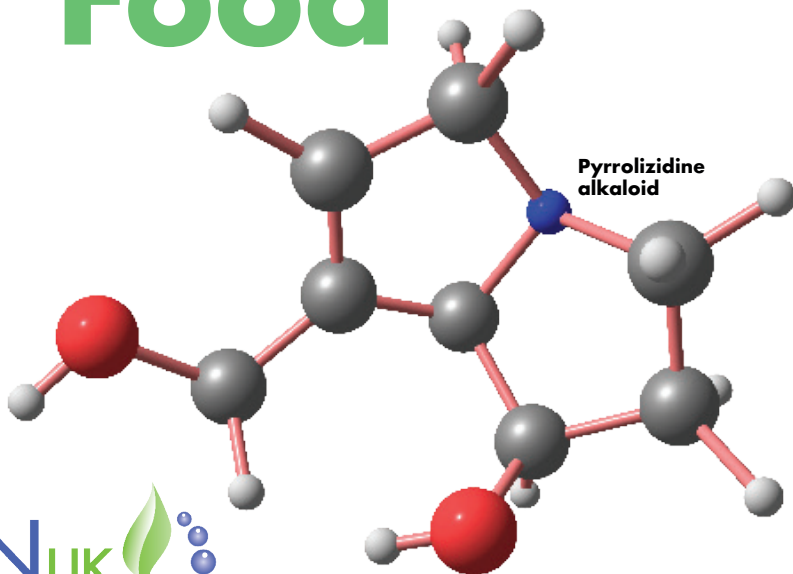


Chemical Contaminants of Food



About CRN UK

The Council for Responsible Nutrition UK (CRN UK) is the UK trade association representing the leading manufacturers and suppliers of food supplements, functional foods and their ingredients (functional foods, in this context, mean weight control products, sports products and other specialist food products designed for a specific function).

Our membership covers ingredient manufacturers and suppliers, food supplement manufacturers, retailers, direct sales companies and laboratories.

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Introduction

Chemical contaminants of food are substances that are not intentionally added to food.

This differentiates these contaminants from the other chemicals, such as food additives and micronutrients, that are intentionally added to improve the organoleptic quality of the food or to extend or maintain the microbiological safety of the food.

The scientific knowledge of chemical contamination is relatively new and has increased substantially since the end of the twentieth century to become a critical component of food safety legislation.

For many decades of the early 20th century, the major chemical contaminants of concern were the heavy metals arsenic, mercury and lead and the mycotoxins produced by the fungus *Claviceps* (Ergot).

By the second decade of the 21st century, the list of contaminants controlled by legislation had grown considerably and includes a very wide range of substances. These include:

- Toxic chemical elements such as the heavy metals and nitrates.
- Environmental contaminants such as dioxins, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH).
- Plant toxins such as pyrrolizidine alkaloids, tropane alkaloids and erucic acid.
- Mycologically produced contaminants from fungal growth on plants.
- Process induced contaminants such



as 3-monochloropropane diol (3-MCPD) and glycidyl esters and acrylamide.

● Synthesised (man-made) chemicals which include pesticides, herbicides, veterinary drug residues, melamine and migration from food contact materials.

One of the driving forces for enhanced awareness of chemical contaminants was the increasing knowledge that some contaminants, particularly some of the organic contaminants such as dioxins, polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs), could have a carcinogenic potential. The advances in toxicology have identified a number of substances found in foodstuffs and their ingredients that may be of greater risk to the health of the consumer than originally thought.

1.0 Toxic Effects of Chemical Contaminants

The wide spectrum of chemical contaminants that are under, or being considered for, legislative control exhibit toxic effects on the human body, ranging from the poisoning of the central nervous system by lead, which is relatively short-term if high concentrations are consumed, to the much longer term carcinogenic and possible teratogenic effects of some of the organic environmental contaminants.

1.1 Toxic Chemical Elements

This category covers the heavy metals already controlled by legislation in many countries and includes lead, arsenic, cadmium, mercury and tin. Nitrates are also the subject of controls on their upper levels in foods. These occur naturally in the environment but higher concentrations can be found in some regions as a result of human activity, such as farming practices, industrial pollution or vehicle exhausts.



Mercury is one of the heavy metals already controlled by legislation

The accumulation in the body can lead to toxic effects. Lead, arsenic, cadmium and mercury are considered to be of public health significance as they are all systemic toxicants that are known to induce multiple organ failure, even at lower levels of exposure.

1.2 Toxicity of Environmental Contaminants

The environmental contaminants found in food and of public health concern are dioxins, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs) and aromatic hydrocarbons.

1.2.1 Dioxins and PCBs

The term dioxin is used to cover a family of chemically and structurally related compounds falling into the group of polychlorinated dibenzopara dioxins (PCDDs) or polychlorinated dibenzofurans (PCDFs). These are ubiquitous in the environment as they can be formed during combustion processes and certain industrial processes.

PCBs were used in a variety of industrial applications from the 1930s and whilst their general use ceased in the mid-1970s, they remain very persistent in the environment, in water courses, the sea and land.

The effects of dioxins on human health have been well documented. Short term exposure in humans can result in skin lesions and altered liver function. Long-term exposure is linked to impairment of the immune system, the nervous system, the reproductive functions and the endocrine system.

Studies on the chronic exposure of animals to dioxins have resulted in several types of cancer. Based on this animal data and on human

epidemiological data, the International Agency for Research in Cancer (IARC) has classified dioxin as a known human carcinogen.

PCBs are a group of compounds with some similarities to dioxins. The health effects of the higher levels of ingestion are similar to dioxins and long-term exposure is also linked to impairment of the immune system and nervous system.

1.2.2 Polycyclic Aromatic Hydrocarbons (PAH)

PAHs are a group of chemical compounds that are formed during incomplete combustion of fuels such as oil, gas, coal and wood and other organic sources such as tobacco. There are over a hundred PAHs, and a number are considered to affect the health of humans if ingested in sufficient quantity. PAHs are known environmental contaminants of foods and water. They have been demonstrated to cause an interference with cellular membranes, and are potent immunosuppressants. They have also been shown to cause carcinogenic and mutagenic effects in animal studies, and are recognised as human carcinogens.

1.2.3 Mineral Oil Hydrocarbons

The chemical compounds mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH) are similar from a chemical point of view to PAHs, though the mineral oil hydrocarbons originate from petrogenic sources and their analytical determination is generally different. As with PAHs, however, contamination of food with MOSH or MOAH can occur at any stage of food production.

Some MOAH are considered to be both mutagenic and carcinogenic, while

Cassava can contain cyanogenic glucosides



certain MOSH may cause adverse effects in the liver.

1.3 Toxicity of Plant Metabolised Contaminants

The human race has to rely heavily on plants to sustain itself and the plant kingdom contains many thousands of species, many of which are commonly used as foods. Unfortunately, many plants used as foods can contain naturally occurring toxicants which can sometimes have serious adverse effects on humans. Two common foods containing these are potatoes and cassava, the latter containing cyanogenic glucosides. Cassava forms part of the staple diet of nearly eight hundred million people worldwide but it has to go through a detoxification process before consumption.

Toxic compounds can be formed in some species of plant as part of their normal metabolism, such as erucic acid in vegetable oils.

1.3.1 Erucic Acid

Erucic acid is a naturally occurring contaminant present in vegetable oils. It is normally in relatively low quantities in most oil seeds. Species of the plant family Brassicaceae, particularly rapeseed, mustard seed and borage oils can be very high. Low erucic acid rape (LEAR)

is therefore grown for food use and high erucic acid rape (HEAR) for industrial use. The levels in mustard oil are generally high. The quantities of erucic acid in an oil can vary from season to season, depending on environmental and climatic conditions.

Studies on animals indicate that ingestion of oils containing higher levels of erucic acid over a period of time can lead to heart condition myocardial lipidosis.

The European Food Safety Authority (EFSA) published its opinion following a safety assessment on erucic acid at the end of 2016, and concluded that there was a possible health risk for children under the age of ten, who have been exposed to high intakes of vegetable oils and fats.

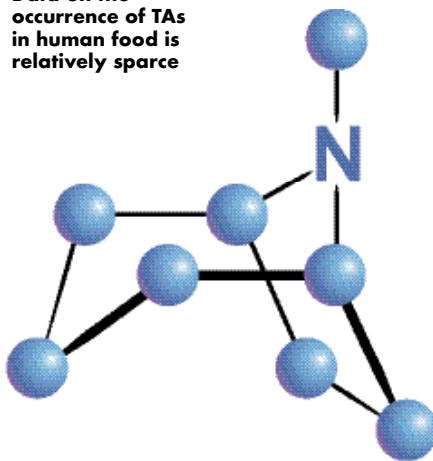
1.3.2 Pyrrolizidine Alkaloids (PAs)

In July 2017, EFSA concluded that the exposure to pyrrolizidine alkaloids, in particular for frequent consumers of tea and herbal infusions, is a possible long-term concern for human health due to their potential carcinogenicity. There were also concerns for honey consumption, particularly for toddlers and children, and for food supplements containing botanicals from the plant families known to produce alkaloids.

Pyrrolizidine alkaloids comprise a large group of natural plant toxins synthesised as secondary metabolites by certain plant species.

A number of these PAs are known to be highly toxic to humans and animals. Short-term toxicity in humans includes the liver and lungs as the main target organs, and it is associated with the onset of hepatic veno-occlusive disease (HVOD). Animal studies have concluded that

Data on the occurrence of TAs in human food is relatively sparse



certain PAs can be considered to be genotoxic and carcinogenic substances.

1.3.3 Tropane alkaloids (TAs)

Tropane alkaloids are secondary metabolites of plants from certain plant families. The families where TAs are most commonly found are the Solanaceae, the Erythroxylaceae and the Convolvulaceae. The Solanaceae comprises over 100 genera and 3000 plant species.

Compared to some of the other chemical contaminants, the data on TAs occurrence in human food and their toxicity in humans is relatively sparse, and most of the work carried out relates to animal feeds. However, studies have shown that there is carry-over of TAs into meats (particularly offal), eggs and milk, although most of the reports indicate that the levels are relatively low. Some TAs such as atropine are used therapeutically in both veterinary and human medicine.

The toxicity in humans of TAs relates

to their pharmacological effects, which include change in heart rate, decreased production of excretions such as those from the salivary, bronchial and sweat glands, inhibition of micturition and inhibition of gastric acid secretion. The limited studies carried out do not indicate any carcinogenic or genotoxic potential of the TAs investigated.

1.4 Contaminants from Mycological Metabolism

Many of the agricultural crops and particularly the cereal crops such as wheat, barley, maize, rye and most of the oil seed plants are at risk of contamination by a number of species of filamentous fungi such as *Aspergillus* sp., *Penicillium* sp. and *Fusarium* sp. Once the fungus has invaded the crop it will spread and grow on the plants. During their metabolism, the fungi will produce toxic substances known as mycotoxins.

A fungal species can produce a number of mycotoxins and several species can

produce the same mycotoxin. The plants are vulnerable during the growing stage but can also become contaminated during harvesting and storage if kept in a damp environment. A hot and humid climate is the best environment for the fungal growth.

Mycotoxins can have a range of health effects on humans depending on the fungal species, and these toxic effects are collectively known as mycotoxicoses. The toxic effects of many mycotoxins are mostly known from veterinary work as a consequence of farm animals feeding on contaminated plants.

The main toxic effect of mycotoxins, such as Aflatoxin from *Aspergillus* sp., is organ damage, particularly of the liver. Aflatoxins are acutely toxic, immunosuppressive and have also been found to be mutagenic, teratogenic and carcinogenic compounds.

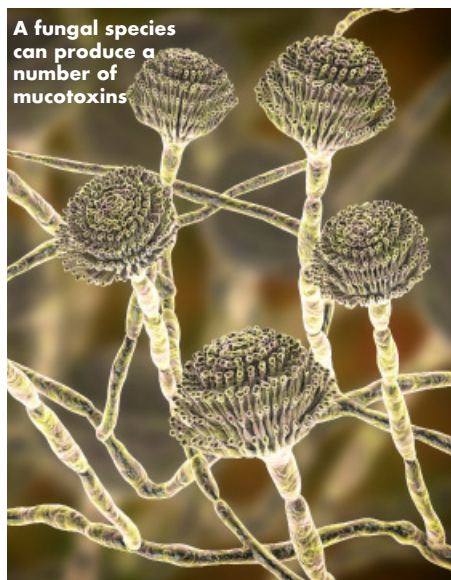
Ochratoxins are secondary metabolites of strains of *Penicillium* sp. and *Aspergillus* sp. and have been shown to be damaging to the kidneys (nephrotoxic), immunosuppressive, carcinogenic and teratogenic.

Trichothecenes are mycotoxins which are mostly produced by members of the genus *Fusarium*. The trichothecenes that most frequently contaminate food are deoxynivalenol (DON) and diacetoxyscirpenol (DAS). The common effects of these toxicants are the depression of immune responses and nausea.

Other mycotoxins produced by *Fusaria* are Zearalenone and Fumonisin.

Another mycotoxin of concern is citrinin, which is found mainly in stored grains but is sometimes also found in edible plant material and fruits.

Citrinin can be produced by a number of fungal species, and often occurs



A fungal species can produce a number of mycotoxins

together with other mycotoxins such as ochratoxin A or Aflatoxin B1 which is produced by the same species. Studies have indicated that the toxic effects of the co-presence of citrinin with these other mycotoxins can be either additive or synergistic.

Citrinin is a nephrotoxic mycotoxin which has also been shown to have genotoxic properties.

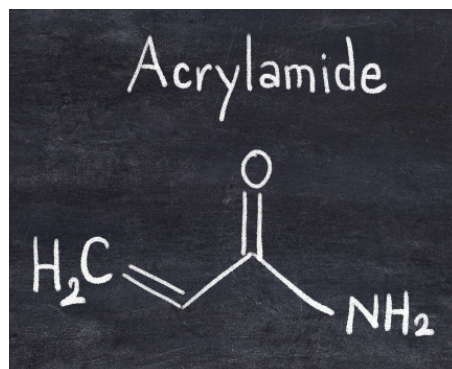
1.5 Process Induced Contaminants

Throughout the last decade of the 20th century and the first decade of the 21st century, it became apparent that substances formed from chemical reactions during the processing of foods could be potentially carcinogenic.

These substances can occur when the food product contains specific combinations of chemicals, and the reactions take place during heat processing.

1.5.1 3-MCPD and Glycidyl esters

3-MCPD and its esters are now known to be formed as a contaminant during the heat processing of oil or fat containing foods in the presence of chloride ions. Glycidyl esters are also a related process- derived contaminant.



The presence of chloride ions in the reaction is essential and there is a risk with heat-processed products containing lipids and salt. Contamination has also been traced back to the presence of chlorine in process water or in cleaning compounds.

3-MCPD has been detected in a wide range of food products, and has also been found in oils of both vegetable and animal origin used for nutritional purposes, for example, fish oils.

Animal studies on 3-MCPD have indicated that it is possibly carcinogenic, and it has been classified by the IARC as 'Probably carcinogenic to humans'.

1.5.2 Acrylamide

Acrylamide is a chemical contaminant formed when a reducing sugar, such as glucose or fructose, and the amino acid asparagine are in the presence of heat. These two components can be found occurring together in a range of foods, such as potatoes and cereal products.

First identified in 2002, acrylamide has now been found to occur in a wide range of common foods, particularly those exposed to a temperature greater than 120°C during processing or cooking.

As acrylamide has been used as an industrial chemical for a long time, its toxicology had been extensively studied before its discovery in food products.

The IARC has already classified the substance as 'Probably a human carcinogen'. It had been identified as a potential genotoxic carcinogen but had also been found to be acutely neurotoxic.

1.6 Synthesised (man-made) Chemicals

There are a large number of man-made chemicals, particularly those intended for



agricultural or veterinary applications, that can commonly contaminate foods if not controlled. Most of these chemicals are controlled by legislation or standards across the world.

1.6.1 Veterinary Drug Residues

The rapid development in human medicines over the past half century has been mirrored by similar development in veterinary medicines.

The use of these medicines on animals used for food such as cattle, sheep, pigs and poultry and fish can result in residues of the drugs being carried over into the meat and potentially being consumed by humans.

Veterinary drugs are used in the food chain to treat or prevent animal diseases or conditions, and some are also used as growth-promoting agents. As a consequence, a diverse range of drugs can be used, a number of which have potential effects on human health.

While there is legislative control on

such drugs used on animals intended as a food source, there can be a risk of contamination entering the food chain if the surveillance is not effective, for example, of imported meats.

1.6.2 Pesticides including Herbicides

Pesticides and herbicides are two categories of chemicals used in agriculture and plant protection.

For many decades there have been concerns over the possible effects on human health of the carry-over of residues of these substances into foods, particularly those used as part of the staple diet.

Over the years, continuous control, surveillance and reduction of maximum levels of residues have resulted in a situation where it is now considered almost impossible to consume sufficient food to attain an intake of the substance that even approaches toxic levels.

It is important that all plant material used for human food complies with any legislated maximum levels assigned for each substance, and that there is documented evidence that none of these limits have been exceeded.

1.6.3 Other man-made substances as contaminants

There are other man-made chemicals that can become chemical contaminants of food, either accidentally or from deliberate fraud. A case of the latter was the melamine adulteration of milk powders carried out in China in 2008.

Melamine, an industrial compound, is a good source of nitrogen and was added to milk powder and baby foods to increase the apparent protein content of the milk.

This resulted in the deaths of six babies, with around 300,000 other babies affected, before the fraud came to light.

This incident led to melamine presence in foods being prohibited by legislation in many countries.

2.0 Toxic Chemical Elements

A number of metals can be found in food, either naturally occurring or as a result of agriculture or industrial processes. Metals such as lead, mercury, arsenic and cadmium are naturally occurring, as they are present in varying quantities in the environment, particularly in soil and water.

Continuous consumption of these metals, particularly lead, arsenic and mercury, leads to bioaccumulation in biological tissues in the body, while cadmium accumulates in bone. This accumulation occurs in food animals as well as humans, which results in a further source of metals for human consumption.

In view of their potential health risks, the four elements lead, mercury, arsenic and cadmium are controlled by maximum levels in food legislation across the world. Lead, mercury and cadmium are referred to as the 'heavy metals'.

Heavy metals occur widely in plants and animals used for human foods but, in general, the levels are relatively low. Higher levels can be found in soil and water in the vicinity of certain industrial processes and it has been found that aquatic plants, particularly marine plants such as seaweeds, tend to contain higher levels of certain metals than land plants.

An opinion by the European Food Safety Authority (EFSA) in 2012 cites fish, such as tuna, cod, swordfish and pike, as the most important contributors of

Seaweed tends to contain higher levels of certain metals than land plants



methylmercury for all age groups in Europe due to quantity consumed. Methylmercury is an organometallic cation with the formula $[\text{CH}_3 \text{Hg}]^+$. It is the major source of organic mercury for humans. It is a bioaccumulative toxicant.

Many of the food additives derived from natural mineral sources, such as calcium and magnesium salts, have to be monitored for heavy metal content, often specified in national legislation and/or global standards.

The most important thing that must be recognised is that the heavy metal content in foods and supplement products is cumulative, and is the sum of all the contributions from the ingredients. These contributions will be proportional to the percentage of the ingredient in the final product. The accuracy of the estimation

of the heavy metal content of a product is reliant on the quality of the analytical data available. It is prudent to calculate the heavy metal content for legal compliance on the maximum levels for each of the individual contaminants given in the supplier's specifications.

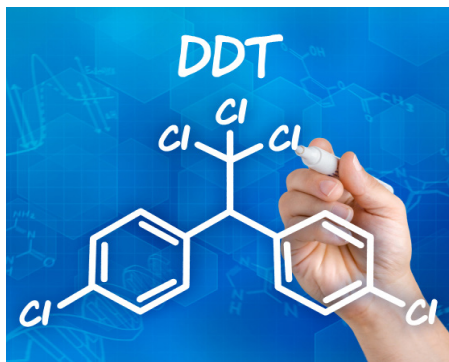
It is essential that the analytical values are for the individual elements (eg. arsenic, lead, cadmium and mercury). In no case is the 'total heavy metal' value acceptable. In terms of food product development, especially for food supplements, it is important that the heavy metal content of each susceptible ingredient is known so that the cumulative amounts in the final product can be calculated from the proportions of the ingredients in the product. In the EU, the control of heavy metals is based on levels in the final product.

3.0 Environmental Contaminants

There are organic chemicals found in the environment which can contaminate both food and water, and which are known to be toxic to human health.

One group of such substances is of particular concern and is internationally classified as Persistent Organic Pollutants (POPs). All the chemicals in this group once released into the environment:

- Remain intact and do not break down for exceptionally long periods, normally many years
- Become widely distributed throughout the environment as a result of natural processes involving soil, water, and, most importantly, air
- Accumulate in the fatty tissues and sometimes other tissues and organs of living organisms, including humans.



They are found in greater concentrations at the higher levels of the food chain

- Are toxic to humans and/or other animal life.

POPs accumulate in the bodies of living organisms by bioaccumulation and are readily absorbed into fatty tissue where, over time and with continuous exposure, the concentrations can become greatly magnified to many thousands of times the original background levels.

The Stockholm Convention currently lists 28 POPs of serious concern to public health. Three-quarters of the list relates to man-made pesticides such as aldrin, chlordane and dichlorodiphenyltrichloroethane (DDT). The presence of these in foods is now strictly controlled by legislation in most countries.

Of importance to the food industry are a number of POPs which are not pesticides, these are for example:

- Polychlorinated dibenzo-p-dioxins (PCDD) – Dioxins.
- Polychlorinated biphenyls (PCBs).
- Polychlorinated dibenzofurans (PCDF) – Furans.

3.1 Polychlorinated dibenzo-p-dioxins (PCDD)

This group of contaminants is commonly known as dioxins and they are ubiquitous

in the environment. Dioxins are chemicals produced as the result of incomplete combustion, mainly from industrial processes. A significant source of dioxins is from the production of metals (such as steel), incineration of municipal, hospital and hazardous waste. They can be produced during the burning of coal, peat and wood, and have been found in vehicle emissions. Dioxins are airborne and can contaminate soils. As a result, they are found as contaminants of both plant and animal food sources.

PCBs have a number of similarities with dioxins (section 3.1). The group consists of 78 congeners, of which seven are considered to be of toxicological concern. The relative toxicity of each of these seven congeners has been assessed and a TEF value assigned.

As with the PCBs, the legislative controls on dioxins are based on TEQs (*see Annex I*), 2,3,7,8-TCDD is regarded as the most potent and TEFs are based on this form.

In terms of functional foods and supplements, the greatest risk of dioxins is from fish oils, fish livers, plant seed oils and some clays used for supplements. These ingredients do need to be subjected to regular testing for the presence of contaminants.

3.2 Polychlorinated biphenyls (PCBs)

PCBs are man-made chemicals originally designed for use as heat exchange substances in electrical transformers and capacitors. In the late 1920s, their use extended to other industrial applications such as components of paints and plastics.

They are a group of chemicals with 209 well defined chemical forms known



as congeners, of which a small number exhibit toxicity.

Currently 12 congeners are considered to exhibit a dioxin-like toxicity in humans. As relative degrees of toxicity have been assessed between the 12 congeners, with some being considered more toxic than others, the World Health Organization (WHO) has produced toxic equivalency factors (TEFs) for each when assessing risk to humans.

For example, congener number 126 has a TEF of 0.1, whereas number 180 has a TEF of 0.00001 - in other words, it is less toxic. The concept of the TEF can be used to assess the potential toxicity of a mixture of congeners in a food.

A calculation using the relative mass of each congener in a mixture and their TEF can give a Toxic Equivalent (TEQ) which is a value providing toxicity information about a specific mixture of congeners in a particular contaminant.

The TEQ is more important to toxicologists than reporting the mass of the PCBs in picograms (equal to one trillionth of a gram), as the TEQ value

can give an indication of the relative toxicity of a particular sample (*see Annex I*).

In countries where PCBs in food are controlled by legislation, the TEQ maximum values form the basis of the controls. Although the manufacture of PCBs was banned in the late 1970s, they are still persistent in the environment, particularly in some areas of the world. They can be found in water courses, lakes and oceans and, as a consequence, can also be found in both fresh water and marine animals. PCBs can be detected in fish oils at significant levels and are removed by the processing and refining of the oils. Also susceptible are seed oils from plants grown in certain areas of the world.

3.3 Polychlorinated dibenzofurans (PCDF)

This group of contaminants is currently known as furans and they are structurally similar to the dioxins. Furans are formed by the same processes that produce dioxins.

Similarly to dioxins, the group of furans

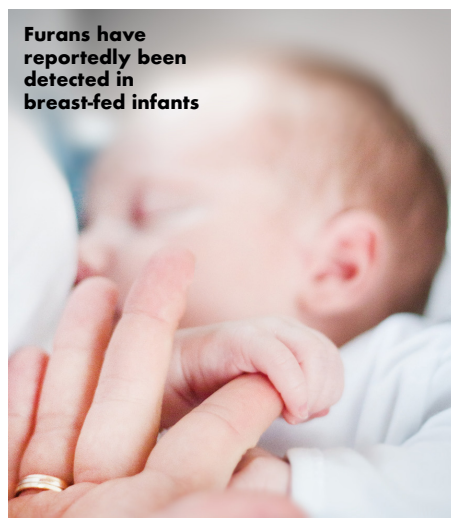
consists of 135 congenors with varying toxicities. Their presence in the environment is very persistent and they can be found in a range of food sources, particularly animal products which are the major source of exposure in humans. There are reports that furans have been detected in breast-fed infants.

A point of difference between contamination by dioxins and furans, and most other food contaminants, is that the quantities of concern are very low. Both the levels of detection and control are at nanogram or picogram levels, whereas most of the other contaminants are controlled at either microgram or milligram levels.

A picogram is equal to one trillionth of a gram (10⁻¹²g) and is one millionth of a microgram. This means that all samples of food suspected of containing these contaminants have to be subjected to very careful and specialised analysis. Under some current legislation, the rejection of a batch of food product can occur if the legal limit is exceeded by one-tenth of a picogram/g.

3.4 Polycyclic Aromatic Hydrocarbons (PAHs)

The term polycyclic aromatic hydrocarbons (PAHs) refers to a group of several hundred chemically-related and environmentally persistent organic compounds of various structures and varying toxicity. As environmental contaminants, they are ubiquitous, airborne and can contaminate soil and water and, hence, food sources of both animal and plant origin. PAHs usually occur in complex mixtures rather than as individual compounds. One compound, benzo(a)pyrene (BaP) was commonly used as a marker or indicator of PAH



Furans have reportedly been detected in breast-fed infants

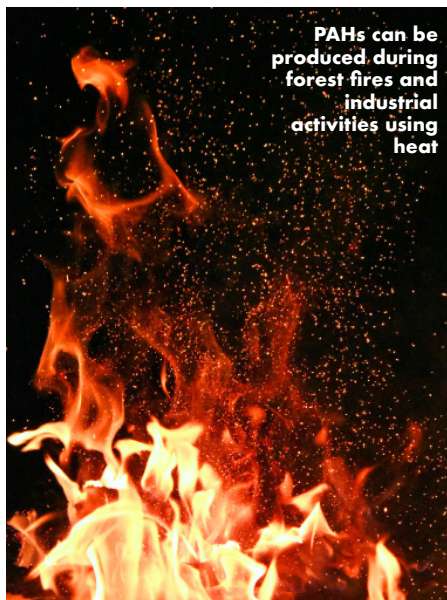
contamination of food and drink. For food safety purposes, the EU now also considers the sum of BaP plus benz(a) anthracene, benzo(b)fluoranthene and chrysene, known as PAH4 as these are better markers.

In a manner somewhat similar to dioxins and furans, PAHs are formed during incomplete combustion of any carbon-based materials, such as coal and wood. They can be produced in quantities during forest fires and are also released during industrial activities using heat, such as waste incineration, oil refining and mining. PAHs can be produced at lower temperatures than dioxins. They have also been detected in vehicle emissions. They are persistent organic contaminants and are slow to degrade in the environment. They can also be produced in a domestic situation such as in frying, grilling and barbecuing of food.

In the EU, EFSA recognises 16 PAH compounds as toxic and potentially human carcinogens. In the USA, the Environmental Protection Agency (EPA) has selected 16 compounds for regulating based on their potential human and environmental effects. The EPA 16 and EFSA 16 overlap but are not the same. Other organisations list 17.

Seven compounds are rated as potential human carcinogens. Benzo(a)pyrene (BaP) is considered to have the highest cancer risk of all of them.

PAHs are highly lipophilic and their bioavailability after ingestion or inhalation is significant in terms of toxicology. Scientific investigations have shown that they can be found in almost all internal organs, and particularly those organs that are rich in adipose tissue. The organs act as storage areas from which the hydrocarbons can be gradually released. Once in



the body, they undergo a series of chemical changes resulting in PAH metabolites such as epoxides. These metabolites may contribute to the carcinogenicity of certain PAH compounds.

In terms of PAH contamination of functional foods and supplements, the main risks are with the botanical ingredients including marine algae, such as spirulina and chlorella. PAHs can also be found in some bee products such as propolis. The environment, soil and air quality in the area where the plants are grown and harvested can have an influence on the quantity of PAHs taken up by the plants.

PAH levels have been found to be particularly high in botanicals grown in regions where there is heavy industry.

The harvesting and post-harvesting treatment needs to be controlled as, for example, drying with certain procedures using oil or wood burners have been

demonstrated to increase the PAH content of the botanicals being dried.

When botanicals for food and supplement use are grown commercially, it is essential the Good Agricultural Practice (GAP) is strictly applied as there is increasing official surveillance of PAHs in botanical food ingredients.

3.5 Mineral oil hydrocarbons (MOH)

Mineral oil hydrocarbons (mineral oils or MOH) have been used in the food industry for over a century. While many were used to lubricate production machinery, a smaller number were classed as 'food grade' and used as processing aids and additives. Their use was widespread in the bread and baking industry, where they were used as release agents on baking tins and on the knives used to cut the dough. The toxicology and safety of mineral oils in food were evaluated in 1970 and 1976 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), who gave an estimate

of the acceptable daily intake (ADI) for humans as 'Not Specified'.

In 2012, the European Food Safety Agency (EFSA) published its scientific opinion on 'Mineral Oil Hydrocarbons in Food'. This opinion concluded that background exposure to Mineral Oil Saturated Hydrocarbons (MOSH) via food was considered to be a potential concern as, based on new toxicological information, foodborne Mineral Oil Aromatic Hydrocarbons (MOAH) with three or more, non- or simple-alkylated aromatic rings may be mutagenic or carcinogenic.

Mineral oil hydrocarbons have been classified into two main groups:

- i. **Mineral Oil Saturated Hydrocarbons (MOSH).** These are paraffin-like, open-chained, commonly branched hydrocarbons, such as alkanes and naphthene-like cyclic hydrocarbons (cycloalkanes).
- ii. **Mineral Oil Aromatic Hydrocarbons (MOAH)** mainly consist of highly alkylated mono- and/or poly-aromatic rings.

A large variety of compounds are included in these two groups. There are also a number of MOSH analogues that can result in the elevation of analytical MOSH values. Such analogues include some mineral oil refined products: poly-alpha olefins in synthetic lubricants and polymer oligomeric saturated hydrocarbons, which are oligomers of certain plastics such as polyethylene and polypropylene.

Mineral oil hydrocarbons and their analogues can enter the food chain at all stages. Some can be naturally occurring waxes and oils in fruits and vegetables, others can be introduced into foods via food additives and processing aids, or





**Erucic acid
is present in
rapeseed oil**

they can enter the food by migration from containers or packaging.

The food can also become directly contaminated by the use of mineral oils in production equipment, oil vapours, combustion gases and particulate airborne matter.

In January 2017, the European Commission, reacting to both EFSA's and the Scientific Panel on Contaminants in the Food Chain (CONTAM)'s concerns over the emerging toxicological evidence on MOAH, published a Recommendation on the need to monitor the presence of mineral oil hydrocarbons in food during 2017 and 2018. This monitoring was to be carried out in a wide variety of food sectors, and include the food contact materials used for those products. In 2020, discussions were ongoing in relation to extending the period and scope of the monitoring.

4.0 Plant Metabolised Contaminants

Plants have been a source of food for millennia and over this time, man has learned to avoid those containing

components with an immediate toxic effect. In some cases, such as cassava, a staple carbohydrate source in some parts of the world, which contains cyanide-related compounds, man had learned to subject the raw cassava to treatment processes to remove the cyanide component. All plant matter contains metabolites, some of which such as flavonoids, are considered to be of nutritional benefit while others can be dangerous. With advances in toxicological knowledge, new plant toxicants are emerging and those of serious health concern are being brought into legal control.

4.1 Erucic Acid

Erucic acid is an omega-9 fatty acid which is present in the oil-rich seeds of the plant family Brassicaceae, particularly rapeseed oil. Animal tests show that ingesting erucic acid over a period of time can lead to a heart condition called myocardial lipidosis. The main toxicological concern is for infants and young children whose low body weights make them susceptible if exposed to fats and oils containing it.

As a consequence, the European Union first set maximum levels for erucic acid in fats and oils in 1976, and similar controls were enforced in other parts of the world.

A plant oil which consistently contains the highest erucic acid levels is mustard oil, which should be used with caution in foods and supplements.

In terms of functional foods and supplements, the sources of vegetable oils used in a product should be selected based on their consistent erucic acid content, which should be compliant with all legal controls or official recommendations. Special care should be taken with the use of vegetable oil products targeted at infants and young children.

4.2 Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids (PAs) are a group of naturally occurring alkaloids based on the chemical structure of pyrrolizidine. PAs are produced by plants of certain plant genera as a defence measure against insect herbivores.

PAs enter the food chain either by the

use of a PA-containing plant or through contamination of food plants by PA-containing plants during cultivation and harvesting. They can also enter the food chain via livestock or poultry fed on PA contaminated feed, and also from bee products such as honey, where the bees have collected pollen from PA-containing plants. The problems of contamination by PA containing plants are considerable. It has been demonstrated that as few as one *Senecio* plant per hectare in a crop of St Johns Wort is sufficient to exceed the current threshold for PA levels.

The Codex Alimentarius Committee on Contaminants has produced a code of practice for '*Weed Control to Prevent and Reduce Pyrrolizidine Alkaloids in Foods*'. This code of practice focuses on weed control and provides guidance on good agricultural management practices to prevent and reduce PA contamination of crops.

The consequences of PA contamination can be serious for human health. PAs are hepatotoxic and have also been shown to be carcinogenic.

One of the issues that has delayed the collection of data on PAs is the agreement on which of the chemical forms should be assayed, and which should form the basis of enumeration for control purposes.

In 2017, the European Food Safety Authority in their review and opinion on PAs listed 17 alkaloids. Subsequently it has increased this list to 21 while some countries have considered 28 or more.

Supplement and functional food companies who have botanicals in their products need to be aware of the risk of PAs and have procedures in place to ensure these risks are controlled.

It is also important that the suppliers of botanical ingredients are aware of the



Bees may collect pollen from PA-containing plants

issues surrounding PAs and the potential for contamination of other botanicals and have instituted testing and controls. In all cases it is essential that Good Agricultural and Collection Practices (GACP) are maintained.

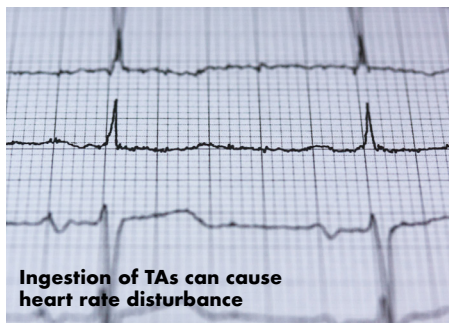
The evidence to date points to the fact that a reduction of PAs can only be obtained by reducing the potential for contamination at both the growing and harvesting stages of the botanical. In the context of botanicals for use in supplements only those sources and suppliers that can be confirmed as applying full and consistent GACP controls should be considered.

4.3 Tropane Alkaloids

Tropane alkaloids (TAs) are secondary metabolites that occur in several plant families, and particularly the family Solanaceae. Over 200 different TAs have been identified in various plants, the current knowledge of their relative toxicity and occurrence in food and animal feed is limited. As with PAs, the major risk of contamination with TAs is from co-harvesting from TA-containing weeds.

Ingestion of TAs can lead to a number of effects in humans including cardiac disorders and heart rate disturbance, depressive activity and effects on the Central Nervous System. They can also cause euphoric states and a number of reports of human TA toxicity relate to the deliberate consumption of plants for their hallucinogenic effects.

The majority of controls on TAs have been on animal feeds. However, there is a greater focus emerging on the contamination of human food with TAs, and more specifically on functional foods and supplement products containing



botanicals. As with PAs, companies need to institute controls on botanical ingredients and also ensure that their suppliers can also demonstrate control.

Surveys carried out on the dietary exposure of TAs in human foods are indicating that some population groups, particularly infants, toddlers and younger children, could exceed the safety guidelines for two of the TAs, atropine and scopolamine. High concentrations of these two substances were reported in tea and herbal infusions, cereal bars and spices, as well as in some corn products.

This could have an impact on functional foods and in the context of spices used in supplements. At present there appears to be no information as to whether TAs are concentrated by the processes used to manufacture herbal extracts.

5.0 Mycologically Produced Contaminants

Fungi comprise a group of organisms of about 99,000 species which contain chitin in their cell walls, differentiating them from plants and bacteria. The group includes the yeasts, moulds and mushrooms, all of which do not have chlorophyll and are unable to photosynthesise. Fungi are heterotrophs and have to get their nutrition via absorption from suitable substrates.

It is while the fungi are deriving their nutrition from the substrate that they produce metabolites. For example, the metabolism of carbohydrate sources by certain yeasts will produce alcohol and these yeasts are used for the production of alcoholic beverages.

Most fungal metabolites are the products of secondary metabolism and they can be produced when fungi (moulds) grow on food plants such as fruits, vegetables and cereal crops. Some of these metabolites are toxic to humans and are referred to as mycotoxins (from mycology, the study of fungi). One mould species may produce many mycotoxins, and several species may produce the same mycotoxin. A number of groups of mycotoxins are associated with plants used as sources of human food and the common cereal crops are particularly susceptible. The important mycotoxins from the point of view of human health are, or

are becoming, the subjects of regulatory control and are internationally considered to be chemical contaminants of food and animal feed. Mycotoxin ingestion in large enough doses can be fatal. In Kenya in 2004, 125 people died and almost 200 became seriously ill after consuming home-grown maize that had been contaminated with aflatoxin, a mycotoxin.

Currently, over 100 countries have regulations covering the presence of mycotoxins in the food and animal feed industries. The mycotoxins of primary concern for regulatory control are:

5.1 Aflatoxins

Aflatoxins are a group of mycotoxins produced by species of the fungus *Aspergillus* such as *A. flavus* and *A. parasiticus*.

Aflatoxins are classified into four types and given the nomenclature B1, B2, G1 and G2. Of the four, Aflatoxin B1 is considered the most toxic as it is directly associated with a number of adverse effects on human health, including liver cancers.

The mycotoxins produced by *Aspergillus* sp. can be present in a range of food sources, especially maize, spices, peanuts and tree nuts. The fungus is prevalent in warm and humid regions of the world and it can contaminate crops at all stages of growth, harvesting and storage. With regard to functional foods and supplements, there is a risk of aflatoxin contamination from all cereal products, maize, dried fruits, groundnuts and tree nuts, and a number of botanical ingredients. In the case of botanicals, of especial concern are *Capsicum* spp, including cayenne and paprika powders, *Piper* spp, *Myristica fragrans* (nutmeg), *Zingiber officinale* (ginger) and *Curcuma longa* (turmeric). If purchasing any of



Some fungal metabolites are toxic to humans

these botanicals, companies should be prudent and insist on routine assays being carried out on the ingredients and incorporate aflatoxin maximum levels into the raw material specifications.

5.2 Ochratoxin

Ochratoxins are a secondary metabolite of species of two fungi, *Aspergillus* sp and *Penicillium* sp.

Ochratoxin is in three forms denominated A, B and C. These three forms are chemically different and ochratoxin C is an ethyl ester form of ochratoxin A. Ochratoxin A has been identified as a carcinogen and a nephrotoxin and is linked to the formation of tumours in the human urinary tract.

Ochratoxins have been found as contaminants of a wide range of food commodities, including vine fruits, and the contamination can be found in fruit

juices and alcoholic beverages, such as beer and wine.

The risk of ochratoxin contamination of supplements and functional foods is mainly from contaminated cereal products, coffee products, grape products and certain botanicals including liquorice and vine fruits.

As with aflatoxins, companies should identify any ingredients at risk of ochratoxin contamination and incorporate appropriate controls into their raw material specifications.

5.3 Citrinin

Citrinin is a mycotoxin originally isolated from *Penicillium citrinum* and has since been found in over a dozen other species of *Penicillium* and also in some forms of *Aspergillus*.

Some of the fungal species now found to produce citrinin have been used in the production of human foods. *P. camemberti* is traditionally used in the process of making cheeses and *A. oryzae* is used in the production of soy sauce, miso and saki. Citrinin can also be present in monascus, a natural food colouring widely used in the Far East. Citrinin contamination has been reported in a wide range of cereal foods such as wheat, corn, barley, oats, rye and rice. It is associated with the 'yellowed rice disease' in Japan.

The significance of citrinin ingestion on human health is currently unclear but it appears to be associated with nephrotoxicity, particularly if ingested with Ochratoxin A. These two mycotoxins commonly occur together. Animal studies with rats showed an increased ratio of kidney weight to body weight after prolonged (32 week) exposure to citrinin. At 40 weeks the





rats also had small adenomas. There are indications that citrinin is genotoxic and probably mutagenic.

It is commonly found as a co-contaminant with Ochratoxin A, as it is produced by the same moulds. It is now becoming reasonable to believe that humans are much more frequently exposed to citrinin than previously thought. Based on available evidence the European Food Safety Authority in 2012 set a level with no concern for nephrotoxicity in humans at $0.2\mu\text{g}/\text{kg}$ body weight per day. Within Europe there has been a specific focus on citrinin in food supplements incorporating red yeast rice, which contains *Monascus purpureus*, and a maximum level in supplements has been imposed.

5.4 Ergot Alkaloids

Historically, ergot was the first mycotoxin to be identified and its effects have been reported for centuries. Ergot alkaloids are ingested by eating grain products,

particularly rye, contaminated with the fungus *Claviceps purpurea*. The most common form of ingestion was from bread made with contaminated flour. The disease, ergotism, which was first recorded in the ninth century was known as St Anthony's Fire and the symptoms can be separated into groups: the first is convulsive and includes spasms, seizures, mania and psychosis, while the second affects the blood supply to the extremities causing dry gangrene and ultimately the loss of affected tissues in the hands and feet.

Modern Good Agricultural Practices and grain cleaning have significantly reduced the incidence of ergotism in humans, although it is still an important veterinary problem. Ergot contamination is controlled by legislation in a number of countries and there are normally strict controls on cereal based products intended for infants and young children.

5.5 Deoxynivalenol

Deoxynivalenol (DON) is a mycotoxin produced by *Fusarium* species of mould.

It can contaminate cereal and grain crops such as corn, wheat, oats, barley and rice. Human exposure occurs when eating either contaminated cereals or foods of animal origin, particularly milk, eggs, liver and kidney, where the animals have consumed contaminated feed.

DON is probably the most common mycotoxin contaminant of grains and their subsequent products. DON toxicity can be characterised by its strong emetic effects after consumption and it can also cause abdominal pain, diarrhoea, dizziness and fever. DON toxin is also known as vomitoxin.

Fusarium contamination of grains occur during warm and wet weather with



a constant high humidity. When the grain is stored it has been found that *Fusarium* growth and DON production cease when the moisture levels in the grain fall below 22%.

The control of the contamination needs strict adherence to Good Agricultural Practice, the use of fungal control agents and strict control and drying of the stored grains to reduce the moisture content.

Where countries have applied legal limits on the presence of DON, the limits normally not only cover the presence of DON in unprocessed cereals but also in dry pasta, bread and baked goods, cereal snacks (such as cereal bars) and breakfast cereals. There are also normally controls on cereals used in foods for infants and young children.

Companies marketing functional foods and nutritional bars containing cereals

should ensure that their raw materials comply with the legal limits for DON in the countries of intended sale.

5.6 T2 and HT2 Toxin

T2 and HT2 mycotoxins are a pair of toxins produced by the growth of *Fusarium* spp. on cereal crops such as oats, wheat, barley, maize and rye.

Exposure to humans of HT2 and T2 toxins can result in a number of adverse effects including severe gastroenteritis, necrosis of skin and muscles, enlarged lymph nodes, laryngeal oedema and after lengthy exposure, slow degeneration of the bone marrow. The toxic effects on farm animals eating contaminated cereals and animal feeds can be very severe.

In August 2017 the European Food Safety Authority established a Tolerable Daily Intake for T2 and HT2 toxins of 0.02µg/kg bw/day and from an exposure assessment concluded that the exposure of these toxins was highest in toddlers and infants.

As with the other mycotoxins prevalent in cereals, T2 and HT2 toxins need to be controlled by Good Agricultural Practice and controls on the storage of the grains.

5.7 Patulin

Patulin is a mycotoxin produced by a number of moulds from species of *Penicillium*, *Aspergillus* and *Byssoschlamys*. *P. expansum* appears to be the organism most frequently responsible for patulin production.

Patulin is associated with over-ripe and mouldy fruits, in particular rotting apples, figs and grapes. It can be found in apple and grape juices but is destroyed by the fermentation process so is not found in cider.

Its presence in fruits and their



Patulin is associated with rotting apples

by-products is regulated in many countries around the world.

While there is yet no evidence that patulin is carcinogenic, it has been reported to damage the immune system in animals and it is also associated with neurotoxicity.

As patulin is found in over-ripe and damaged fruit, which has attracted the mould growth, its control is through good harvesting and storage practices. There is an increased risk of toxin production from long-term storage of raw fruits after harvest and being held at ambient temperatures.

With regard to supplements and functional foods, there is a possible risk of patulin contamination in products based on fruits, such as dried fruit and dried fruit juice nutritional bars or drinks. Many countries impose legal controls on levels of patulin in products aimed at babies, infants and young children.

5.8 Zearalenone (ZEA)

Zearalenone (ZEA) is a mycotoxin produced by some species of *Fusarium* and *Gibberella*, particularly *F. graminearum* and *F. culmorum*.

ZEA, also known as RAL and F-2 mycotoxin, occurs in a range of cereals commonly consumed by humans such as flour, bran, maize, maize oil and baked goods such as bread and pastries.

ZEA is of human health concern as it has been classified as an endocrine disruptor, as it mimics the reproductive hormone oestrogen.

Animal studies show that the clinical effects of ZEA can include an enlarged uterus, swelling of the vulva and vagina (vulvovaginitis), enlarged mammary glands and periods of infertility in pigs. It has also been found to have an adverse effect on testosterone synthesis. A European Food Safety Authority opinion stated that toxicodynamic information indicates that it is likely that the human female would not be more sensitive to zearaleone and its metabolites than the female pig (on which clinical studies were based). The same opinion stated that limited data indicates that dietary exposure of ZEA in vegetarians could be up to 2-fold higher than for the general population.

Studies indicate that ZEA is not carcinogenic.

The main sources of contamination for humans is from grains, grain-based foods and grain milling products. It can be found in bread and fine bakery wares, and also in corn germ oil and wheat germ oil. Breakfast cereals are a common source of dietary exposure.

With regard to supplements and functional foods, the products likely to be at risk of contamination are cereal bars and cereal products for infants and young children.

5.9 *Fusarium* Toxins

Over 50 species of *Fusarium* produce toxin and have a history of infecting food crops, particularly cereal crops such as wheat and maize.

Some of these toxins have been discussed previously, such as DON, ZEA and T2 and HT2 toxins, but there are a number which could have an adverse effect on human health but which have not yet been fully investigated.

One group, the fumonisins, are mycotoxins that can have an adverse effect on human health and which are found on maize and cereal crops worldwide. At the Codex Alimentarius Commission meeting held in July 2014, maximum levels for the presence of fumonisins in raw maize grain were set at 4mg/kg and for maize flour and maize meal 2mg/kg. These values have been incorporated into the legislation of a number of countries, including the European Union member states.

5.10 *Alternaria* Toxins

Alternaria species are ascomycete fungi. For some time they have been known to be major plant pathogens but more recently they have been identified as human allergens causing a number of

allergic reactions and potentially leading to the development of asthma.

There are 299 species in the genus and they form air-borne spores. There is currently no specific toxicity data for these mycotoxins, but some authorities are considering whether to set maximum levels for food categories that may be major contributors to dietary exposure. These categories are likely to include cereal grains and products derived from cereals and could potentially impact on some functional foods, such as cereal bars.

6.0 Process Induced Contaminants

It has been known for centuries that chemical reactions occur during the processing of foods and drinks, and man has used them to his advantage. One common reaction, known as the Maillard



The Maillard reaction leads to the browning of foods

reaction, is the browning of foods that also gives the browned food its distinctive flavour. This reaction was elucidated by Louis-Camille Maillard, a French chemist, in 1912. He found that the browning was caused by a chemical reaction between amino acids and reducing sugars in the presence of heat in the range of 140 to 165°C. The use of the Maillard reaction is an important part of the culinary repertoire.

From the early part of the 21st century research is showing that some of the chemical reactions that can occur in foods may not be so benign, and can result in the production of compounds with an adverse effect on human health.

6.1 3-monochloropropane-1, 2 diol (3-MCPD)

3-MCPD and its esters is a member of a group of food contaminants known as chloropropanols. 3-MCPD has been classified by the IARC as Group 2B 'Possibly carcinogenic in humans' and has come under regulatory control in a number of countries.

3-MCPD is formed as a product of a reaction between a lipid source and a chlorine source in the presence of heat. It was originally discovered in Asian sauces such as soy and hoisin sauces, and in hydrolysed vegetable protein (HVP) based products where hydrochloric acid is added to the foods during processing to speed up the breakdown of proteins into amino acids. 3-MCPD is found in Asian foods where hydrochloric acid is used in place of the slow traditional fermentation processes.

In 2008 the UK Food Standards Agency reported on a survey of food products and found a number of branded foods, including sliced bread, crackers, cheese

3-MCPD has been found in palm and vegetable oils



and beef-burgers, with 3-MCPD levels above the estimated safe limits. In 2016 its occurrence was found in teabags and paper cups for hot beverages.

Palm oil has been found to be especially at risk of 3-MCPD contamination.

3-MCPD has also been found in ingredients relevant to the supplement and functional food industry, such as vegetable oils and fish oils. Its presence in these oils can be traced to the refining and processing of the oils, particularly where high temperatures and de-odourisation are used.

In January 2017, the European Food Safety Authority updated its Tolerable Daily Intake value for 3-MCPD in food to 2.0µg/kg bw/day.

6.2 Glycidyl Esters

Glycidyl fatty acid esters (2,3-Epoxy-1-propanol fatty acid esters) are commonly found in similar circumstances to 3-MCPD.

Glycidyl esters are found in refined vegetable oils, with palm oils and fats having high levels. By-products of these oils such as margarines and spreads are the main source of human exposure, but in recent years it has become clear that fish oils and other marine oils can also contain high levels of glycidyl esters.

The esters are formed during the refining of the oils, especially if temperatures during refining are around 200°C. When consumed, the esters are converted into glycidol in the body, and it is the glycidol for which there is evidence of both genotoxic and carcinogenic effects.

6.3 Acrylamide

Acrylamide is a chemical that has been used in a number of industrial processes such as the production of paper, dyes and some plastics. As acrylamide has for some time been considered a possibly carcinogenic industrial chemical, exposure to the substance by workers in the relevant industries has been monitored. Smokers and people exposed to tobacco smoke are also exposed to acrylamide, with smokers having three to five times the levels of the chemical in their systems compared with non-smokers.

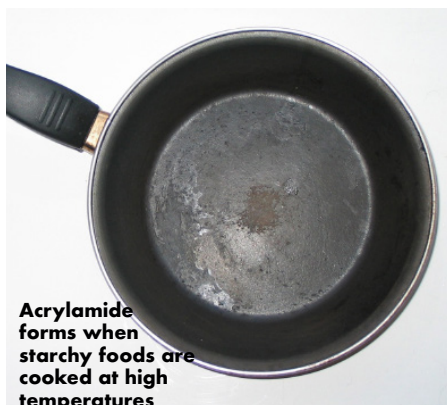
At the start of the 21st century a study in Scandinavia showed that some subjects that should not have been exposed to acrylamide (i.e. not industrial workers and non-smokers) had surprisingly high levels of acrylamide in their blood. Further investigation showed that the

exposure was due to the presence of acrylamide in foods, particularly fried and baked starchy foods. The first scientific paper of this study was published in 2002. Subsequent work has established that acrylamide is formed when foods containing both the amino acid asparagine and a reducing sugar are subjected to high temperatures, such as in baking, roasting and frying.

The IARC classifies acrylamide as a 'probable human carcinogen' and in the USA it has been listed as 'reasonably anticipated to be a human carcinogen'.

In 2017 the European Union introduced legislation requiring the food industry to introduce practical measures to mitigate the formation of acrylamide in a range of susceptible foods as part of their food safety management systems. Companies are required to undertake representative sampling and analysis as appropriate to monitor the levels of the contaminant in their products, and to keep records of the measures taken and the results of the tests. This law applies to manufacturers producing a wide range of baked and fried starch-based foods, which are listed in the regulation.

With regard to functional foods and supplements, the products covered by the



EU legislation include baby foods and processed cereal foods for infants and young children, cereal bars and breakfast cereals.

6.4 Chlorate and Perchlorate from Processing

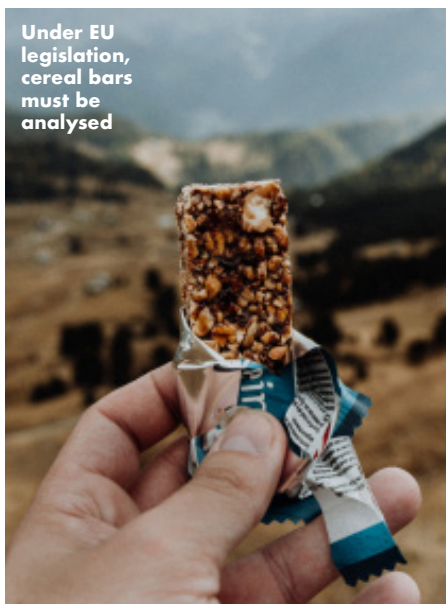
For a number of years, the presence of chlorate and perchlorate in water has been identified as a health concern, and more recently it has been found that chlorate can be formed in foods during specific processing conditions. Although the toxicology and risk assessment for these two substances are related, their occurrence in water and food occurs through different routes.

6.4.1 Chlorate

Chlorates (molecular formula ClO_3^-) are strong chemical oxidants with herbicidal and biocidal activity. They have previously been used as pesticides and as a component of biocidal products, though these uses are now prohibited in many countries. Within the EU, chlorates have not been authorised for use in pesticides since 2008, with a complete ban from 2010, and sodium chlorate is no longer permitted to be used in biocide products.

Drinking water is the main source of chlorate in the diet, with the chlorate appearing as a by-product of the water or water system's treatment with chlorine disinfectants. However, chlorate can be present in food from the use of chlorinated water in irrigation or food processing, and from residues of chlorine-based sanitisers used during the cleaning of food processing equipment.

The most affected food categories are fruits and vegetables, with the frozen varieties often accounting for the highest levels of chlorate.



While there is considerable evidence of the presence of chlorates from the washing and processing of fruits and vegetables, data on its occurrence in other foods is sparse. There have been reports of high levels being found in 80% of the samples of food supplements tested, but there are no details of the potential source of the contamination. Likewise, there have been reports of chlorates being found in products containing kelps and sea salt. Chlorates have also been found in a range of herbs and spices. Evidence is emerging of chlorate presence in dairy products, with two samples of low-fat yoghurts giving high results.

In terms of toxicity, ingested chlorate appears to target the thyroid gland in humans and has the specific effect of decreasing the availability of iodine. It is a competitive inhibitor of thyroid iodine uptake and this can lead to long-term conditions such as the development of toxic multi nodular goitre, particularly in

populations with mild to moderate iodine deficiency.

The ingestion of large doses of chlorate, in the order of 50mg chlorate/kg bw/day, has induced lethality in humans.

A report by the European Food Safety Authority published in June 2015 concluded that the youngest population group (babies, infants and toddlers) showed the highest dietary exposure to chlorates. Within the EU, controls placed on chlorate levels in specific foods under the pesticides legislation.

6.4.2 Perchlorate

Unlike chlorate, perchlorate can occur naturally in the environment in deposits of nitrate and potash, with one mechanism for its presence being atmospheric production and deposition over long periods of time. However, the primary factor behind its occurrence in the environment is human action, with the main source of contamination of water and food most likely being the use of fertilisers of natural origin, such as Chilean nitrates. Contribution to perchlorate contamination can also occur

from industrial processes, particularly the use of ammonium perchlorate as a solid propellant for rockets and missiles and perchlorate use in fireworks and explosives, and from the degradation of chlorine-based products such as sodium or calcium hypochlorite.

Perchlorate has been reported to occur in a wide range of foods, including vegetables, fruit, milk and dairy products, juice, beer, wine and bottled water. And in the EU, vegetables, vegetable product, milk and dairy products were identified in EFSA's chronic exposure assessment as the most important contributors to perchlorate exposure across the population.

As with chlorate, perchlorate appears to have an adverse impact on iodide uptake in the thyroid gland, reducing the ability to produce thyroid hormones. In addition, it is a potential carcinogen.

In the EU, maximum levels have been set under the contaminants legislation for perchlorates in foods.

7.0 Synthesised (Man-made) Contaminants

The international trade in food commodities and processed foods brings with it the risk of chemical contamination, particularly when the laws of the exporting country and the importing country are at variance.

While the major groups of contaminants enter the food chain by routes outside the direct control of the food producers, such as the presence of heavy metals or mycotoxins, there are a large number of man-made substances developed over the past century, which are still used in some areas of the world or are very persistent.

For example, there are certain



More than 1000 active compounds have been registered as pesticides across the world



pesticides and biocides still used in some areas of the world that are banned in many other countries or regions.

7.1 Pesticides

A large group of synthesised chemicals comprises many substances used over decades as pesticides and herbicides. Pesticides are designed to specifically target and kill insect pests on crops, whereas herbicides target and kill undesirable plants or 'weeds' which can hinder the growth of a crop. It is inevitable that these substances will leave residues on the crops.

More than a thousand active compounds have been registered as pesticides across the world and these, used singly or in combination, have been developed into tens of thousands of commercial products. The vast number of substances and their combinations makes it very difficult to be at all specific about

the toxic effects of pesticides in general. By their nature, pesticides are toxic to varying degrees and the hazard for any particular chemical group can be illustrated by the equation:-

$$\text{Hazard} = \text{toxicity} \times \text{exposure}$$

In general terms the human toxicity of the main groups of pesticides can be given as:-

Animal studies indicate that some pesticide groups are carcinogenic while others such as chlordane and lindane are tumour-promoters.

In terms of food supply for a rapidly increasing human population, pesticides are an important agricultural tool, so rather than ban them outright the World Health Organisation (WHO) and the Food and Agriculture Organization (FAO) under the auspices of the United Nations have been working to obtain commonality of national controls on the levels of pesticide residues in food

CLASS	EXAMPLES	AREA OF EFFECT
Organochlorines	DDT, toxaphene, dieldrin, aldrin	Reproductive, nervous, endocrine, & immune system
Organophosphates	Diazinon, glyphosate, malathion	Central nervous system
Carbamates	Carbofuran, aldicarb, carbaryl	Central nervous system
Pyrethroids	Fenpropanthrin, deltamethrin, cypermethrin	Poorly understood

commodities and foods. The Codex Alimentarius Commission maintains an on-line database on Maximum Residue Limits (MRLs) for pesticides in both foods and animal feeds, as does the European Commission for the European Union. The MRLs have been incorporated into the food legislation of most countries.

7.2 Ethylene oxide

Ethylene oxide (ETO or EtO) is a highly reactive and flammable gas with sterilising properties. It has the molecular formula C_2H_4O and is used industrially in the manufacture of ethylene glycol. EtO has been used for decades for the sterilisation of medical devices and certain food ingredients, such as herbs and spices, as it destroys most viruses, bacteria and fungi, including bacterial spores. The IARC classifies EtO as a known human carcinogen.

Where EtO is used for the sterilisation of food ingredients, techniques such as aeration have been developed to remove residues of the gas and reduce the formation of reaction by-products, such as 2-chloroethanol. Analysis for detection of EtO sterilisation should include tests for EtO residues and 2-chloroethanol.

However, it should be noted that 2-chloroethanol is also a standalone chemical entity that is used in some industrial applications, and it may additionally be formed via certain other chemical reaction pathways.

The use of EtO is prohibited in certain regions of the world, including in the EU, where it is not allowed for the treatment of foods, thus companies should ensure that their raw materials comply with the legal limits for EtO in the countries of intended sale.



8.0 Deliberate Contaminants (Adulterants)

Sadly, over the centuries there have been numerous attempts to obtain extra pecuniary advantage from the adulteration of food.

What is now regarded as the first law on food quality was enacted in England during the reign of Henry II (1154 – 1189). This law was concerned with the adulteration of flour with substances such as chalk. When a food or food ingredient is either in short supply or suddenly becomes more expensive, the risk of deliberate adulteration increases. Within the supplement and functional food industry, there have been many examples of such practices, including the addition of cheaper vegetable oils to fish oils, particularly cod liver oil, the addition of other substances to bulk out the bee product propolis and the attempts to simulate aloe vera gel.

Adulteration is an aspect of food fraud which requires constant vigilance, hence the need for good traceability, auditing of suppliers and suitable identification and purity tests.

Occasionally, an adulteration can result in a serious impact on human health leading to fatalities. This was the situation

which first emerged in China in 2008, although it can be traced back to an adulteration of pet foods in 2007. The problem was caused by the addition of a substance called melamine to foods. Melamine is rich in nitrogen and is widely used in the production of certain plastics. In its pure state it is normally in the form of white crystals. It has the chemical formula $C_3H_6N_6$ which means the 66% w/w of the substance is nitrogen.

In China, as in many countries, the initial tests for milk quality include values for water and protein content. The deliberate dilution of milk at the milk collecting stations to increase volumes meant that, as a consequence, protein content of the milk was also diluted.

The most commonly used test for protein content is the Kjeldahl method, which is based on digestion of the sample, a distillation step, followed by titration. The final value is of organic nitrogen and the total Kjeldahl nitrogen value is used as a surrogate for the protein value in a food. The nitrogen value is multiplied by an international conversion factor established for the particular food group. For example, the factor for dairy products is 6.38 whilst that for calculating protein in meats is 6.25.

As melamine is a high source of nitrogen, some unscrupulous individuals

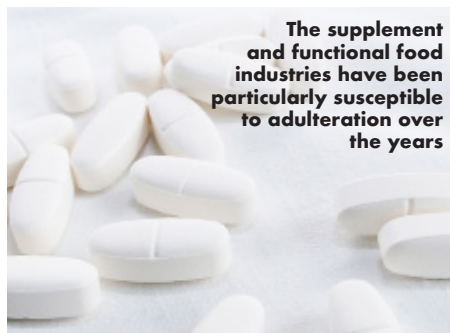
in China began adding powdered melamine to the milk to bring the nitrogen (protein) content up to the required value.

Melamine when consumed had an adverse effect on human health, with the first target organs being the kidneys. The consequences of the Chinese melamine issue affected a large number of countries across the world, particularly as a large proportion of the milk was dehydrated and exported as dried milk. Official reports on the total number of people affected by the melamine adulteration vary but the most widely quoted figure is that 54,000 infants and young children were made ill in China, with some estimates much higher. The exported milk powder was used in other parts of the world in baby foods, other foods and confectionery, particularly chocolate, resulting in very high volumes of product having to be scrapped, with consequential financial losses.

The melamine issue accentuates the constant need for vigilance and good quality control in relation to the purchasing and supply of ingredients. Over the years the supplement and functional food industries have been especially susceptible to fraud and adulterations, and this is a high risk when certain active ingredients suddenly become very popular but there is a finite source of supply. There have been a number of situations where the demand for a botanical ingredient has outstripped the annual production and adulteration has occurred.

9.0 Control of Contaminants

Specialist foods such as supplements and functional foods tend to contain a range of food additives and ingredients from a



wide variety of sources. Many of these ingredients are used in small quantities when compared to most other food products.

In addition, the manufacturers of specialised foods are almost at the end of the food chain and each ingredient will most likely have been handled by a number of agents or brokers between its original production and its arrival at its final manufacturing site.

The control of chemical contamination must start with the origin of the ingredient, such as the field or orchard as in the case of ingredients of botanical origin. If contaminated at source, for example, by dioxins or polycyclic aromatic hydrocarbons, there is a greater likelihood that the contamination will be concentrated by the dehydration or extraction of the ingredient rather than reduced.

Heavy metals or persistent environmental contaminants in an ingredient can be very difficult or impossible to remove or reduce, or the cost of removal can be commercially prohibitive.

A contaminated ingredient will contaminate the final product at a level proportional to the percentage of the ingredient in that product. Thus, if an ingredient contains a contaminant at five times the legal level and it is used at 25% w/w of a product, the final product will also be above the legal level. Within the EU it is illegal to use any ingredient which exceeds the legal limit, even if it will be diluted in the final product.

As the final product manufacturer is so remote from the source and manufacturing of the majority of the ingredients, it is essential that effective controls and systems are in place to ensure that they do not take delivery of contaminated



ingredients.

The onus on control has to be on the producers and suppliers of an ingredient who should be able to demonstrate compliance of a batch with all contaminants controlled by legislation in the countries of intended sale of the final product. If the supplier cannot guarantee to meet these requirements they should not be approved of as a source of supply.

9.1 Controls by Manufacturers of Final Products

A manufacturer of supplements and/or functional foods can take a number of practical steps to ensure compliance with the law.

This requires a detailed assessment of each ingredient and food additive to determine both the potential for contamination and also the legislative controls on either the ingredient or the final product. The presence of contaminants should be considered to be part of a Hazard Analysis and Critical Control Point (HACCP) programme.

Once the potential contaminants have been determined they should be included in the raw material specifications with the upper limits and test methods. The raw material specification should be the

quality specification that has to be met for all listed parameters before the raw material can be accepted.

Many of the tests for the organic contaminants such as mycotoxins, dioxins and PAHs are expensive, and should be carried out on every lot (batch) of an ingredient at the largest representative bulk stage. The manufacturer of the ingredient should be responsible for testing and certifying.

Skip testing has to be very carefully considered and scientifically evaluated on a case by case basis and only used if considerable chronological data are available covering a number of years and seasons. Skip testing carries with it serious risks.

In 2006 a company in the United Kingdom introduced skip testing for dioxins in cod liver oil. Subsequently an official control test on a packed product found that the cod liver oil was above the then European Union maximum levels for dioxins resulting in a substantial recall of a range of products containing the oil. The company sustained a very large financial loss. Investigations showed that whilst the tested batch was just below the limit, the skipped batches were over.

In the context of supplement and functional foods the group of ingredients most likely to contain more than one contaminant are the botanicals that, depending on the region in which they are grown and harvested, can be

susceptible to contamination by a range of heavy metals, mycotoxins, polycyclic aromatic hydrocarbons, dioxins and pesticide residues. All these contaminants should be considered when preparing raw material specifications for botanicals. It is also important to be aware that the extraction processes used for the preparation of botanical extracts do not always eliminate contaminants present in the source material, and it has been demonstrated that a number of organic contaminants, such as PAHs, can be concentrated in the final extract.

Failure to undertake appropriate and adequate testing of the raw materials for chemical contaminants has been shown to be a false economy, as once the ingredients have been incorporated into the final product it is far more expensive to destroy a packed product if it is found to be contaminated above a legal limit.

It is essential that a product manufacturer establishes a good scientific dialogue with the raw material supplier and that the raw material supplier carries out the required testing, even if it means incurring costs of analyses that have to be passed on to the customer.

Contractually it should be, or should be made, the supplier's responsibility to undertake appropriate testing and to be able to certify that the raw material is compliant with the legislation in respect of all contaminants.

The Codex Alimentarius Committee on Contaminants in Foods (CCCF) was established to assess the evidence and endorse permitted maximum levels, or guideline levels, for contaminants and naturally occurring toxicants in human foods and animal feeds.

The Committee's remit also includes the development of Codes of Practice for the



**Skip testing
is risky**

reduction or elimination of contaminants. The Codes of Practice already published, and available on the Codex Alimentarius website, include almost all the contaminants covered by different national legislation, such as heavy metals, dioxins in food, mycotoxins and pyrrolizidine alkaloids.

As CCCF is an international organisation under the auspices of the United Nations and supported by almost all the countries in the world, the Codes of Practice and Codex Standards and the maximum levels on contaminants given in the Codex General Standard for Contaminants and Toxins in Food (GSCTF) should act as a basis for discussion with suppliers from third countries, particularly where their national legislation does not cover a particular contaminant.

Manufacturers of supplements and functional foods should understand that the acceptance of a contaminated ingredient into their warehouse can be a source of major problems and potentially considerable expense to the company.

For those companies producing their products in the EU or exporting to the EU, Article 3 of EU Regulation (EC) No 1881/2006 on 'Setting maximum levels for certain contaminants in foodstuffs' specifically prohibits the use in food of any ingredient not complying with the maximum levels for any contaminant listed in the Annex to the Regulation.

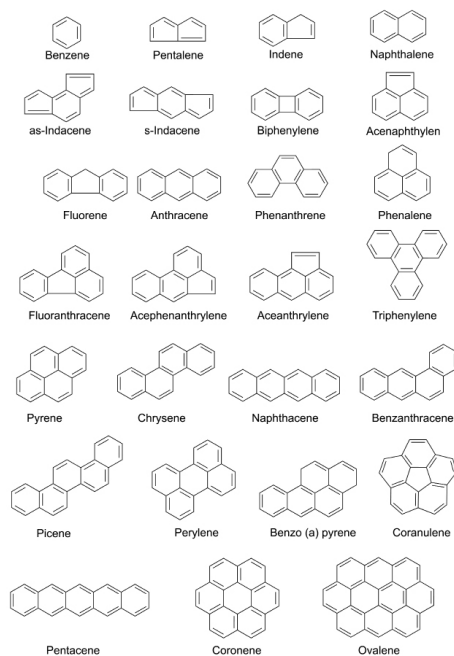
It also states that food and ingredients with a high level of a contaminant must not be mixed with one with a lower level, i.e. to bring the level down to below the limit. In addition, foodstuffs subjected to sorting or other physical treatment to reduce contamination levels must not be mixed with foods intended for direct

human consumption or with foodstuffs intended for use as a food ingredient, and foodstuffs found to contain mycotoxins must not be deliberately detoxified by chemical treatments.

Other EU legislation prohibits the sending, or returning, of products or ingredients with contaminants above the legal limits to any other country, unless the government of that country agrees to accept them. Usually, the only option for a contaminated consignment in the EU is destruction.

9.2 Analysis of Chemical Contaminants

The very wide range of inorganic and organic chemicals that can be found as contaminants in food provides a number of challenges to the industry in terms of accurate analyses. These challenges are enhanced by the very wide





Microgram and picogram controls require analytical instrumentation validated to the levels of detection needed

variety of matrices found in compounded foods, and in this respect supplements and functional foods with their wide and diverse range of ingredients can be one of the more complex categories in terms of analysis. The situation is exacerbated by the range of analytical instruments and the levels of detection required for compliance with food legislation internationally.

This can be illustrated by the requirements for a supplement range containing botanicals and vegetable oils. This would probably require testing for heavy metals, mycotoxins, dioxins and PAHs. The heavy metals are measured in milligrams or a thousandth of a gram while the mycotoxins and PAHs are controlled at microgram levels or millionths of a gram. The legislation for dioxins and PCBs, however, are at picogram level or a trillionth of a gram.

Relationship to a Gram

Milligram	0.001 g
Microgram	0.000001 g
Nanogram	0.000000001 g
Picogram	0.000000000001 g

This disparity in levels means that the microgram and picogram controls require

analytical instrumentation validated to the levels of detection needed. For example, the tests would need to be able to accurately quantify the contaminant at least to a decimal of the legal limit. This means for a microgram limit the test should detect to 10^{-7} g or lower and for picograms to 10^{-13} g. Therefore, laboratories can only be used for control purposes if they can meet the required level of detection.

This requirement can severely limit the availability of suitable equipment and can often mean that manufacturers have to rely on contract laboratories. The very high capital cost of these instruments, and the cost of providing skilled technicians to use them make it prohibitive to carry out this specialised testing 'in house'.

As it is inevitable that for most manufacturers there will need to be some sub-contracting of the analyses for chemical contaminants it is essential that the company establishes a scientific dialogue with the contract laboratory.

This dialogue must include:

- **Confirmation that the method of**

analysis and the equipment to be used has been validated for the particular analysis and levels of detections required to meet legal compliance.

- Confirmation that only those personnel who have been trained and validated for the required testing will be used for the companies testing and that any changes in personnel will be notified to the company.

- Documentary evidence that the methodology used for the tests has been carried out to the requirements of the legislation where a method is prescribed in law, and that the analytical criteria have been met.

- Confirmation that all 'in house' modifications have been validated and fully documented and accredited for the ingredient and product matrices being tested.

- Evidence that the laboratory routinely participates in proficiency tests.

The participants on behalf of the company taking part in the dialogue must have sufficiently detailed technical/scientific knowledge of the testing to be

The 2005 dioxin in cod liver oil crisis meant that product worth millions of pounds had to be destroyed



able to completely assess the outcome of the discussion.

It has to be accepted that, because of the issues outlined above, the testing for many of the organic contaminants is expensive. The purchasing of contract analytical testing has to be based on the laboratory expertise and the quality standards in the laboratory. This is not an area where there are many options and the contracting company needs to carry out a full due diligence investigation if offered competitive quotations that are very significantly cheaper.

During the dioxin in cod liver oil crisis of 2005, a number of companies had gone to laboratories giving low quotes for what was a very expensive test, only to subsequently discover that their product which had been given negative results by the laboratories for dioxins had not achieved the level of detection required by the law, as the results were based on 10^{-10} or 10^{-11} and not on 10^{-13} required to give an accurate result. Thus, product worth millions of pounds had to be destroyed for the sake of a few thousand pounds of apparent savings.

It is important that all analyses undertaken for the purposes of legal compliance are based on officially recognised sampling procedures for either the raw materials or the finished product.

In some regulatory regimes, such as the EU, the sampling procedures are incorporated into the law and where this is the case the methodology must be used.

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ANNEX I

Dioxins, Furans and Polychlorinated Biphenyls

Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessment of Polychlorinated dibenzo-p-dioxins, Dibenzofurans, and Dioxin-Like Polychlorinated Biphenyls¹

Compound	2005 TEF ²
DIOXINS Polychlorinated dibenzo-p-dioxins (PCDDs)	
2,3,7,8-Tetrachloro dibenzo-p-dioxin (TCDD)	1
1,2,3,7,8-Pentachloro dibenzo-p-dioxin (PeCDD)	1
1,2,3,4,7,8-Hexachloro dibenzo-p-dioxin (HxCDD)	0.1
1,2,3,6,7,8-Hexachloro dibenzo-p-dioxin (HxCDD)	0.1
1,2,3,7,8,9-Hexachloro dibenzo-p-dioxin (HxCDD)	0.1
1,2,3,4,6,7,8-Hexachloro dibenzo-p-dioxin (HxCDD)	0.01
Octachloro dibenzo-p-dioxin (OCDD)	0.0003
FURANS Polychlorinated dibenzofurans (PCDFs)	
2,3,7,8-Tetrachloro-dibenzofuran (TCDF)	0.01
1,2,3,7,8-Pentachloro-dibenzofuran (PeCDF)	0.03
2,3,4,7,8-Pentachloro-dibenzofuran (PeCDF)	0.3
1,2,3,4,7,8-Hexachloro-dibenzofuran (HxCDF)	0.1
1,2,3,6,7,8-Hexachloro-dibenzofuran (HxCDF)	0.1
1,2,3,7,8,9-Hexachloro-dibenzofuran (HxCDF)	0.1
2,3,4,6,7,8-Hexachloro-dibenzofuran (HxCDF)	0.1
1,2,3,4,6,7,8-Heptachloro-dibenzofuran (HpCDF)	0.01
1,2,3,4,7,8,9-Heptachloro-dibenzofuran (HpCDF)	0.01
Octachloro-dibenzofuran (OCDF)	0.0003
POLYCHLORINATED BIPHENYLS (PCB congener number)	
3,3',4,4'-Tetrachloro-biphenyl (77)	0.0001
3,4,4',5-Tetrachloro-biphenyl (81)	0.0003
3,3',4,4',5-Pentachloro-biphenyl (126)	0.1
3,3',4,4',5,5'-Hexachloro-biphenyl (169)	0.03
2,3,3',4,4'-Pentachloro-biphenyl (105)	0.00003
2,3,4,4',5-Pentachloro-biphenyl (114)	0.00003
2,3',4,4',5-Pentachloro-biphenyl (118)	0.00003
2',3,4,4',5-Pentachloro-biphenyl (123)	0.00003
2,3,3',4,4', 5-Hexachloro-biphenyl (156)	0.00003
2,3,3',4,4',5'-Hexachloro-biphenyl (157)	0.00003
2,3',4,4',5,5'-Hexachloro-biphenyl (167)	0.00003
2,3,3',4,4',5,5'-Heptachloro-biphenyl (189)	0.00003

1 Numbers in brackets after the chemical names for PCBs refer to the allocated congener number.

2 Adapted from van den Berg et al. (2006); WHO's Web site on dioxin TEFs, available at: http://www.who.int/ipcs/assessment/tef_update/en/

Sample Calculation for Toxicity Equivalence (TEQ):

Using the 2005 WHO TEFs (Van den Berg et al. 2006), the Toxicity Equivalence for each DLC is estimated by multiplying the measured DLC concentration by the TEF corresponding to the DLC. The TEQ for the media sample is determined by summing the individual TEQ for TCDD with DLCs in the mixture. For example:

Individual concentration of TCDD and DLCs in an environmental sample:

2,3,7,8 TCDD.....	10 ppt (parts per trillion)
2,3,4,7,8- PeCDF	30 ppt
PCB 126.....	20 ppt
TEFs	
2,3,7,8 TCDD.....	1
2,3,4,7,8- PeCDF.....	0.5
PCB 126.....	0.1

Individual TEQ:

2,3,7,8 TCDD.....	10 ppt x 1 = 10 ppt TEQ
2,3,4,7,8- PeCDF.....	30 ppt x 0.5 = 15 ppt TEQ
PCB 126.....	20 ppt x 0.1 = 2 ppt TEQ

Total TEQ

10 ppt + 15 ppt + 2 ppt = 27 ppt TEQ

ANNEX II

The 21 PAs for which the European Commission has agreed the analytical methodology with the EU Reference Laboratory (EURL) are as follows:

echimidine	lycopsamine-N-oxide
echimidine-N-oxide	retrorsine
europine	retrorsine-N-oxide
europine-N-oxide	senecionine
heliotrine	senecionine-N-oxide
heliotrine-N-oxide	seneciphylline
intermediate	seneciphylline-N-oxide
intermediate-N-oxide	senecivernine
lasiocarpine	senecivernine-N-oxide
lasiocarpine-N-oxide	senkirkine
lycopsamine	

14 additional pyrrolizidine alkaloids are known to co-elute with one or more of the above identified 21 pyrrolizidine alkaloids when certain analytical methods are used:

indicine	possible co-elution with lycopsamine/intermediate
echinatine	
rinderine	
indicine-N-oxide	possible co-elution with lycopsamine-N-oxide/intermediate-N-oxide
echinatine-N-oxide	
rinderine-N-oxide	
integerrimine	possible co-elution with senecivernine and senecionine
integerrimine-N-oxide	possible co-elution with senecivernine-N-oxide and senecionine-N-oxide
heliosupine	possible co-elution with echimidine
heliosupine-N-oxide	possible co-elution with echimidine-N-oxide
spartioidine	possible co-elution with seneciphylline
spartioidine-N-oxide	possible co-elution with seneciphylline-N-oxide
usaramine	possible co-elution with retrorsine
usaramine-N-oxide	possible co-elution with retrorsine N-oxide



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