15
Other Biologically Active Substances in Food

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15.1 The Chemical Complexity of Food

Food is a complex mixture of a wide variety of chemical components. It is more than just a collection of nutrients. In addition to the nutritionally important components such as protein, fat, carbohydrate, water, vitamins, minerals and dietary fibre, food contains other components which may have biological activity. These include colours, flavours, food additives, natural and artefactual contaminants, and many other products of plant and animal metabolism. This complexity is represented schematically in Table 15.1.

In contrast to nutrients, the other constituents of food are usually more numerous and present in minute amounts. For example, an apple is composed of approximately 98.5% by weight of water and carbohydrate. The remaining 1.5% contains over 100 components, mostly associated with the colour and flavour of the apple (Table 15.2).

We can further systematically consider the major classes of biologically active substances in food which are not regarded as nutrients. Most of these are phytochemicals (plant-derived), but some are uniquely derived from animals. The plant-derived compounds may, however, appear in the animal tissue eaten by humans. They may fall into any one of these categories (Table 15.3): non-provitamin A carotenoids; polyphenols such as flavonoids, isoflavonoids and catechins; indoles, isothiocyanates; sulphoraphane and other organosulphur compounds; monoterpenes; xanthines; non-digestible oligosaccharides and non-digestible protein.

15.2 Biologically Active Components in Food

The biological and health significance of a particular food depends on several factors, including the chemical nature of its components, its physical form, and the amount consumed. Nutrients in food provide energy, regulate body processes and serve as components of body structures. Other food components, which in the conventional sense do not appear to have a nutritive function, can also be important to body functioning and health. Information about the role of diet in health and disease has been obtained from studying human populations and from laboratory investigations. Some of these studies have identified particular foods and food components as important factors in disease prevention and causation. A great deal of scientific research has been directed at evaluating the effect on health of different food components.

Table 15.1 Schematic list showing the chemical complexity of food

Food	Nutrients		
		Macronutrients	Carbohydrate
			Protein
			Fat
			Dietary fibre
			Water
			Unidentified macronutrients?
		Micronutrients	Vitamins
			Minerals
			Unidentified micronutrients?
	Non-nutrients	Food additives	Synthetic additives
			Nature-identical additives
			Natural additives
		Contaminants	Industrial pollutants
			Production and processing contaminants
			Natural contaminants
			Unknown contaminants
		Processing artefacts	Colours
			Flavours
			Other identified components
			Unidentified artefactual components
		Naturally occurring non-nutrients	Colours
			Flavours
			Other identified components
			Unidentified natural components

It is important to examine the conditions under which biologically active components in food exert their effects. For example, some compounds in food have been shown to exhibit anticarcinogenic behaviour under some conditions yet enhance tumour response when different test carcinogens, animal species, target organs or exposure protocols are used. Careful evaluation is needed to ensure that protective compounds do not compromise normal physiological functions or enhance or promote other risks.

15.3 Protective Factors in Food

Although nutrients such as dietary fibre, β-carotene and vitamins C and E are considered to be protective against some types of cancer, there is also evidence that other substances in plant foods may provide protective effects. For example, some components found in food which have inhibited the development of cancer in laboratory animals are listed in Table 15.4. Some of these components occur naturally in cruciferous vegetables such as brussels sprouts, cabbage, broccoli and cauliflower (see Table 15.5).

The protective effect against cancer associated with the consumption of cruciferous vegetables is supported by epidemiological studies. This association cannot be entirely

Table 15.2 Components identified in apple aroma

Hydrocarbons	*Esters (cont.)*	*Acids*
1-Butoxy-1-ethoxyethane	Ethyl acetate	Acetic
Diethoxyethane	Ethyl butyrate	Benzoic
1-Ethoxy-1-hexoxyethane	Ethyl formate	Butyric
1-Ethoxy-1-methoxyethane	Ethyl hexanoate	Formic
1-Ethoxy-1-(2-methylbutoxy)-ethane	Ethyl 2-methylbutyrate	Hexanoic
	Ethyl 2-methylpropionate	*n*-Hexenoic
1-Ethoxy-1-propoxyethane	Ethyl octanoate	3-Methylbutyric
1-Methyl-naphthalene	Ethyl pentanoate	4-Methylpentanoic
2-Methyl-naphthalene	Ethyl 2-phenylacetate	2-Methylpropionic
2,4,5-Trimethyl-1,3-dioxolane	Ethyl propionate	Octanoic
	trans-2-Hexen-1-yl-acetate	Pentanoic
	Hexyl acetate	Propionic
Alcohols	Hexyl butyrate	
Butanol	Hexyl propionate	
Ethanol	Methyl acetate	*Aldehydes and ketones*
Geraniol	2-Methylbutyl acetate	Acetaldehyde
Hexanol	3-Methylbutyl acetate	Acetone
n-Hexenol	3-Methylbutyl 3-methylbutyrate	Acetophenone
trans-2-Hexen-1-ol	Methyl butyrate	Butanal
3-Hexen-1-ol	Methyl formate	2-Butanone
Methanol	Methyl hexanoate	Diacetyl
2-Methylbutan-1-ol	Methyl 2-methylbutyrate	Formaldehyde
3-Methylbutan-1-ol	Methyl 3-methylbutyrate	Furfural
2-Methylpropan-1-ol	2-Methylpropyl acetate	Hexanal
Pentanol	2-Methylpropyl propionate	2-Hexanone
Propanol	Pentyl acetate	2-Hexenal
2-Propanol	Pentyl butyrate	2-Methylbutanal
	Pentyl 2-methylbutyrate	3-Methylbutanal
Esters	2-Phenylethyl acetate	2-Methylpropanal
Benzyl acetate	Propyl acetate	Nonanal
Butyl acetate	2-Propyl acetate	Pentanal
Butyl butyrate	Propyl butyrate	2-Pentanone
Butyl hexanoate	Propyl pentanoate	3-Pentanone
Butyl propionate	Propyl propionate	Propanal

Source: Adapted from Burdock, GA. *Fenarol's Handbook of flavour ingredients*. Vol 2, 3rd ed. Boca Raton: CRC Press, 1995: 816.

explained on the basis of the known nutrients in these vegetables and suggests, that at their level of consumption of these foods, some or all of these substances may effectively inhibit the development of some types of cancer. These foods may also be carriers of other substances whose health significance remains to be identified or recognized.

A more detailed consideration follows for those categories of phytochemicals and other substances under active investigations to evaluate their health properties.

Table 15.3 A general classification of some examples of biologically active components in foods which are not nutrients, additives or contaminants. (This list is by no means exhaustive)

Phytochemicals	Non-provitamin A carotenoids	(e.g. lutein, lycopene)
	Polyphenols	(e.g. flavonoids, isoflavones, lignans, resorcylic acid)
	Organosulphur compounds	(e.g. isothiocyanates, indoles, sulphoraphane, allyl sulphide)
	Monoterpenes	(e.g. limonene)
	Xanthines	(e.g. caffeine)
	Salicylates	(e.g. methyl salicylate)
	Amines	(e.g. L-dopa)
	Non-digestible oligosaccharides	(e.g. fructooligosaccharides)
	Non-digestible protein lignins	(e.g. hydroxyphenylpropane polymers)
Animal-derived compounds	Steroid hormone	
	Morphiceptin (peptide)	
	Immunoreactive thryotrophin releasing hormone (TRH peptide)	
Compounds generated during heat processing	Maillard reaction products	
	Thermally oxidized products (THOPS)	

Table 15.4 Components shown to inhibit the development of some types of cancer in laboratory studies

	Component
Nutrients	Ascorbic acid
	α-Tocopherol
	β-Carotene
	Selenium
Non-nutrients	Phenols
	Flavones
	Indoles
	Isothiocyanates
	Allyl sulphides
	Protease inhibitors

Table 15.5 The known components of Brussel sprouts (*Brassica oleracea* L. *var. Gemmifera* DC)

Allyl-isothiocyanate
Anteisoheptacosan-1-ol
Anteisomontanyl alcohol
Antepentacosan-1-ol
Arachidonic acid
Arginine
Ascorbic acid
sec-Butyl-isothiocyanate
Caffeic acid
Calcium
Carbohydrates
β-Carotene
Citric acid
Copper
p-Coumaric acid
1-*O*-*p*-coumaroyl-β-D-glucose
Coumestrol
Cystine
Fats
Ferulic acid
1-*O*-feruloyl-β-D-glucose
Fibre
Folate(s)
Fumaric acid
Heptacosan-1-ol
Hexacosan-1-ol
Histidine
2-Hydroxybut-3-enyl-glucosinolate
Indole-3-acetonitrile
Indole-3-carbinol
Indole-3-carboxaldehyde
Indole-3-carboxylic acid
Indoyl-3,3′-dimethane-carboxylic acid
Iron
iso-Hexacosan-1-ol
iso-Leucine
iso-Octacosan-1-ol
Triacontan-1-ol
Leucine
Linoleic acid
α-Linolenic acid
Lysine
Magnesium
Malic acid
Manganese
Methionine
4-Methoxyindol-3-yl-methylglucosinolate
Molybdenum
Montanyl alcohol
Niacin
Octacosan-1-ol
Oleic acid
Oxalic acid
Palmitic acid
Palmitoleic acid
Pantothenic acid
Pentacosan-1-ol
Phenylalanine
Phosphorus
Phytosterols
Potassium
Prop-2-enylglucosinolate
Protein
Quercetin
Quinic acid
Riboflavin
Rutin
Selenium
Sinapic acid
1-*O*-*p*-sinapoyl-β-D-glucose
Sodium
Stearic acid
Succinic acid
Tetracosan-1-ol
Thiamin
Threonine
α-Tocopherol
Triacontan-1-ol
Tryptophan
Valine
Vitamin B_6
Water
Zinc

Source: Adapted from Duke JA. *Handbook of phytochemical constituents of GRAS herbs and other economic plants.* Boca Raton: CRC Press, 1992.

Box 15.1 Tomatoes

Eating foods containing vitamin C has been well correlated with a decreased incidence of gastric cancer. However, this is not the only protective factor. For example, naturally occurring components such as the phenolic antioxidants chlorogenic acid and *p*-coumaric acid found in many plant foods, including tomatoes, have been found to prevent the formation of some carcinogens. Furthermore, tomatoes contain a red pigment, lycopene, a carotenoid which has no provitamin A activity, but which can act as an antioxidant and a trapper of free radicals.

Box 15.2 Cranberry juice

Many bacterial infections are initiated when bacteria become attached to the surfaces of the respiratory, digestive or urinary tracts in the body. Some components of food have been shown to inhibit this attachment and prevent or minimize infection. In studies with animal and human cells, cranberry juice has shown two types of anti-adhesive activity towards pathogens. The activity is believed to be due to fructose and an unidentified high molecular weight constituent in the juice. These studies are supported by recent work in the United States which has shown that cranberry juice is beneficial in the prevention of recurrent urinary tract infections in elderly women.

Box 15.3 Fruits and vegetables

Many fruits and vegetables, as well as tea and wine, contain relatively high levels of naturally occurring phenolic components. Many of these components have antioxidant properties as well as an important influence on the colour and flavour of these foods. Recent population studies have found an association between a lower risk of heart disease in men with increased consumption of phenol-containing foods and beverages.

15.3.1 Carotenoids

Carotenoids possess other biological actions, apart from provitamin A activity, including antioxidant, immuno-enhancement, antimutagenesis and anticarcinogenesis. Owing to the antioxidant property of carotenoids, the possibility exists that these compounds may contribute to protection against coronary heart disease as well as cataract and retinal (macular) degeneration which are linked to oxidative stress, lipid peroxidation and free radical damage. Cells involved in the generation of specific immune responses can also be adversely affected by free radicals and products from lipid peroxidation processes. Incubation with β-carotene has been shown to protect human neutrophils against free radicals. It has also been suggested that antioxidant vitamins may play a role in cancer risk reduction and cancer prevention by reducing premalignant lesions such as cervical dysplasia, leucoplakia and atrophic gastritis. Carotenoids might also enhance an immune response which could lead to reduction of tumour growth.

15.3.2 Flavonoids and isoflavones

Flavonoids are a large group of polyphenolic compounds that occur naturally in vegetables and fruit and in beverages such as tea and wine. The most important groups of flavonoids are anthocyanins, flavonols, flavones and flavonones. Flavonoids have been studied in relation to their improvement of vascular fragility, increase cellular permeability and vitamin C-sparing activities. Some flavonoids such as quercetin, kaempferol and myricetin have antimutagenic and anticarcinogenic effects *in vitro* and *in vivo*. In a

large number of epidemiological studies which have investigated relationships between diet and cancer, a protective effect of the consumption of vegetables and fruit on various forms of cancer is found. This protective effect was originally attributed to vitamin C and carotenoids present in these foods. However, the significance of other potentially protective compounds such as flavonoids present in vegetables and fruit has become an important issue. It appears that a number of the biological effects of flavonoids may be explained by their antioxidative activity and ability to scavenge free radicals. Other mechanisms for their reported anticarcinogenic potential include their capacity to inhibit the promotion phase of carcinogenesis; and to modulate the balance between activation and inactivation processes of specific enzymes in the liver.

A small number of isoflavones, such as genistein and daidzein, display oestrogenic activity in animals and humans. This hormonal effect is attributed to the similar spatial arrangement of functional groups on isoflavones and oestrogens, allowing these isoflavones to bind to the oestrogen receptors. Furthermore, genistein is also found to inhibit endothelial cell proliferation and *in vitro* angiogenesis.

Isoflavones occur principally, although not exclusively, in legumes (Leguminosae family). They are at particularly high levels in certain legumes which are regularly consumed by people and animals. Indeed, many traditional human diets which have relatively high legume consumption (soya, lentils, chick pea, etc.) consequently have high isoflavone contents, particularly of those with oestrogenic activity.

15.3.3 Other polyphenols

Several animal models have demonstrated anticarcinogenic effects of polyphenols extracted from green tea in multi-organ carcinogenesis models. A number of investigators have identified epigallocatechin gallate (EGCG) as the principal antimutagenic and anticarcinogenic compound in green tea. The anticarcinogenic activity of EGCG may be related to several factors, such as its effect on the tumour promotion stage of cancer processes; its effect on DNA-adduct formation; on scavenging of free radicals; or the increase of antioxidant activities. There is circumstantial evidence to suggest that simultaneous intake of green tea polyphenols with food products may exert a protective effect. Beneficial effects of drinking tea in relationship to blood pressure, serum cholesterol and other lipids have been reported in human studies.

Several phenolic flavonoids in red wine exert potent antioxidant effects, and as such may act as chemopreventive components. A red wine extract, from which the alcohol has been removed, inhibited the oxidation of low-density lipoproteins. It appears that phenolic components with antioxidant capacity found in red wine may collectively reduce the oxidation of lipoproteins and reduce thrombosis and thereby contribute to the amelioration of atherosclerosis and morbidity and mortality from coronary artery disease.

15.3.4 Isothiocyanates and other organosulphur compounds

Isothiocyanates, indoles and sulforaphane, which are found in cruciferous vegetables such as broccoli, Brussels sprouts and cabbage (see Table 15.5) have been shown to trigger enzyme systems that block or suppress cellular DNA damage, reduce tumour size and decrease the effectiveness of oestrogen-like hormones. Allylic sulphides, found in onions

and garlic, enhance immune function, increase the production of enzymes that help to excrete carcinogens, decrease the proliferation of tumour cells, and in large doses may reduce serum cholesterol.

15.3.5 Monoterpenes

Limonene is a monocyclic monoterpene found in the essential oils of citrus fruits, spices and herbs. The presumed potential of limonene as a chemotherapeutic and chemopreventive agent for human breast and possible other cancers is based on results of animal studies showing chemopreventive activity against mammary, skin, liver and lung tumours. Limonene and related monoterpenes may represent a novel class of cytostatic cancer chemotherapeutic agents that induce tumour cell redifferentiation with little toxicity to the host.

15.3.6 Salicylates

Salicylates in food have mainly been of interest to workers investigating food sensitivity. However, health protective effect from food salicylates may, in part, resemble effects of acetyl salicylic acid (aspirin). Aspirin, of course, is of interest in protecting against macrovascular disease, such as coronary heart disease, stroke, and against neoplastic disease of the gut; the same may be true of food salicylates.

15.3.7 L-Dopa

There are anecdotal reports and a paper by Kempster and Wahlqvist (1994) that patients with Parkinson's disease will benefit from meals of broad beans (*Vicia faba*). Broad beans contain rather large amounts of the amino acid dihydroxyphenylalanine (L-dopa) and the response to these beans may even be better than to conventional L-dopa medication in some cases.

15.3.8 Animal-derived compounds

Animal foods may contain certain phytochemicals from the food consumed by the animal. They also may provide peptides following the digestion of animal proteins which have hormone-like action. An example is morphiceptin, which is a peptide with opioid activity, derived from milk proteins. It has been shown to have potent analgesic and cataleptic activities in rats when injected into the cerebral ventricles. Of course, hormones of one animal eaten by another animal may have hormone-like action as the compounds go up the food chain, ultimately in humans. Most cell messenger compounds, commonly known as cytokines—generally labile peptides, are unlikely to survive through the food chain to have biological effects in humans who eat animal-derived foods.

15.3.9 Compounds occurring during food processing

Biologically active compounds are also generated during food preparation. Maillard (carbohydrate-protein derivatives) and THOPS (thermally oxidized products) are

produced during food frying. Other biologically active compounds are produced during the preparation of alcoholic beverages such as wine and beer, and in dairy products such as cheese and yoghurt. The biological effect of many of these compounds has been poorly studied.

15.4 Functional Foods

Functional foods have been defined in the following way (Australian National Food Authority (1994)):

> Functional foods are similar in appearance to conventional foods and are intended to be consumed as part of a normal diet, but have been modified to subserve physiological roles beyond the provision of simple nutrient requirements.

What has become clear is that one class of phytochemicals may have several functions (i.e. are multifunctional compounds). A good example is the flavonoids which have been shown to be antimutagenic (and for some, mutagenic), oestrogenic, antioxidant, immunomodulant and anti-angiogenic. On the other hand, a particular function may be provided by more than one class of phytochemicals. For example, oestrogenic compounds include isoflavones, lignins, and resorcylic acid compounds.

The growing array of phytochemicals (those non-nutrients ultimately derived from plants) which are being shown to have biological effects including those which are health protective, opens up opportunities for development of functional foods to serve particular physiological or pathological needs.

15.5 Toxicants in Food

Some biologically active components in food can also contribute to chronic and acute illness. Examples of naturally occurring components in foods and their effects are listed in Table 15.6. Whether consumption of foods containing these toxicants poses a hazard to human health depends on their concentration in the food, the amount consumed and individual susceptibility to the component. Interactions between food components in the same and different foods may also influence their safety. For example, the formation of potentially carcinogenic *N*-nitrosamines from amines and nitrite can be catalysed by some co-occuring dietary components and inhibited by others. Therefore, under some circumstances, foods containing these substances may be consumed with impunity.

A wide range of extraneous substances are unintentionally or accidentally incorporated into food as a result of agricultural practices, processing, packaging, growth of microorganisms, storage and industrial pollution (Table 15.7). In addition, these adventitious additives or contaminants can enter the food supply as a result of misuse, unusual growing conditions, accidents or other incidents such as nuclear fallout or illegal waste disposal. These contaminants can affect the quality and safety of food. Whether they constitute a health hazard will depend on a combination of factors that include their concentration in the food, the amount of food consumed, individual susceptibility to the substances, and any interactions that could modify their toxicity. It is often extremely

Table 15.6 Some naturally occurring toxicants that are normal components of plant foods and their effects

Toxicant	Major food source	Effect/action
Caffeine	Coffee, tea, cocoa, cola-type beverages	Diuresis, cardiac stimulant, CNS stimulant, stimulant of gastric acid secretion, smooth muscle relaxant, animal teratogen
Cucurbitacins	Melons, squash, zucchini (bitter varieties)	Cramps, diarrhoea, collapse
Cyanogenic glycosides	Cassava, some varieties of limba bean, apricot kernels, bitter almonds, apple seeds	Cyanide poisoning, tropical ataxic neuropathy?
Cycasin	Cycads (*Cycas circinalis*)	Cancer in animals
Favism-causing compounds	Broad beans (*Vicia faba*)	Acute haemolytic anaemia*
Glycoalkaloids (solanine, chaconine)	Potatoes	Gastrointestinal and neurological symptoms, animal teratogen
Glucosinolates	Brussels sprouts, cabbage, cauliflower, mustard, turnip	Goitrogenic activity
Gliadins	Wheat, rye, barley	Gluten enteropathy (coeliac disease)*
Haemagglutinins	Many species of legume	Agglutination of red blood cells (*in vitro*), growth depression
Hypoglycin	Akee fruit	Acute hypoglycaemia
Lathyrogens	*Lathyrus sativus* (lathyrus pea, chickling vetch)	Paralysis, skeletal abnormalities
Nitrate/nitrite	Cabbage, celery, lettuce, spinach	Methaemoglobinaemia, cancer?
Oxalic acid	Rhubarb, spinach, tea	Gastroenteritis, renal damage, decreased calcium utilization
Oestrogens	Soybeans	Oestrogenic activity in animals
Protease inhibitors	Many species of legume	Decreased growth
Psoralens	Celery, parsnips	Photocarcinogen, mutagen
Pyrrolizidine alkaloids	Comfrey, some herbs	Liver disease, cancer

* Hazardous only for a minority of genetically sensitive individuals. CNS, central nervous system.

Table 15.7 Sources of food contamination

Source	Examples
Agricultural practice	Insecticides, herbicides, rodenticides, fungicides, antibiotics, promoters, coccidiostats, cadmium
Food processing	Cleaning agents, lubricants, pieces of equipment, hair
Food packaging	Inks, plasticizers, monomers, lead, adhesives
Food storage	Insects, insect frass, rodents, rodent excreta
Industrial pollution	Lead, mercury, polychlorinated biphenyls
Microorganisms	Aflatoxins, ergot, *Salmonella*

difficult to assess the effects of long-term exposure to low levels of any food component. Concern about the potential health effects of food contaminants usually follows from their demonstrated effects on occupationally exposed groups (e.g. workers exposed to relatively high concentrations of vinyl chloride in the manufacture of PVC), or those exposed to localized high concentrations resulting from accidental overuse or spillage (e.g. from consumption of fish from the polluted water of Minamata Bay in Japan which contained high levels of mercury). These toxicants are discussed further in Chapter 23.

15.6 Conclusions

There is emergent need for the following:

1. Food composition tables to reflect phytochemicals and, possibly, substances that are unique to the animal-derived foods, which have health consequence.
2. Nutritional epidemiology which takes into account a possible link between consumption of non-nutrients from food and health outcomes.
3. Clinical nutrition trials which test the potential health protective or therapeutic opportunities that phytochemicals may provide.

A problem in considering the place of phytochemicals in human health is that there are numerous compounds, alongside a few known essential nutrients, and, therefore, that their net interactive effect ultimately requires a study of food itself and food patterns, or that food components intake be subject to sophisticated mathematical modelling. The advance of informatics may help resolve this dilemma.

When particular bodily function or disease processes are considered alongside the phytochemical or other non-nutrient food components which may modulate physiological functions, the potential for making relevant functional foods becomes apparent. For example, products might be designed to prevent or manage obesity through altering appetite, the sensory response to food (taste, smell, look, texture and sound in eating) or energy utilization. Such developments will, however, need to take into account the various caveats outlined above.

Further Reading

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Essentials of human nutrition

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Oxford New York Tokyo

OXFORD UNIVERSITY PRESS

1998

Oxford University Press, Great Clarendon Street, Oxford OX2 6DP
Oxford New York
Athens Auckland Bangkok Bogota Bombay
Buenos Aires Calcutta Cape Town Dar es Salaam
Delhi Florence Hong Kong Istanbul Karachi
Kuala Lumpur Madras Madrid Melbourne
Mexico City Nairobi Paris Singapore
Taipei Tokyo Toronto Warsaw
and associated companies in
Berlin Ibadan

Oxford is a trade mark of Oxford University Press

Published in the United States
by Oxford University Press, Inc., New York

A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data

Essentials of human nutrition/edited by J.I. Mann and A. Stewart Truswell
1. Nutrition. I. Mann, Jim. II. Truswell, A. Stewart.
QP141.E82 1998 612.3'9–dc21 97-28309

ISBN 0 19 262757 0 (Hbk)
ISBN 0 19 262756 2 (Pbk)

Typeset by Newgen Imaging Systems (P) Ltd, Chennai, India

Printed in Great Britain
by Bookcraft (Bath) Ltd,
Midsomer Norton, Avon