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SOME ESTABLISHED FACTS AND SOME NEW CONCEPTS IN FOOD TOXICOLOGY A REVIEW[a]

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According to widespread public opinion, environmental contaminants and food additives are major chemical hazards in food. In contrast, scientific evidence shows that levels of environmental contaminants, such as heavy metals or residues of pesticides, have greatly decreased in the last three decades and are much below the tolerable limits; food additives are strictly regulated and their proper use justifies no food safety concerns. The concept that a "de minimis" value or a Threshold of Toxicological Concern (TTC) can be identified for any chemical is gaining ground in food toxicology. The popular belief that compounds of natural origin are intrinsically safer than synthetic ones is not supported by scientific evidence. – Nutrition oriented cancer research in the past was preoccupied with the idea that food contained man-made carcinogenic substances. Their detection and elimination was thought to reduce and perhaps avoid the risk of cancer. A paradigmatic change has occurred: from the hunt for carcinogenic chemicals in food, research has moved to the study of food constituents preventing cancer and to their mechanism of action. The occurrence of health-promoting food constituents forms the basis of the present interest in "functional foods". However, criminal actions leading to hazardous contamination of food do occur, the Spanish oil catastrophe of 1981 being an extreme example of this. Continued vigilance will be required to protect consumers from unsafe products.

Keywords: food contaminants, food additives, natural toxicants, food safety

The topic of food safety has attracted enormous public interest in recent years. Outbreaks of BSE (bovine spongiform encephalopathy), enteropathogenic *E. coli*-infections, salmonellosis, campylobacteriosis and other feed and food borne diseases have turned attention to microbiological hazards. Nevertheless, chemical hazards associated with food consumption still appear to be predominant in the minds of consumers. Confidence in food safety has been shaken by instances such as the illegal marketing in 1981 of rapeseed oil contaminated with aniline derivatives in Spain, which resulted in *toxic oil syndrome* in some 20 000 people; in several hundred cases the disease ended fatally (ABAITUA BORDA et al., 1998). This was probably the worst case of food-related mass poisoning in the 20th century, anywhere in the world.

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Fortunately, such cases of criminal manipulation of food are rare. In general, health risks caused by chemical contamination of food products are much less important than microbiological risks. Moreover, whereas the incidence of food borne infectious diseases has increased in most parts of the world in recent years, the risks associated with chemical contaminants of food have decreased (Table 1). Space will not be available to discuss all of these substances; a more extensive account has been presented elsewhere (DIEHL, 2000).

Table 1. Decrease in levels of food contaminants

Compared to the situation in the 1970s, today's food supply contains LESS
Lead
Mercury
Cadmium
Solvent residues (chlorinated hydrocarbons)
Ethylene oxide, ethylene chlorohydrine
Benzpyrene and other constituents of smoke
Nitrite, nitrosamines
Food preservatives
Residues of persistent pesticides (such as DDT)
Polychlorinated biphenyls (PCBs)
Polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs)
Chloropropanol
Diethylstilbestrol and other anabolic hormones
Mycotoxins (such as aflatoxin)
.....and this list is not complete

Persistent pesticides and PCBs

Since RACHEL CARSON published her bestseller *Silent Spring* in 1962, residues of pesticides in food were increasingly considered a serious risk to human health. The use and production of persistent pesticides, such as DDT or hexachlorobenzene, was more and more restricted after about 1970. This resulted in decreasing residue levels in food, and this in turn led to decreasing concentrations of these substances in the human organism, as reflected in breast milk (Fig. 1 and 2). In tropical countries, where malaria is widespread and damage caused by agricultural pests is more serious than in moderate climates, persistent pesticides could not be quickly banned. Not surprisingly, DDT-levels in breast milk in such countries are much higher than in European countries (Fig. 3. Note the logarithmic scale). There is no indication that these much higher exposures to DDT are causing higher morbidity or mortality.

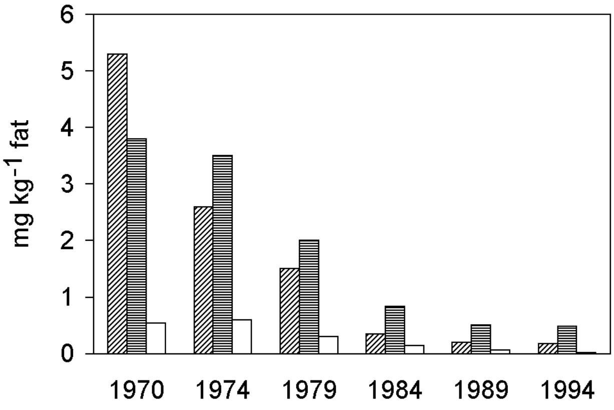

Fig. 1. Decrease in the concentration of residues of three chlorinated hydrocarbon pesticides in breast milk in Germany, mean values 1970–1994 (DIEHL, 2000). ▨: HCB; ▤: DDT/DDE; □: beta HCH

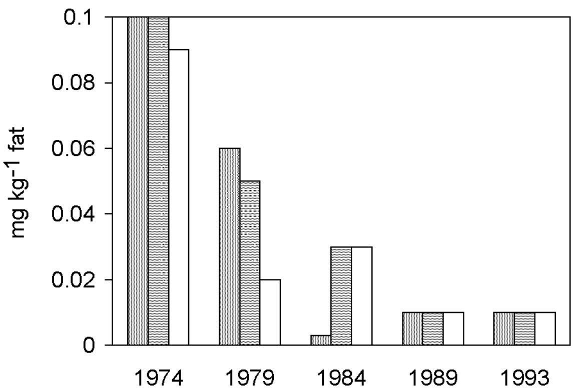

Fig. 2. Decrease in the concentration of residues of another three chlorinated hydrocarbon pesticides in breast milk in Germany, mean values 1974–1993 (DIEHL, 2000). ▥: Heptachloroepoxide; ▤: dieldrin; □: lindane

Another group of very persistent organochlorine compounds are the polychlorinated biphenyls or PCBs. Because of their chemical stability, nonflammability and electrical insulating properties they were used on a large scale since the 1930s as hydraulic fluids, softeners in plastics and paints, and insulating fluids in transformers, capacitors and other electric equipment. Their persistence in the environment led to increasing contamination of the biosphere, until use and production were phased out. As demonstrated in Fig. 4, PCB-levels in breast milk in Germany are now much lower than in the 1970s. Reports from many other countries confirm a worldwide decreasing trend.

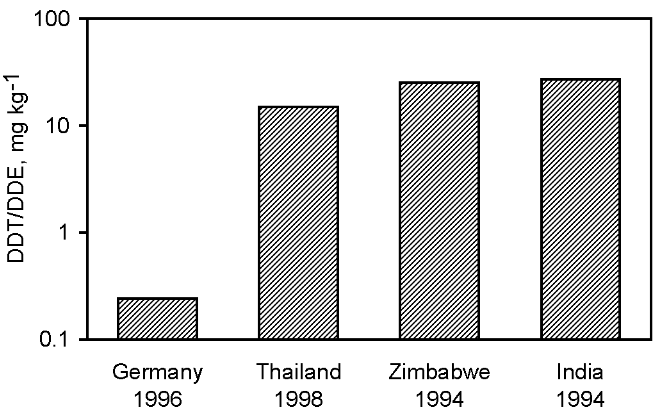

Fig. 3. Concentration of DDT/DDE in breast milk in Germany and in three tropical countries in the 1990s (STÜTZ & SCHERBAUM, 2000, adapted)

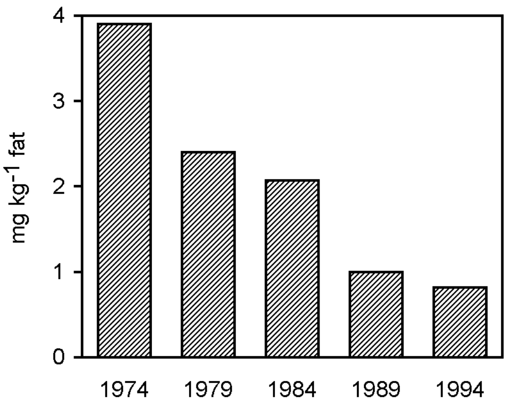

Fig. 4. Decrease in the concentration of polychlorinated biphenyls (PCB) in breast milk in Germany, mean values 1974–1994 (DIEHL, 2000)

Heavy metals

Heavy metals occur naturally and ubiquitously in the earth's crust. Their presence in food is therefore inevitable. Some, such as iron and chromium, are essential in human nutrition. Toxic effects of some heavy metals, especially lead, cadmium and mercury, have been known in occupational medicine for a long time. Fears of mass poisoning resulting from the presence of elevated levels of heavy metals in food were caused by reports from Japan reaching the Western world in the late 1960s. Itai-Itai disease, caused by consumption of cadmium-contaminated rice, afflicted hundreds of people in some areas of Japan. Minamata disease, caused by consumption of seafood contaminated with methyl mercury, also claimed many victims. The need for regulations to minimize contamination of the environment by heavy metals was recognized by governments all over the world. Release of mercury-containing industrial effluents into rivers and lakes was sharply reduced, the use of cadmium pigments in paints and plastic materials was restricted, leaded gasoline was phased out. Canned food used to be a major source of dietary lead intake, because cans were sealed with lead solder, from which lead could migrate into the food. Leadfree solder and, increasingly, the use of cans made of steel or aluminum has removed this source of contamination. As a result of such measures, the concentration of potentially harmful heavy metals in food has decreased, as demonstrated in Table 2 for the situation in Germany. Similar trends have been observed in other countries.

The decreased contamination of food is reflected in decreased levels of heavy metals in the human organism. Mean blood lead levels in adult females in Berlin in 1995 were about one third the levels of 1975, a little higher in smokers as compared to nonsmokers (Fig. 5). The effect of smoking on blood cadmium levels is much more pronounced (Fig. 6). However, excepting occupationally exposed people and itai-itai victims in Japan, the kidney lesions typical of cadmium poisoning have not been observed, even in heavy smokers. The occurrence of mercury in ocean fish, which has caused much excitement some 30 years ago, has been recognized as a natural phenomenon, except in fish from certain estuaries and other coastal areas where contaminated rivers have caused elevated mercury levels. Measures taken to minimize contamination have resulted in decreasing mercury levels in fish from such areas. Ocean water contains – and has always contained – mercury from geological sources. A certain level of mercury in marine products is therefore unavoidable. In general, predatory fish have higher mercury concentrations than species living on plankton, and older fish have higher concentrations than younger specimens. These are natural consequences of bioaccumulation.

Table 2. Decrease of dietary intake of heavy metals; adults in Germany, mg/person and week[a]

Year of report	Lead	Cadmium	Mercury
1976	3.90	0.48	0.21
1984	1.03	0.24	0.11
1994	0.08	0.09	(no data)
Tolerable according to JECFA[b]	1.5	0.42	0.3

[a] (DIEHL, 2000)
[b] FAO/WHO Joint Expert Committee on Food Additives

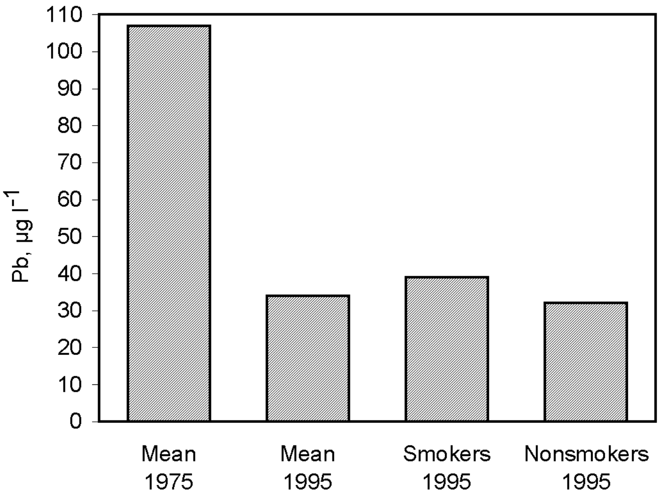

Fig. 5. Decrease in lead levels in blood of adult females in Berlin from 1975 to 1995 (SINN, 1981; FROMME et al., 1997, adapted)

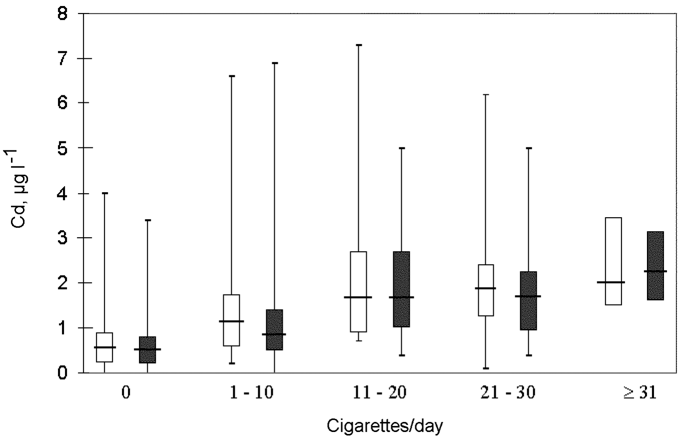

Fig. 6. Effect of smoking on blood cadmium levels in male and female adults, Germany 1987/88 (WETZEL et al., 1994, with permission). ■: Men; □: women; ⊟: median (25–75 percentile); I 2.5–97.5 percentile

Food additives

RACHEL CARSON's warnings were not only directed against pesticides. She considered the use of additives by the food industry as another serious health hazard. Toxicologists, even those who did not agree with CARSON's dire predictions, considered the strong increase in the use of food additives that occurred in the 1950s as undesirable.

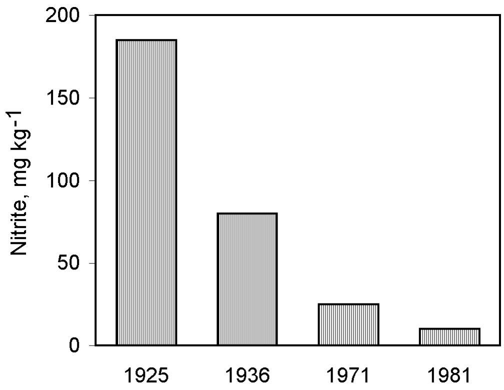

Fig. 7. Decrease in average nitrite concentration in cured meats in the U.S.A., 1925–1981 (HARTMAN, 1983, adapted)

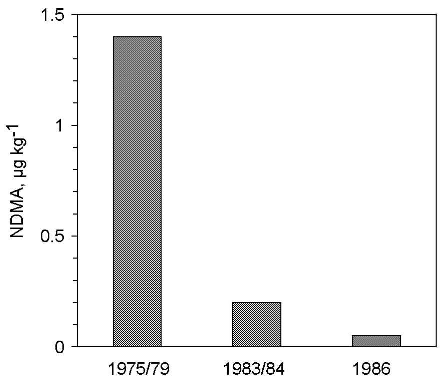

Fig. 8. Decrease in average concentration of N-nitrosodimethylamine (NDMA) in cured meats in the Netherlands, 1975–1986 (ELLEN et al., 1990, adapted)

Consumer organizations in many countries protested against "chemicals in our food". Legislators reacted to these demands. Some additives were banned completely, the use of many others was severely restricted. Nitrite, for example, formerly used rather freely in the curing of meat, is now used very sparingly. This is demonstrated in Fig. 7 for the situation in the United States of America. Nitrite can react with amines present in many foodstuffs, forming nitrosamines, which have been shown to cause cancer in various animal species. The lower use of nitrite, together with the addition of ascorbic acid (vitamin C) in the curing process, has resulted in a welcome decrease in nitrosamine levels in cured meats, as shown in Fig. 8, based on data from the Netherlands.

Similar developments have occurred with many other food additives, especially the preservatives. Many food manufacturers now label their products NO PRESERVATIVES ADDED. This is a rather amazing development in view of the increasing incidence of food borne diseases. The use of some food additives has increased, especially those used in “light foods”: non-nutritive sweeteners, emulsifiers, stabilizers and thickeners. Food additives are strictly regulated and controlled, and – in contrast to widespread public opinion – their proper application justifies no food safety concerns.

Natural toxicants

On the other hand, most consumers are not aware of the very real risks associated with the presence of natural toxicants in food (WATSON, 1998). Those who believe that natural products are intrinsically good and that processing and additives can only damage them do not seem to realize how small a fraction of nature’s products can be used as food. By trial and error man has learned which plants are edible and which should be avoided. Of the several hundred-thousand plant species existing in the world, only a few hundred are regularly eaten and only a few dozen are important as staple foods. Many of the important foods are inedible in the raw state. An example is the soybean (Table 3). Its conversion into products such as tofu, miso, tempeh, soy flour or soybean oil makes valuable foods by removing or inactivating the deleterious constituents. Such beneficial effects are often overlooked when unprocessed food is praised or “minimal processing” is demanded (DIEHL, 1996a).

Another example is maniok or cassava, one of the ten most important food plants, and the most important starchy root or tuber of the tropics. All parts of the plant contain glycosides of hydrocyanic acid, substances which on decomposition yield the highly poisonous HCN. Before consumption the poison must be removed from the tubers by careful processing, i.e. soaking, grating, drying or fermentation. As much as 1.5 g HCN kg^{-1} d.m. (dry matter) may be produced in fresh roots from bitter varieties grown for their high yields. Insufficient processing can lead to extensive outbreaks of acute intoxications.

Natural toxicants also occur in food plants cultivated in Europe. Potato tubers, for instance, normally contain 50 to 100 mg kg^{-1} d.m. of the glycoalkaloid solanine, a cholinesterase inhibitor, and this can go up to over 500 mg in greening potatoes. Hundreds of cases of human poisoning, sometimes fatal, due to the ingestion of greened potatoes have been documented. An outbreak of solanine poisoning among British schoolboys serves as one example (MCMILLAN & THOMPSON, 1979).

Table 3. Some natural constituents of soybeans

Constituents of raw soybeans that may cause adverse health effects:
Protease inhibitors
Hemagglutinins
Allergens
Oligosaccharides
Saponins
Goitrogens
Phytate

Unprocessed soybeans are inedible. Processing can inactivate these constituents.

Brussels sprouts contain goitrogenic glucosinolates. Diets containing 5% or more of the dry matter as cooked Brussels sprouts caused increased liver weight, increased prothrombin time and other symptoms of toxicity in rats (DE GROOT et al., 1991). If foodstuffs such as potatoes or Brussels sprouts had to be newly introduced (as "novel foods") they would hardly be permitted. The span between consumption level and adverse effect level would be considered too small. This is not a warning against consumption of potatoes or Brussels sprouts. They are perfectly healthy foodstuffs. The examples serve only to demonstrate that the often assumed dividing line between natural food ("good") and man-made products ("bad") does not exist.

The occurrence of natural toxicants is not limited to food of plant origin. Some of the most potent toxins known, such as tetrodotoxin, saxitoxin and maitotoxin, are found in seafood. The marine toxins are not produced by the fish, but by algae consumed by the fish or by bacteria living in the intestinal tract of fish. For instance, an estimated 10 000 to 50 000 cases of ciguatera poisoning are reported annually in coastal regions of the Pacific and Indian Oceans and of the Caribbean Sea. Ciguatera toxin, a complex mixture of ciguatoxin, maitotoxin and other toxins, has been found in over 400 species of fish. It is produced by dinoflagellates of the species *Gambierdiscus toxicus.*

Mycotoxins

This group of natural toxicants has received special attention from researchers and legislators in recent years. Under laboratory conditions several hundred mycotoxins have been identified in pure cultures of fungi and the chemical structures of close to 100 of them have been elucidated. Fortunately, only about 20 of the fungal toxins are known to occur in foodstuffs at levels to be of concern for food safety. Three mycotoxins or groups of mycotoxins will be discussed in the following. They were chosen in order to illustrate developments in this field and to demonstrate the wide variety of toxic effects invented by nature.

Aspergillus flavus and *A. parasiticus* growing on grains, nuts, spices and many other foodstuffs can produce mycotoxins, of which aflatoxin B_1 is the most toxic and the most potent carcinogenic substance. Epidemiological studies established a strong association between the incidence of primary liver cancer and aflatoxin consumption in several populations in Africa and Asia. It is still not clear, however, to what extent aflatoxin, hepatitis infection and alcohol abuse contribute to the very high incidence of liver cancer in some African countries. Consumption of mouldy feed by dairy cattle can lead to the presence of aflatoxin M in milk and dairy products. Since the aflatoxins were described by British authors in 1961 as the cause of a mass poisoning of turkeys fed mouldy peanuts ("turkey X disease"), regulations setting maximum limits for aflatoxins in food have been introduced in most countries. The introduction of such a regulation in Switzerland in 1977 has reduced the frequency of aflatoxin M_1 levels exceeding 50 ng kg^{-1} in milk from 77% of samples tested in 1976 to 1% in 1980 (AEBI et al., 1984). These developments in Switzerland can be considered as typical for most other countries in Europe.

Ochratoxin A (OTA) is produced in grain crops by several species of *Aspergillus* in tropical climate and by several species of *Penicillium* in temperate climate. It was first described by South African authors in 1965 and was found to be nephrotoxic, embryotoxic, teratogenic and immunosuppresive in several species of animals. It is carcinogenic in rats and mice and suspected as the cause of Balkan endemic nephropathy in humans. From affected grain crops OTA can get into bread, pasta, beer, and – via feed – into pork. Monitoring programs in Germany have detected OTA in the blood serum of about 50% of people sampled (up to 8 μg l^{-1}), and in human breast milk (up to 0.03 μg l^{-1}). Regulatory limits for OTA in food have been established in some countries, such as Hungary (5 μg kg^{-1} in cereals and milled products; 10 μg kg^{-1} in roasted coffee and other plant derived products). A study carried out in Germany from 1990 to 1992 showed the same levels of OTA in grains as in the previous period of 15 years. However, levels in flour, bread and pasta products were considerably lower than in the earlier period, probably indicating the effect of quality control measures introduced by grain trade and milling industry (MAJERUS et al., 1993).

Among the most recently detected mycotoxins are the fumonisins. They are produced on maize by several species of *Fusarium*. They were first isolated and characterized in South Africa and were since detected in maize and maize products from many other parts of the world. They cause equine leukoencephalomalacia, porcine edema and probably human oesophageal cancer. They are non-genotoxic and the mechanism of carcinogenicity apparently does not involve interaction with DNA.The fumonisin-induced changes to cellular membranes, specifically those related to fatty acid changes in the major membrane phospholipids, appear to be key elements in explaining the cytotoxic effects and altered growth response of cells caused by fumonisins.

The three examples of mycotoxins may suffice to illustrate the scope of the mycotoxin problem. They have also served to show the importance of applying science and technology to improve the health safety of the food supply (DIEHL, 1996b).

Food toxicology revised

Concern about the presence of chemical contaminants in food was mostly based on the assumption that these substances may increase the risk of cancer. In the 1950s to 1980s many people believed (laypersons as well as scientists) that only manmade chemicals caused cancer and that "the war against cancer" could be won by removal of these chemicals from the environment (EFRON, 1984). At that time many authors claimed that even a single molecule of a carcinogenic substance could cause cancer, and "zero contamination, zero exposure, zero risk" was often demanded. In American food legislation the Delaney Amendment of 1958 expressed these sentiments; it prohibited the use as a food additive of any substance that had caused cancer in man or in any species of animal, regardless of the applied dose or the mode of application.

Toxicological thinking has undergone a radical change since that time. An important turning point was the publication of DOLL and PETO's report on the causes of cancer (1981). Based chiefly on evidence from epidemiology, the British cancer researchers concluded that dietary practices (such as overnutrition and unbalanced diets), tobacco use and infections were the most important causes of cancer – not environmental contaminants, not food additives. The American toxicologist PARIZA (1989) concluded: "It is virtually certain that today the levels of dietary carcinogens are not the limiting factor in determining cancer risk. There is no reason whatever to believe that further reduction in the already very low levels of carcinogens in our diet will perceptibly reduce the incidence of cancer" – a bold statement at that time, but now widely accepted.

The idea that manmade chemicals in food were an important cause of cancer was dismantled by American biochemist AMES and co-workers (1990). They showed that about half of all natural chemicals tested in high-dose animal feeding studies caused cancer. All plants contain natural pesticides which serve to protect the plant against microbes, insects and animal predators. Nature's pesticides are the major "toxic chemicals" ingested by man. At the same time animal tests revealed that plants also contain many substances with anticarcinogenic properties. Many epidemiological studies were carried out in recent years to find out how this influences cancer incidence in man. A diet rich in fruit and vegetables is recommended as a protection against cancer (WCRF/AICR, 1997). [Interestingly, the same recommendations apply to the prevention of atherosclerosis and its consequences. Large epidemiological studies indicate that a dietary pattern rich in fruit, vegetables, whole grains, and nuts will substantially reduce the risk of coronary heart disease (HU & WILLETT, 2001)]. Whereas cancer studies some 30 years ago were dominated by the search for carcinogenic substances in food, there are now many more studies on anticarcinogenic substances and on their mechanism of action. Many bioactive substances, such as carotenoids, phytosterols, polyphenols, flavonoids, have been shown to have antimicrobial, antioxidative or antiinflammatory effects or to stimulate the immune system, regulate blood glucose levels or lower blood cholesterol. These observations led to the present interest in "functional foods", which are said to provide positive health benefits over and above normal nutrition (SCHMIDL & LABUZA, 2000). In his most recent publications, AMES (2001) has proposed that common micronutrient deficiencies, as associated with inadequate consumption of fruit and vegetables, cause DNA-damage by the same mechanisms as radiation and as many carcinogenic chemicals, and may be a major cause of cancer. A change in paradigma: the search for chemicals causing cancer has been largely replaced by the search for food constituents preventing cancer.

It should also be recognized that a demand for zero contamination cannot be fulfilled. Whether there is detectable contamination or not depends on the sensitivity of analytical methods. As demonstrated in Table 4 for the case of DDT, when no DDT is detected by the most sophisticated methods now available, there may still be 10^{10} or 10^{11} molecules of DDT per kg of analyzed material. The same applies to all chemicals.

Table 4. There is no zero contamination

The number of molecules in one mole (Avogadro's number) is 6×10^{23}.
Example DDT. Molecular weight 350.
350 g DDT kg^{-1}: 6×10^{23} molecules DDT kg^{-1}
350 mg DDT kg^{-1}: 6×10^{20} molecules DDT kg^{-1}
350 µg DDT kg^{-1}: 6×10^{17} molecules DDT kg^{-1}
350 ng DDT kg^{-1}: 6×10^{14} molecules DDT kg^{-1}
350 pg DDT kg^{-1}: 6×10^{11} molecules DDT kg^{-1}

This is approximately the limit of present-day analytical detectability.
Conclusion: Even if the analyst finds "nothing", a very high number of molecules of various substances may be present.

We live in an ocean of chemicals, of natural or man-made origin, many of which are carcinogenic in high-dose animal studies. With every breath we take and with every bite of food we swallow we expose our organism to billions of molecules of thousands of compounds. Fortunately our body cells have numerous defence mechanisms that make them very well buffered against low doses of toxins, whether synthetic or natural (AMES & GOLD, 1991). It all comes back to the renaissance physician and chemist PARACELSUS (1492–1541) who taught:

"What is there that is not a poison?
All things are poison and nothing is
without poison. Solely the dose
determines that a thing is not a poison" (DEICHMANN et al., 1986).

Recognizing that zero risk cannot be achieved, we must be satisfied with "reasonable certainty of no harm". Many food toxicologists now accept the concept that a "de minimis" value or a Threshold of Toxicological Concern (TTC) can be identified for any chemical, including those of unknown toxicity, taking chemical structure into consideration (BARLOW et al., 2001). Wider acceptance of the TTC concept by national governments would benefit consumers, industry and regulators. By precluding extensive toxicity testing and safety evaluations when human intakes are below such a threshold, this would focus limited resources of time, cost and expertise on the testing and evaluation of substances with greater potential to pose risks to human health and contribute to a reduction in the use of animals. The fact that the TTC concept is receiving increasing recognition among toxicologists indicates a clear departure from the days when utopic demands of zero exposure and zero risk dominated many discussions about food safety.

Safer food and its impact on health

As demonstrated by some examples presented above, application of science and technology to the safety of the food supply, often in combination with stricter regulations, has led to measurable improvements in the toxicological quality of the food products now on the market. Has this actually resulted in better health? The question is difficult to answer, because health is influenced by many factors. One indicator of the health status of a population is the average life expectancy. As can be seen from Fig. 9 (DGE, 2000), life expectancy in Germany has continuously increased in the last decades. Women are better off than men, for reasons not yet fully understood.

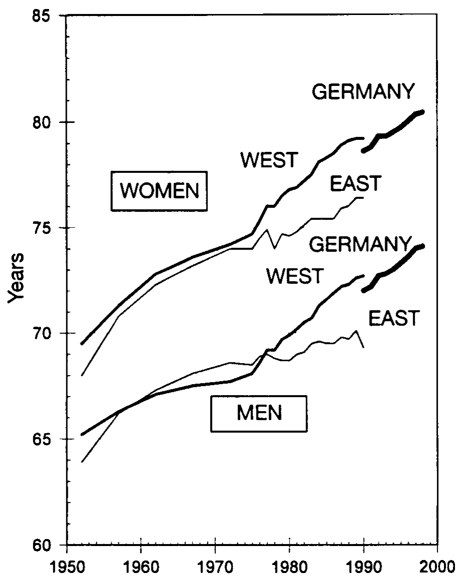

Fig. 9. Increase in average life expectancy in Germany, in former West Germany and in former East Germany, 1952–1998 (DGE, 2000, with permission)

There was a remarkable difference between West and East Germany. After unification the situation in the eastern parts of Germany has gradually matched developments in the west. A similar increasing trend is reported from most other countries. This amazing extension of the human life span counts among the great achievements of our time.

The argument is sometimes heard that the increased life expectancy is only due to better survival chances of infants, caused by better child care, immunizations and antibiotics. However, the population statistics show that the chances of adults to reach old age have also improved markedly. How much of this is due to better nutrition, how much to better medical care, how much to improved housing or working conditions, nobody knows. But it is most unlikely that this phenomenal improvement could have been achieved with a toxicologically unsafe food supply. Health reports of national and international agencies agree that in all industrialized countries – and increasingly also in many developing countries – the greatest dietary risk is overnutrition and unbalanced nutrition, not chemically contaminated food (WHO, 1990).

This overall positive evaluation of the toxicological safety of the food supply should not create the impression of a perfect world. Food control will always be necessary. In the food industry, as in any human activity, there will always be a few who are more interested in a quick profit than in providing an optimally safe product. Continued vigilance will be required to detect adulterations and to keep unsafe food off the market.

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