chapter ten

Adverse effects of food contaminants

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10.1 Introduction

From Part 1 of this textbook it is already clear that food contaminants originate from many sources, including human activities. This and other factors make it difficult to give an equivocal definition of the term food contaminant. For example, the substance involved may be either synthetic or natural. Also, its presence in the food may be accidental or deliberate. So, the definition varies from country to country and from book to book, but in any case, unlike food additives, food contaminants are unwanted in foodstuffs.

The naturally occurring contaminants (toxins) are the subject of Chapter 11. This chapter looks at the technical contaminants of which the main source is the large-scale application of fertilizers, pesticides, growth stimulants, and antibiotics in farming. Further, contaminants can originate from production and use of other synthetic chemicals, e.g., packaging and canning materials (see Part 1). Technological food contaminants can be divided into two subcategories: *metals* (inorganic as well as organic derivatives) and *organic chemicals*. The majority of the human population is chronically exposed to low levels of these contaminants. In a number of cases, e.g., Hg, Cd, Pb, and polyhalogenated aromatic hydrocarbons, the substances may accumulate in tissues and organs. Following chemical contamination, acute toxic effects seldom occur, and if so, mostly in occupational settings. At present, acute toxicity of contaminants is not a matter of great concern as far as food safety is concerned. An overall evaluation of the health risks due to dietary intake of contaminants, however, also includes chronic toxicity.

Table 10.1 Relative importance of actual food hazards

1	Microbiological contamination	100,000
2	Nutritional imbalance	100,000
3	Environmental contaminants, pollutants	100
4	Natural toxicants	100
5	Pesticide residues	1
6	Food additives	1

Source: Ashwell, 1990.

The toxicology of contaminants focuses primarily on long-term effects, such as mutagenicity, carcinogenicity, and teratogenicity. This is based on the assumption that low doses of contaminants may cause long-term effects in humans because of (a) the long human lifespan, (b) interactions between contaminating food components, and (c) effects of other (dietary) factors.

Only small amounts of contaminants are ingested. Therefore, the manifestation of toxic effects may be delayed. Further, there is the possibility of combined actions. In that case, it is difficult to find a relationship between the presence of a certain contaminant in food and a toxic effect.

It shoud be noted that in general food contaminants *do not give rise to concern*, as they usually do not exceed limit values. In Table 10.1, six main categories of hazard are listed, in order of relative importance. The ranking, based on criteria such as severity, incidence, and onset of biological symptoms was originally proposed by Wodicka in 1971. It gives a good idea of the proportion of risks associated with the intake of food contaminants to the risks from the intake of additives (lower risk), nutrients, and contaminants of microbial origin (higher risk). There is a growing awareness regarding the dramatically increasing number of man-made enviromental pollutants. This may give rise to concern about other man-made compounds like food additives, whereas in general, additives do not pose health hazards.

The cases presented in this chapter are not intended to give a complete survey of all categories of food contaminants. Mainly, the toxic effects of food contaminants and the underlying mechanisms of the major groups are discussed. For extensive reviews on the toxicology of food contaminants, see the literature references at the end of this chapter.

10.2 Metals

Of the approximately 100 elements in the Earth's crust, 20 to 30 are known to be necessary to the human body. This section discusses some nonessential metals, including organometallic complexes. The toxicology of essential minerals is the subject of Chapter 12.

Knowledge of the mechanisms underlying toxic effects is needed for an adequate setting of limit values such as NOAEL and ADI. In order to understand this procedure, the following terms should be understood: *critical organ*, *critical effect*, and *critical concentration*. Prior to the discussion of the toxicology of the food contaminating nonessential metals, these terms need to be defined:

Intermezzo

- *Critical concentration*: target cell/organ concentration at which adverse (reversible/irreversible) functional changes occur. These changes are called *critical effects*.
- *Critical organ*: organ in which the critical concentration is reached first under specified conditions for a given population.

Table 10.2 Calculated hypothetical total daily intake of cadmium and contributing sources

Individual	Source of cadmium	Intake in µg
Non-smoker living in rural area	air	0.0005
	food	4
	water	2
	total	6
Smoker living near cadmium source and eating contaminated food	air	25
	food	84
	water	2
	tobacco	4
	total	115

Source: Hallenbeck, 1985.

- PPC_{10} is the concentration at which in 10% of the population the critical organ is affected. Further, the terms *subcritical concentration* and *subcritical effect* are used. They relate to the conditions under which the first disturbances can be expected. They warn that critical concentrations (causing critical effects) may soon be reached.

10.2.1 Cadmium

For people not occupationally exposed to cadmium (Cd), dietary intake is the main route of exposure to cadmium. This is shown by Table 10.2, listing data on the routes of exposure and the daily intake by adults. Smoking of 20 cigarettes per day causes an intake of 4 µg of cadmium. In comparison with dietary intake, this does not seem to be too much. However, one should take into account that the absorption of Cd is much lower after oral intake (4 to 8%) than on inhalatory exposure (15 to 40%).

Cd is present in nearly all foodstuffs. In noncontaminated regions, food usually contains less than 0.1 mg Cd/kg. High concentrations (1 to 10 mg/kg) can be found in the organs of cattle, in seafood, and in some mushroom species.

Like most inorganic contaminants, Cd is only absorbed to a small extent from the gastrointestinal tract. Its ability to accumulate in the body may be accounted for by its long biological half-life.

After uptake from the gastro-intestinal tract, Cd is bound to the low molecular weight protein metallothionein (Mt) in the cells of the intestinal wall and in the liver. Mt plays a key role in the homeostases of trace elements such as Zn and Cu in the organism, and in the detoxication of nonessential metals such as Cd, Hg, and Pt. Cd–Mt complexes are gradually released from the intestinal wall and the liver into systemic circulation. After renal excretion by glomerular filtration, the complexes are reabsorbed by the renal proximal tubule cell. It is believed that free ionic Cd resulting from lysosomal degradation of Cd–Mt causes damage to the kidneys.

Several factors are known to affect the absorption of Cd and its distribution over the body. The latter, for example, is determined by the Cd content of the diet. At low doses, Cd accumulates mainly in the kidneys. After high doses, the intestinal Mt-pool is saturated and free Cd will reach the liver. As a result, acute oral toxicity has been observed mainly in the liver and the erythropoietic system, while long-term exposure to low Cd levels (orally and inhalatory) has been found to result in toxic effects in the lungs, kidneys, and bones. It is important to note that in most long-term animal studies where renal and other effects were examined, the renal effects preceded or occurred simultaneously with the other effects.

Also, many dietary factors are known to influence the absorption and distribution of Cd in humans. Various metals may interfere very efficiently with the uptake of Cd.

High-fiber and low-fat diets with adequate mineral levels of calcium, zinc, iron, and phosphorus are known to lead to a lower total body retention of Cd than diets high in fat with a marginal mineral status.

Cadmium has been shown to interfere with the metabolism of vitamin D, calcium, and collagen. These effects manifest themselves as osteoporosis and osteomalacia in humans as well as in animals. An illustrative example is the Itai Itai bone disease ("ouch ouch" disease). This disease occurred as an epidemic among the inhabitants of the Fuchu area in Japan, who for a long time ingested rice that was highly contaminated with Cd (300 to 2000 µg Cd per day). The etiology of this disease points to a combination of factors. Not only the exposure to Cd, but also a deficient diet (low in protein, calcium, and vitamin D) were found to be responsible for the development of this disease in that particular area.

In occupational settings and in studies in rodents, it has appeared that long-term inhalatory exposure to Cd is associated with an increase in prostate cancer and lung cancer. However, the potential carcinogenicity of cadmium has not been clearly shown in oral studies.

In addition to the dose and dietary factors, the *speciation* of Cd in the diet appears to be an important factor in determining its uptake from food. There is a clear need for data on the form in which Cd is present in food. In animal tissues, Cd occurs mainly as metallothionein complexes. Foods originating from plants are an even more important source of dietary Cd than food of animal origin. In plants, Cd is bound to phytochelatins, proteins that have several properties in common with metallothioneins. Information on the toxicological risks due to the oral intake of Cd bound to metallothionein is limited. Cd and Cd–Mt differ in intensity of toxicity. After parenteral administration, Cd–Mt is more nephrotoxic than inorganic Cd. This seems not to be the case after oral administration. It has been suggested that after a low intake, the metabolic routes of both Cd forms are similar. After uptake from the gastro-intestinal tract, Cd may be released from Cd–Mt. After a high intake, there seems to be a difference in metabolic fate, leading to a higher availability of Cd after intake of inorganic Cd. A difference in Cd availability between foods will certainly have important consequences for the evaluation of risks due to Cd intake and the estimation of tolerable Cd levels in different types of food. The kidneys are the critical organs for long-term oral exposure to Cd, and renal effects always precede or occur simultaneously with other effects. Epidemiological studies in occupational settings have shown that 10% of a population of industrial workers at the age of 45 shows symptoms of renal dysfunction once the renal Cd concentration has reached a level of 200 mg/kg kidney cortex. For the general population, it has been calculated that this level will be reached in 45-year old individuals after a daily dietary Cd intake of ±400 µg. (Table 10.3).

Table 10.3 Calculated average cadmium kidney cortex concentration at age 45 for non-smokers with cadmium intake via food only

Average daily cadmium intake at age 50		100	200	300	400	500	600	700
Geometric mean cadmium concentration in kidney cortex* (mg/kg)		61	102	143	183	224	265	305
Estimated proportion (%) with kidney cortex cadmium above their individual-critical concentration	A	2.7	11	22	34	44	53	60
	B	1.8	7.8	17	26	35	44	51

Note: Body weight = 70 kg.

A: PCC_{50} = 250 mg Cd/kg and PCC_{10} = 180 mg Cd/kg, log-normal distribution of critical concentrations.

B: PCC_{50} = 300 mg Cd/kg and PCC_{10} = 200 mg Cd/kg, log-normal distribution of critical concentrations.

* Assumed to have a log-normal distribution with geometric SD of 2.

Source: Friberg et al., 1985, 1986.

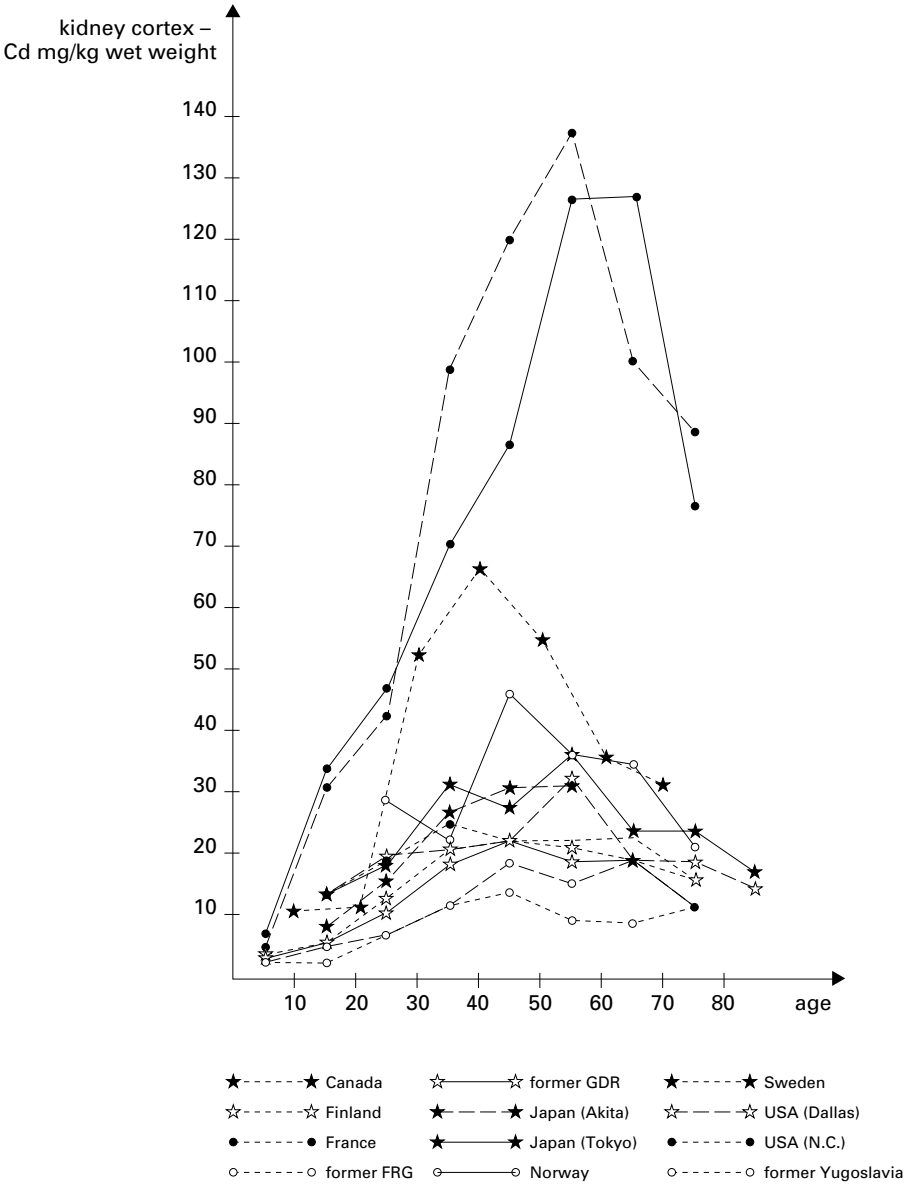


Figure 10.1 Average concentration of cadmium in kidney cortex in relation to age. Results from 12 different studies in 10 countries are summarized. The averages are based on data from smokers, non-smokers, females, and males combined. Source: Friberg et al., 1985, 1986.

The FAO/WHO provisional tolerable daily intake (see Chapter 16, Section 16.3.2.1) of Cd, 70 µg, leads to kidney cortex concentrations of 40 to 60 mg/kg (compare these figures with the actual renal Cd concentrations in 10 countries, given in Figure 10.1).

Differences in Cd availability resulting from the intake of different forms of Cd or the effects of other dietary factors are not taken into account in the estimation of tolerances. Another factor contributing to the Cd retention in the body is the smoking behavior of the population. A cigarette contains 0.8 to 2 µg Cd, from which 25 to 40% is absorbed on inhalation. This means that smokers may have higher Cd tissue levels than non-smokers (Figure 10.2).

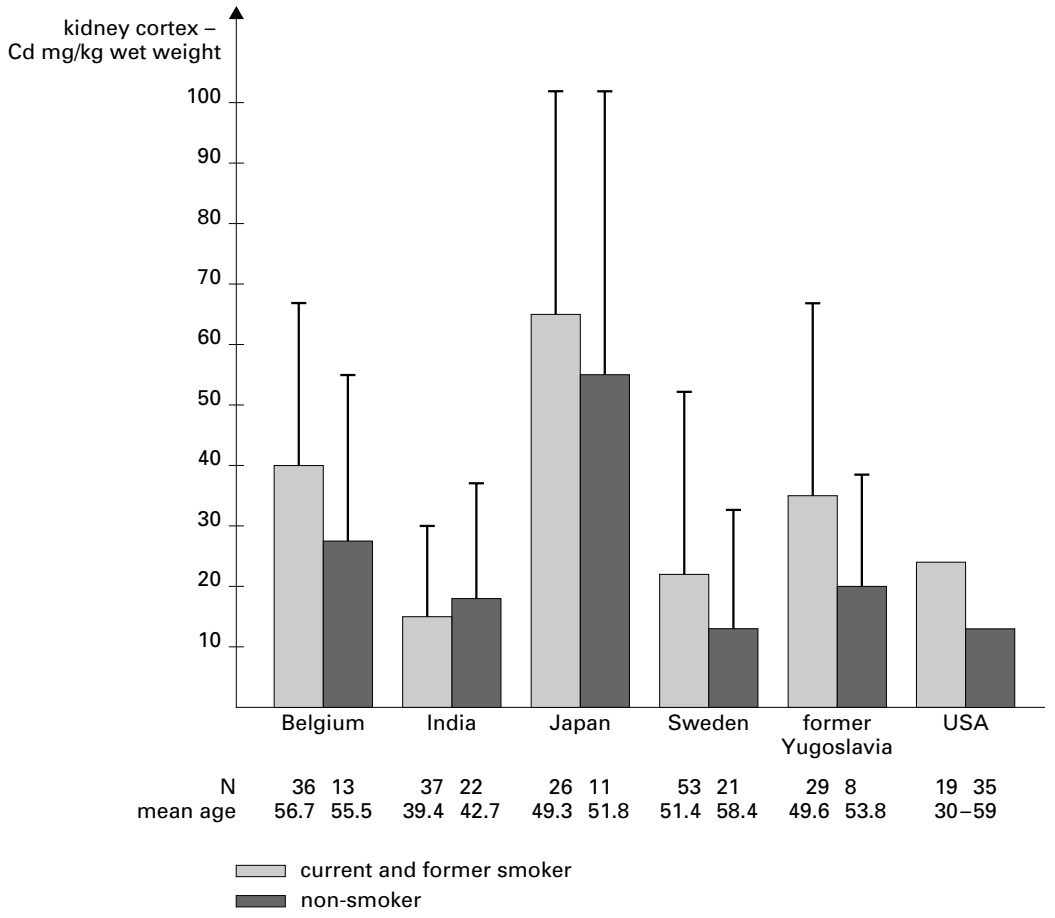


Figure 10.2 Cadmium kidney cortex concentration (geometric mean values) in relation to smoking habits among subjects (30 to 69 years of age) studied in Belgium, India, Japan, and (former) Yugoslavia. Also included in the figure are data from Sweden and the US (subjects aged 30 to 59). Source: Friberg et al., 1985, 1986.

10.2.2 Mercury

The widespread use of mercury (Hg) in industry and agriculture (e.g., as fungicidal derivatives) has led to serious environmental pollution and, as a result, to contamination of food, particularly of fish and meat. Tissues and organs of fish have such a high affinity for mercury (Hg) that it can accumulate by a factor 9000 compared to the environment. In fish, mercury is present as methylmercury. Methylmercury is the most toxic form and is formed by intestinal bacteria and bacteria in the slimes of the skin. Bacterial methylation of mercury has also been found in the organic fraction (sediment) of aquatic systems. Methylmercury is more extensively absorbed from the gastrointestinal tract than inorganic mercury, namely 85 to 95% and 8 to 12%, respectively.

The toxicity of Hg is related to the absorbability from the gastrointestinal tract. Insoluble mercurous chloride or elemental mercury does not cause toxic effects in man up to 500 g, while organic Hg complexes are far more toxic than inorganic Hg. After absorption, Hg^{2+} ions are bound to metallothionein in the blood. The metabolism of Hg–Mt is similar to that of Cd–Mt. Nephrotoxicity may occur after long-term accumulation.

Hg in the organic form is almost completely absorbed from the gastro-intestinal tract. A large part of the body burden of organic mercurials is found in the red blood cells. Methylmercury has been shown to pass the blood-brain barrier more readily than other Hg forms; inorganic Hg cannot pass the barrier. This makes the nervous tissue, especially the brain (atrophy of cerebral cortex), one of the target organs. The fetal brain is more sensitive to methylmercury than the adult brain (teratogenicity!). Dysfunction of the nervous system is believed to be preceded by biochemical disturbances such as inhibition of protein (enzyme) synthesis. The first symptoms of methylmercury intoxication — convulsion, anorexia, weight loss, and fatigue — are difficult to recognize. They are very unspecific and show high interindividual variation. Characteristic effects are paresthesia (tingling of extremities), loss of coordination, reflex changes, and mental deterioration. Methylmercury intoxication is mostly seen in occupational settings. Besides the speciation of Hg, interactions of Hg with other trace elements such as copper, zinc, and selenium are important. For instance, Korean fishermen who consumed Hg-containing tuna fish appeared to be extremely tolerant of Hg. They showed no neurotoxic effects, although their mercury blood levels rose to above 10 mg/l. The critical blood concentration of mercury is 20 µg/l (neurotoxic effect!). It has been suggested that the fishermen's resistance is related to the high selenium content of tuna fish.

The provisional tolerable weekly intake (PTWI) (see Chapter 16, Section 16.3.2.1) of mercury is 0.21 mg (WHO, 1973). The daily dietary Hg intake mainly depends on fish consumption and methylmercury levels in fish. In general, Hg intake is less than 10 µg per day.

10.2.3 Lead

Contamination of food with lead (Pb) appears to be inevitable. Lead originates from natural sources as well as from human activities (see Part 1). The majority of organic lead in the environment is accounted for by the anti-knock gasoline additive tetraethyllead. Since the introduction of lead-free gasoline, the concentration of air-borne Pb and the lead content of food are decreasing. Contamination of food of vegetable origin with lead is rather high. In food of animal origin, the lead content is very low, if not nil. For example, the milk from cows grazing on grass with 100 times the normal lead level contained only 4 times more lead than the milk from cows grazing on uncontaminated grass. Increases in the lead level of foods are mostly due to indirect contamination from packaging material and handling.

Lead is absorbed more easily by children (about 40%) than by adults (about 10%). The distribution of lead can be described by a three-compartment model, including bone tissue (95%), blood (2%), and soft tissues (3%). Lead blood levels (PbB) parallel the concentrations in soft tissues. Therefore, the effects of Pb are usually related to the PbB level. A clinical manifestation of lead poisoning is anemia due to a decreased lifespan of the erythrocytes and interaction with several enzyme systems in heme synthesis (Figure 10.3).

The most sensitive indicator of hematological changes after exposure to lead is inhibition of the enzyme δ-aminolevulinic acid (δ-ALA) dehydratase. ALA blood levels increase at PbB levels of 40 to 80µg/l. However, the toxicological significance of the inhibition of this enzyme (i.e., change in hemoglobin levels) is not yet fully understood. Anemia clinically manifests itself at higher PbB levels. The WHO (1987) has set the lowest-observed-adverse-effect level (LOAEL) (see Chapter 21, Section 21.4.4.3) at 200 µg/l blood. Recent findings have shown that exposure to low lead levels may lead to neurological disorders which used to go unnoticed, in particular in the developing brains of children. Prenatal exposure to lead is also of great concern, as Pb passes the placenta, and the blood-brain barrier of the fetus.

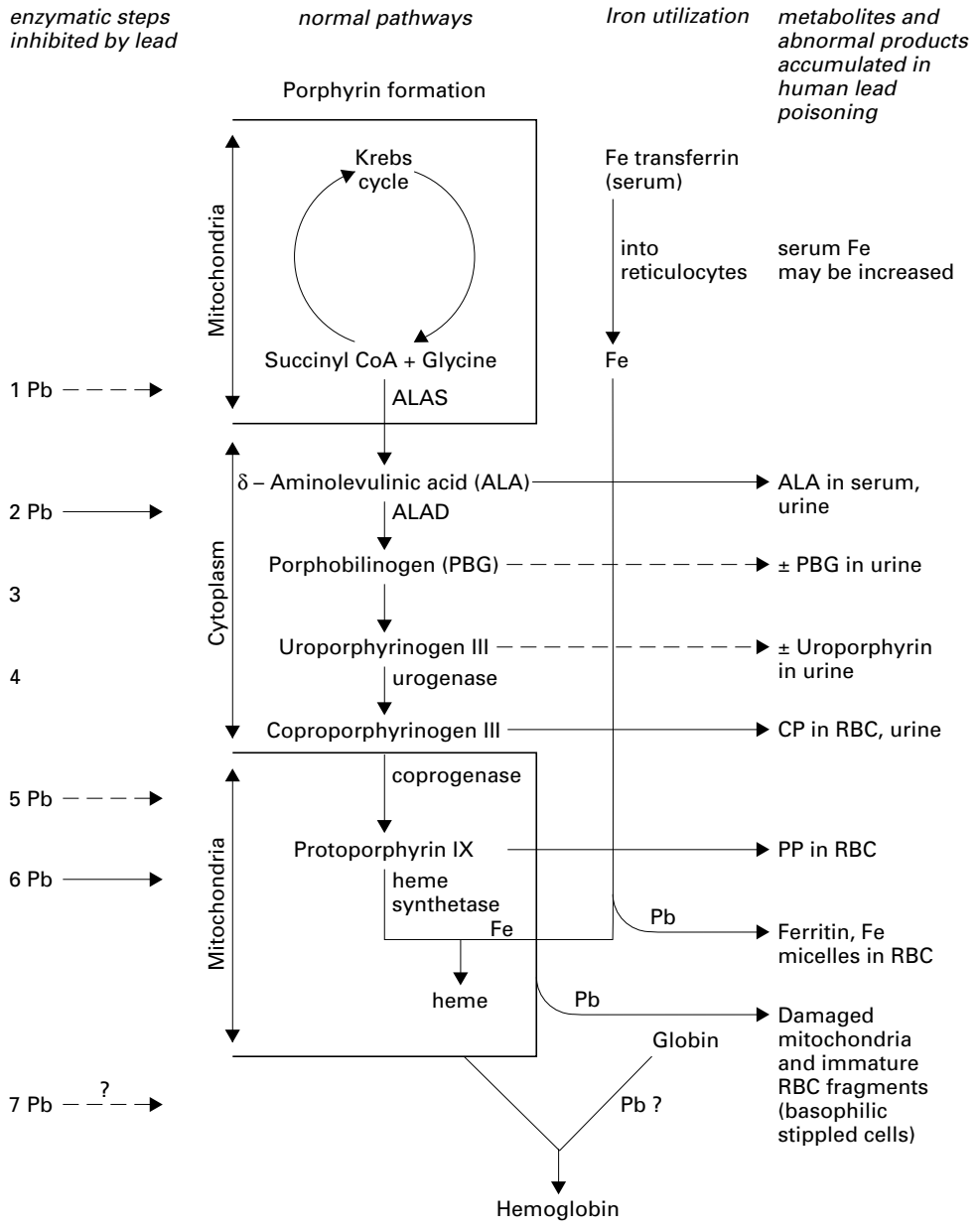


Figure 10.3 Lead interferes with the biosynthesis of heme at several enzymatic steps (Source: Goodman et al., 1990).

The absorption of Pb is higher in children than in adults. Generally, children are exposed to higher lead levels from the environment (dust, pica). Furthermore, children are particularly sensitive. Today's concern about lead intake has drawn the attention to neurotoxicity at prenatal lead blood levels and to the effect of lead on the development of the child after birth. For babies, the lead intake from milk powder and dust is estimated at ±35 µg and ±40 µg per week respectively. The lead intake by babies from drinking water with a lead content of 50 µg/l is estimated at ±25 µg per day. However, the lead intake by sucklings should not exceed 25 µg/kg per week according the WHO standardization. This means that the average lead level in drinking water is probably too high for babies.

10.3 Organic chemicals

Well-known types of organic substances occurring as food contaminants are pesticides, drugs, antibiotics, and industrial chemicals. Food-contaminating industrial chemicals include mainly polyhalogenated aromatic hydrocarbons, carbamates, and plasticizers. Chemicals such as organic solvents (chloroform, benzene, methylene chloride) and plastics (styrene and acrylo polymers) cause concern in occupational settings (skin, lungs) rather than in food consumption.

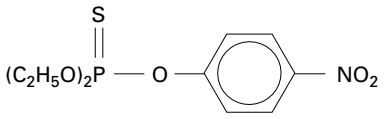
The following subsections deal with pesticides, notorious environmental pollutants such as polychlorinated biphenyls, dibenzodioxins and dibenzofurans, and feed additives.

10.3.1 Pesticides

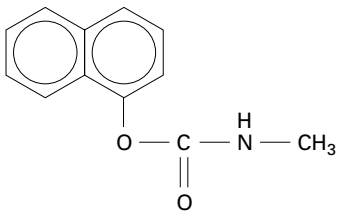
Pesticides are hazardous compounds which are used to control or eliminate unwanted species of insects (insecticides), acarides (acaridicides), fungi (fungicides), higher plants (herbicides), rodents (rodenticides), or nematods (nematodicides).

The biocidal action of pesticides includes a variety of disturbances of physiological processes, such as inhibition of acetylcholinesterase by insecticidal organophosphates, blockade of neurotransmission by chlorinated hydrocarbons, and inhibition of oxidative phosphorylation by herbicidal dinitrophenols.

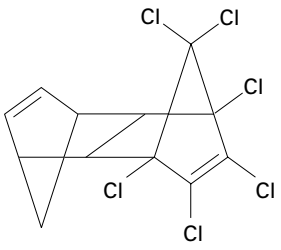
The insecticidal organophosphates and carbamates inhibit acetylcholinesterase, the enzyme that regulates neurotransmission by hydrolyzing acetylcholine. Another group of insecticides, the chlorinated hydrocarbons, cause blockade of neurotransmission by interaction with the sodium/potassium channels, resulting in inhibition of nerve membrane depolarization. A third group of pesticides, the herbicidal dinitrophenols, are uncouplers of the oxidative phosphorylation. Most of these biological targets also exist in man. Therefore, it is not surprising that accidental massive poisoning following inaccurate use of pesticides regularly occurs all over the world.



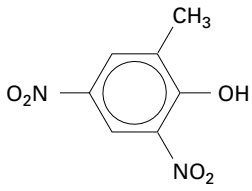
Parathion, an insecticidal organophosphate



Carbaryl, an insecticidal carbamate



Aldrin, an insecticidal
chlorinated hydrocarbon



Dinitro – o – cresol,
a herbicidal dinitrophenol;

Organochlorine and carbamate pesticides can also induce long-term effects: cancer and malformations. The former pesticides are highly lipid-soluble and are only slowly broken down. Therefore, they persist in the environment for a long time and accumulate in food chains.

Table 10.4 NOAELs and ADIs of some pesticides

Pesticide	NOAEL (μg/kg B.W.) (species)	ADI (μg/kg B.W.)	Safety factor	Max. Residue* in meat, fish (μg/kg)
Mutagenic and carcinogenic				
aldrin/dieldrin	25 (rat/dog)	0.1	250	1–86
DDT	50 (rat)	5	10**	3–10
methyl parathion	100 (human)	1	100	—
captan	1.25×10^4 (monkey) 1×10^5 (rat)	100	125	26–40
Mutagenic and non-carcinogenic				
dichlorvos	33 (human)	4	8	
malathion	5000 (rat) 200/day (human)	20	10	4–96

* High residues are found particularly in meat, fish, and poultry.

** In spite, of its carcinogenic potential for humans, the applicable safety factor for DDT is only tenfold. The ADI is conditional; only permission for application when no available subtitutes can be used.

Source: Concon, 1988.

The carcinogenic organochlorine pesticides include aldrin and dieldrin. They need metabolic activation to become carcinogenic. The main targets in rats and mice are liver and lung. An example of the carcinogenic insecticidal carbamates is carbaryl. The members of this group become carcinogenic on conversion to nitroso compounds in the reaction with nitrite.

Further, pesticides have been reported to induce malformations when given to mammals during pregnancy, e.g., aldrin, dieldrin, and carbaryl. However, carcinogenicity and teratogenicity have not yet been confirmed in valid epidemiological studies. As a result, the ADIs of most pesticides are based on animal data. This calls for continuous attention to potential hazards to humans due to the presence of pesticides in food. Therefore, safety factors of 100 or higher are applied (Table 10.4). This means that the ADI is usually 1% of the no-adverse-effect level observed in the most sensitive species. In the few cases where toxicity data in humans were available, a safety factor of 10 has been applied, accounting for intraspecies variation in man.

The organochlorine pesticides have been largely replaced by carbamates. The latter are less persistent in the environment. Further, their carcinogenic potential is lower than that of the organochlorine pesticides.

10.3.2 Halogenated Aromatic Hydrocarbons

10.3.2.1 Polychlorinated biphenyls

The polychlorinated biphenyl (PCB) content of animal food is decreasing in recent years. This is due to the ban on the use of PCBs. Notwithstanding, the levels of PCBs can still be high because of their low biodegradability.

PCBs are known to cause:

- chloracne
- induction of phase I (i.e., oxidases, reductases) as well as of phase II (i.e., conjugases) xenobiotic-metabolizing enzymes
- cancer
- teratogenic effects
- neurotoxic effects

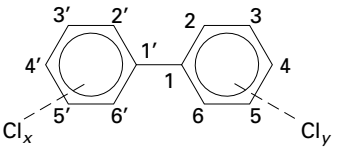
The most prominent effect in humans is persistent chloracne on the skin of the head and chest. This skin disease is believed to result from acanthosis and hyperkeratosis of the skin. Hair follicles are ultimately plugged by keratinaceous material and the glands around the follicles become cystic. The majority of studies on enzyme induction by PCBs concerned the cytochrome P-450-dependent monooxygenase. Evidence has been obtained that the mechanism underlying the induction of cytochrome P-450 isoenzymes consists of a sequence of events, the first of which is binding to a receptor protein, the so-called Ah (aromatic hydrocarbon) receptor. The ligand–Ah receptor complex is transferred to the nucleus. Interactions of the complex with structural genes result in stimulation of the transcription of those genes. This leads to an increasing synthesis of the enzymes coded for by the genes.

The mechanism of the carcinogenicity of PCBs involves promotion rather than initiation. They stimulate the growth of tumors (induced) in liver, skin and lungs. Although PCBs have been reported to be carcinogenic in animals, there are only a few reports suggesting that these compounds are also carcinogenic in man. Tumors were found in 8 of 22 people involved in a rice oil accident in Japan, and in 7 of 92 industrial workers exposed to arochlor.

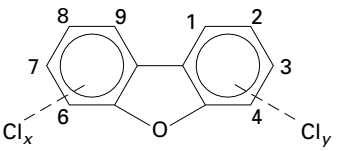
Several of the toxic effects are similar to those of pesticides like dieldrin and aldrin: teratogenicity and neurotoxic effects. In both cases, the underlying mechanisms are not yet exactly known.

10.3.2.2 Polychlorinated dibenzodioxins and dibenzofurans

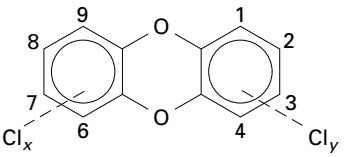
Polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) originate from several sources.



PCBs



PCDFs



PCDDs

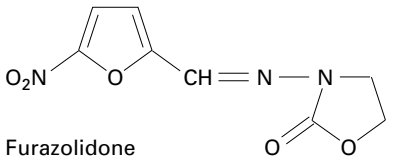
PCDD/PCDF emission can result from the incineration of domestic waste containing low-molecular chlorinated hydrocarbons and PCBs. PCDDs and PCDFs are also formed during the production of organochlorine compounds such as polychlorobenzenes, polychlorophenols, and PCBs. The most toxic polyhalogenated aromatic hydrocarbon is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a well-known contaminant of the herbicide 2,4,5-trichlorophenoxyacetic acid(2,4,5-T). TCDD has an oral LD_{50} of 22 to 45 μg/kg in rats.

Many TCDD-induced effects are similar to effects caused by PCBs and other structurally-related compounds. Hepatic monooxygenase activity is elevated. PCDDs and PCDFs are also highly teratogenic (0.25 μg/kg). Further, immunosuppression and thymic atrophy have been reported in experimental animals (after 10 μg/kg).

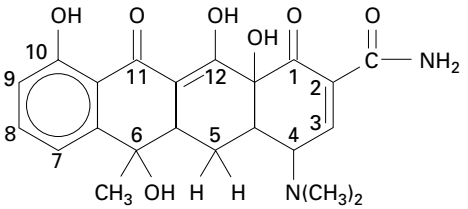
Enzyme induction, immunosuppression, and thymic atrophy by TCDD and structurally-related compounds are believed to be mediated via stereospecific and irreversible binding to the Ah receptor (see Section 10.3.2.1). An essential structural requirement is coplanarity. The structures of the halogenated aromatic hydrocarbons involved should be as planar as that of TCDD.

10.3.3 Antibiotics in use as feed additive

An important concern of veterinary toxicology is the possible transmission of harmful substances from meat, milk, and other foodstuffs to the human population. This concerns primarily antibiotics in use as feed additives. They include tetracyclines, nitrofurans, and sulfonamides. Recently, the detection of metabolites of the nitrofuran furazolidone in meat products revived the discussion on the acceptability of this veterinary drug. Oxytetracycline and also furazolidone are suspected of being carcinogens, and oxytetracycline has been reported to react with nitrite to yield (carcinogenic) nitrosamines.



Furazolidone



Tetracycline

congener	*substituent(s)*	*position(s)*
Chlortetracycline	— Cl	(7)
Oxytetracycline	— OH, — H	(5)
Demeclocycline	— OH, — H; — Cl	(6; 7)
Methacycline	— OH, — H; = CH_2	(5; 6)
Doxycycline	— OH, — H; — CH_3, — H	(5; 6)
Minocycline	— H, — H; — $N(CH_3)_2$	(6; 7)

In addition, the majority of the antibiotics in use as feed additives pose a serious (indirect) health hazard to humans. Ingestion of these antibiotics may lead to an increased resistance of bacteria. This may imply:

- transfer of antibiotic-resistant bacteria to humans via food intake, originating from animals treated with antibiotics or infected by resistant bacteria;
- transfer of the resistance factor (R-factor) from resistant non-pathogenic bacteria to other bacteria which will lead to widespread resistance.

10.4 Summary

Food contaminants are substances that are unintentionally present in food. This chapter deals with nonnatural contaminants originating from production and technological applications. This category of food contaminants can be divided into two subcategories: metals and organic chemicals.

Exposure levels are quite low, and the appearance of toxic effects is usually delayed. Therefore, causal relationships are not easily to establish. The toxicology of food contaminants primarily focuses on long-term effects such as carcinogenicity, teratogenicity, and neurotoxicity. Absorption, disposition, and toxicity of food contaminants are determined by a large number of factors, including dietary habits, age, sex, speciation, and dietary factors, such as fat, proteins, and minerals. For heavy metals, extensive research has been carried out to establish dose–response relationships and to elucidate the underlying toxicity mechanisms. For pesticides and complex mixtures of halogenated aromatic hydrocarbons, on the other hand, the dose–response relationships are still unknown. As a result, the safety factor, accounting for the differences between the acceptable intakes and the actual intakes, is higher for mixtures of organic chemicals than for heavy metals. This does not mean that heavy metals are of less concern. The testing of mixtures of substances for toxicity at relevant dose levels must be emphasized.

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