	4-96 hours (mean 12h)	Fish, crustaceans
Salmonella spp.	Diarrhoea, fever, nausea, vomiting	8-72 hours (mean 12-36h)	Undercooked poultry, reheated food, cream-filled pastries
Yersinia enterocolytica	Fever, abdominal pain, diarrhoea	24-36 hours	Raw and cooked pork and beef
Escherichia coli	Fever, cramps, nausea, diarrhoea	8-44 hours (mean 26h)	Faecal contamination of food or water
Shigella ssp.	Diarrhoea, bloody stools with mucus, fever	1-7 days (mean 1-3d)	Faecal contamination of food
Campylobacter jejuni	Fever, abdominal pain, diarrhoea	1-10 days (mean 2-5d)	Raw milk, poultry, eggs, meat
Listeria monocytogenes	Septic abortion, septicaemia, meningitis, encephalitis. Often fatal	1-7 weeks	Milk and dairy products, raw meat, poultry and eggs, vegetables and salads, seafood

Table 4: An example of six steps from a HAACP plan for chilled chicken salad

STEP:	1. Growing and Harvesting	2. Raw Material Processing	3. Supply Storage Temperatures
Hazard	Chemicals, Antibiotics	Chemical, Microbiological	Microbiological
Control	Raw material specifications	Certified supplier	Raw material specifications
Limit	Regulatory approved residues	Free of pathogens and foreign material	Chicken < -12°C Vegetables < 4°C
Monitoring	Certificate of compliance	Monitor supplier HACCP program	Check coolroom records daily
Action if limit exceeded	Reject lot	Reject as supplier	Investigate time/temp abuse
Responsibility	Receiving operator	Purchaser	Storeperson

STEP:	4. Ingredient Assembly	5. Bagging	6. Labelling
Hazard	Microbiological	Microbiological	Incorrect dates, Traceability
Control	Temperature control specs	Correct seal settings	Legible, correct dates and codes
Limit	Food < 4°C	Upper tolerance limit on sealer	Use proper labels
Monitoring	Check temperature once per shift	Check setting every 15min.	Each batch at changeover
Action if limit exceeded	Report to supervisor	Examine all packages	Destroy incorrect labels
Responsibility	Cook	Seal inspector	Packer

Source: Adapted from Microbiology and Food Safety Committee of the National Food Processors Association. *'HACCP Implementation: A Generic Model for Chilled Foods'*. J Food Prot 1993;56:1077.

Table 5. Rankings of possible carcinogenic hazards

Daily human exposure	Carcinogen and dose per 70kg person	Index of possible hazard (HEPR, %)
Natural dietary toxins		
Wine (250mL)	Ethyl alcohol, 30mL	4.7
Basil (1g of dried leaf)	Estragole, 3.8mg	0.1
Peanut butter (32g, one sandwich)	Aflatoxin, 64ng	0.03
Cooked bacon (100g)	Dimethylnitrosamine, 0.3µg	0.003
Food additives		
Diet cola (1 can)	Saccharin, 95mg	0.06
Pesticides		
DDE/DDT (daily diet intake)	DDE, 2.2µg	0.0003
EDB (daily diet intake)	EDB, 0.42µg	0.0004