Chapter 4

Nature Knows Best—Chemicals From the Geobiological Sphere

The Harris family is out on their weekly shopping duties. Apart from the regular groceries, sodas, and toiletries they also shop for some luxury goods: some perfume for both the ladies and men in the household, a few bottles of wine, and a nice bouquet of flowers to liven up the dining room. Interestingly, their choices of these luxury products are determined to a major extent by chemistry. The "aroma" of wine, the "fragrance" of the perfumes of choice, and the "bouquet" of flowers are in fact none other than words that designate the pleasantries of certain chemicals (organic molecules) coming off these luxuries. The chemicals we sense with our nose have found their way into our everyday language. Concerning the wine, taste follows smell, and merge once the first sip is taken. The complex of no less than 25,000 chemicals determines whether we are dealing with a good wine.

But the Harris's are not done yet. They also frequent a specialty store that sells health products. There, they buy a few bottles of bioflavonoid capsules, antioxidants that purportedly improve cardiovascular health, and some bio-vitamin C, which they think is obviously better than the synthetic counterpart. Fortunately, the store also sells painkillers, so a bottle of aspirins is added to the purchases (Fig. 4.1).

In this chapter, we will take a close look at the chemical content of the produce the Harris's have bought. Despite the fact that chemistry is a highly specialized field of research, everyday terms we pointed at here represent the intimate relationship between man and his chemical environment: from the food we eat to the air we breathe, from dietary supplements to medicinal drugs we consume to improve health or cure a disease.

Interestingly, for decades now modern man divides the chemical sphere he lives in into two parts: the natural—regarded as benign for the most part—and the synthetic—man-made chemicals that usually are thought to spell danger. Based on its origin, any chemical is considered to be easily recognized as either safe or dangerous. So, pesticides used during crop production, or antibiotics given to cows with an infection, or food additives such as food coloring and flavor enhancers are generally regarded as a threat to human health.

We will unfold this peculiar dichotomy and show that these two seemingly divided worlds—natural vs synthetic and safe vs dangerous—overlap

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FIGURE 4.1 Pictures of bouquet of flowers and a bottle of quercetin (a flavonol).

far more than generally realized. Ironically, with the advent of the chemical industry and research in the 19th century, the discovery and production of an increasing number of different chemicals facilitated the growing realization that the natural world itself harbors an immense amount and diversity of chemicals. And this realization fed the growing field of toxicology throughout the 20th and 21st centuries. We will review both ends of the scale of the environment, i.e., the personal level on the one hand—food and drugs—and the global level on the other—the geobiological sphere.

THE CHEMICAL WORLD OF FOOD AND COFFEE

The way humans are exposed to the wealth of chemicals is mostly through the diet that varies widely across countries and continents. Just to give an idea of how much food is consumed: an individual eats, during his or her lifetime on average, some 30 tons of food.

The interest in food and its health impacts is a never-ending source for TV shows, glossy's, cookbooks, professional and academic articles. Man seems to have returned to the ancient idea that food is far more than needed for survival: food is life and should increase vitality and health for as long as possible. However, the fact that chemistry is addressed in all this is hardly ever mentioned. Indeed, humans have become very wary of everything chemical. Foods that have been "tainted" with pesticides, antibiotics, coloring and flavoring, and other processing techniques immediately raise our suspicions. The "natural" has been "polluted" with "the chemical." And that idea foolishly has become the mental furniture of our day and age.

Overall, most people will enthusiastically embrace the idea that the foods we buy at the store should be, and in fact usually are, quite safe. The food industry, governments, and consumer organizations advertise this widely. Yet, food is a complicated mix of many thousands of different chemicals with all sorts of biological activities, not easily categorized as either good or bad. Thus, apart from the nutrition we require daily, many other chemicals slip in our "system" that have all sorts of effects on our health, for better or for worse. This we have addressed to some extent in the first chapter. And we haven't even started cooking yet!

Indeed, preparing a meal in the kitchen or food being processed industrially—frying, baking, boiling, roasting—changes the chemical composition of our food quite extensively and increases the number of chemicals we consume. This fact alone brings us in a world beyond unprocessed foods as can be obtained at the supermarket or from local farmers.

The chemical changes in foods caused by moderate heat modify or intensify flavor chemicals that are natural to a food. The so-called browning reactions at higher temperatures produce new flavors that are characteristics of the cooking process. Caramelization is one example of a browning reaction. When we heat plain table sugar, sucrose, it first melts into a thick, colorless syrup. After a while it slowly changes color, becoming light yellow, and gradually intensifies to dark brown. At the same time, its flavor develops a full aroma with some acidity and a hint of bitterness. If this browning reaction goes too far, it produces an unpleasant bitter mixture. If kept in check, the complex chemistry renders a sugar-derived product applied in all sorts of candy and other sweets (Fig. 4.2).

Thus, with some cooking skills tasty results can be created. A cook is none other than a chemist producing many hundreds of chemicals in one go. And not all these newly formed chemicals add flavor and aroma to our dish. Let's look at one of the most common morning brews in the world: coffee.

It is valued for its uplifting and stimulating qualities and its specific flavor and aroma. The chemical responsible for the stimulating effect is caffeine and is a repellent to discourage pests and herbivores to eat that plant. But before we can actually prepare a good breakfast brew, a lot of processing of the coffee beans needs to be done.

Coffee beans are picked, processed, and dried once the berries of the *Coffea* plant that contain them are ripe. Dried coffee beans are roasted to varying

FIGURE 4.2 Picture of fudge.

FIGURE 4.3 Pictures of coffee plant, coffee berries almost ready for harvesting, coffee beans, and an espresso shot from an E61 brew head.

degrees, depending on the desired flavor. It is only through roasting that the beans gain the characteristic and cherished aroma and flavor. Roughly a thousand chemical compounds have been identified within the roasted coffee bean that adds to the overall brew. And more are discovered every day (Fig. 4.3).

Within this overall mix, some chemicals formed during roasting have less than desirable characteristics. Polycyclic aromatic hydrocarbons (PAHs) for instance are formed during especially higher temperatures. PAHs are a group of carcinogenic organic compounds. It is estimated that intake of PAHs through the consumption of coffee is some 150 ng per day, i.e., 150 billionths of a gram. The total daily PAHs intake from all sources is estimated to be roughly 1700 ng, or 1.7 μg.

How dangerous these compounds in fact are, and how to assess those risks, is subject of Chapter 5, From Prevention to Precaution—Valuing Risks. What is known from research is that regular enjoyment of coffee does not increase

FIGURE 4.4 Picture of barbeque.

the rate of cancer. In fact, coffee consumption has all sorts of beneficial effects and that is good news for all of us who need their daily dose of java.

With our food processing both at home and in the factory, we chemically change our food. That, of course, is nothing new. With the discovery of fire, our ways to prepare food transformed and opened up new venues of flavors and aromas. However, the moment science turned its gaze on food and food processing, it revealed a far bigger chemical landscape than anticipated: the geobiological sphere.

Let's go back to coffee. The PAHs that can arise from roasting the beans are also found on barbequed meat. Cooking over a smoky wood fire deposits PAHs from the burning wood onto the meat. We could prevent this by cooking meat over a smokeless charcoal fire. But, if fat drips on the coals and burns, that will create PAHs that again will deposit on the meat. Or, PAHs are formed if the fat ignites on the meat surface itself.

So, barbequing requires quite a bit skill as to prevent unwanted chemicals. However, it also shows that the environment delivers quite a bit of chemistry to the dinner table not linked to the skills of the cook (Fig. 4.4).

An interesting example of this "environmental chemistry" involves organohalogens. These organic chemical compounds contain the elements fluorine, chlorine, bromine or iodine, the halogens. Focusing on the most abundant of the halogens, chlorine, it obtained its infamy in World War I when German troops used it in its elemental gaseous form as a chemical weapon on April 22, 1915, near Ypres against Allied troops.

In most households, chlorine is found in the form of bleach, the unmistakable smell of which we associate with a freshly cleaned restroom and, happily, not with war. Most cooks, either professional or amateur, also use chlorine in the form of sodium chloride, table salt, as to add flavor to the dish.

We need salt in order to stay healthy, and it is used in many different processes in our bodies. For instance, chloride is used in the stomach for the formation of hydrochloric acid. On average, we carry between 100 and 200 g of salt in our bodies depending on our mass.

FIGURE 4.5 Picture of table salt crystals.

The chlorination of drinking water as to keep it free from water-borne diseases, such as typhoid, cholera, and meningitis, has been a common, cheap, and highly effective practice for almost a century. It does affect taste, but keeping infectious organisms away from drinking water is top priority in any country (Fig. 4.5).

The amount of salt in the world is staggering. Chloride in seawater amounts to some 1.8%. The world production of salt is close to 300,000,000 tons per year. It seems strange therefore that chlorinated hydrocarbons are thought to result from the chemical industry only. So, any organochlorides found in the environment must be the result of industrial pollution or the result of chlorination of drinking water, so the story goes.

One of the most notorious organochlorides is perhaps DDT (dichlorodiphenyltrichloroethane in full), a now banned insecticide. Dioxin is another example that is regarded by some as the most toxic man-made chemical ever (more on that later). In the late 20th century a ban on production and use of all chlorinated hydrocarbons was strongly advocated by especially environmental NGOs.

However, once we penetrate deeper into the geobiological sphere, the more we come to understand that nature itself delivers an overwhelming amount of organochlorides from all kinds of sources: plants, molds, sea creatures, erupting volcanoes, forest fires, and so on. Some of these compounds are produced in amounts that dwarf human production such as chloromethane. Indeed, it is estimated that some 75% of all chlorinated substances found in the environment come from biological sources and geological sources such as volcanic eruptions. And that includes dioxins. Many natural sources have been discovered that produce dioxins. It is even suggested that our own immune response is responsible for the generation of minute amounts!

Seafood is especially interesting as the marine environment contains so much chloride and the other halogens to a lesser extent. In other words, sea

FIGURE 4.6 Picture of Limu kohu.

creatures and plants are literally surrounded by halogens. It is therefore no real surprise then that many different organohalogens have been discovered in edible seafood. For instance, the chemically prolific red algae *Asparagopsis taxiformis* and *Asparagopsis armata* ("Limu kohu"—pleasing seaweed), which are prized by Hawaiians for their flavor and aroma, contain the relatively novel (*E*)-1,2-dibromoethene, (*Z*)-1,2-dibromoethene, and tribromoethene.

Even more interestingly, a study confirmed one of the most heavily brominated enol esters (pentabromo-2-propenyl di- and tribromoacetate) ever found in nature produced by *A. taxiformis*. These two compounds were confirmed by chemical synthesis in the laboratory (Fig. 4.6).

Polybrominated biphenyl ethers (PBDEs) used as fire retardants have been restricted from commercial use by cause of their toxicity and bioaccumulation in the environment. However, PBDEs that mirror and even surpass the toxicity of man-made counterparts have been found naturally produced by marine sponges, especially of the order Dysideidae. Naturally produced PBDEs permeate the marine environment and even bioaccumulate in marine animals and are carried over to the human food chain. Recently, the genetic background of the natural synthesis of PBDEs has been mapped.

Should we worry then about this immense smorgasbord of chemicals that make up our food? We have been taught to fear "chemistry" and our food is teeming with all sorts of chemicals that, in some cases, include chloride, and we are not just talking about table salt. These chemicals are either innately present in the consumables, are delivered by environmental sources, or are added during the process of cooking.

Some decades ago, humans weren't aware of organohalogens at all. It was easy to focus on dioxins and DDT and a few other chemicals and try to ban them from our world by law, so we thought. Food was "clean" if it was produced naturally (organic, biological) and wasn't industrially processed. Our world was orderly divided between natural and synthetic, good and bad, healthy and unhealthy, clean and dirty.

FIGURE 4.7 Picture of *Chrysanthemum*.

And humans still cling to this idea. People like to protect themselves by choosing those products that are portrayed as natural and as a result, it is thought, free from harm. Organic farming, despite of its higher-priced produce, has become popular based exactly on the notion of naturalness and safety. Also, we like to buy not just vitamin C as supplement but preferably bio-vitamin C, although it is impossible to indicate any chemical difference between them. The Harris's, in other words, seem to buy into this story.

The reality that innate plant protection naturally comes from pesticides that are produced by plants or sealife themselves is far from new. In our romantic worldview of food and food production, we seem however to have lost the basics. The world of bacteria, molds, plants, and animals is one of assault and defense. And chemistry plays a big role therein.

The flowering plants of the genus *Chrysanthemum*, for instance, have been known for centuries to repel and kill insects. The responsible pyrethrins isolated in the beginning of the 20th century form the basis for the pyrethroids, manufactured chemicals that are very similar in structure to the pyrethrins, but are more toxic to insects and last longer in the environment than pyrethrins. So, nature formed the toolbox for chemists to improve upon insect control in crops (Fig. 4.7).

Comparing the consumption of natural and synthetic pesticides, humans roughly consume 1500 mg of natural pesticides and their breakdown products every day compared to approximately 0.09 mg of synthetic pesticide residues. It seems then that our fear of "the chemical" is misplaced but also gives a false sense of security.

SELECTIVE TOXICITY

As food contains so many natural "toxic" chemicals, couldn't food be used as medicine? The answer to that question is simply yes. A quote attributed to Hippocrates "Let food be thy medicine and medicine be thy food" holds today more than ever especially in view of our increasing knowledgebase. Toxicity and medicine are usually not seen as closely linked, let alone food and toxicity. Medicine should be safe, just as food, seems to be the general consensus.

In medicine we look for chemicals, drugs, that have a very specific effect on a disease state. Thus, we want as little side effects as possible: that is safety. However, the particular effect we prize in good medication is nothing other than selective toxicity against the disease we want to cure. Medication, thus, is *targeted toxicity*: the more focused the toxicity, the better the medication, and the fewer the side effects. These side effects are nothing other than broad and thereby undesirable toxicity.

Paul Ehrlich initiated this notion of targeted toxicity with his discovery of receptors at the beginning of the 20th century. It opened up a whole new world of understanding and disease treatment. To Ehrlich, receptors were small, chemically defined areas on large molecules (proteins). He wrote that "combining group of the protoplasmic molecule to which the introduced group (the molecules of medication; authors) is anchored will hereafter be termed receptor." This image of receptors in essence hasn't changed much but became more detailed for many different kinds of receptors. The action of drugs is characterized by a selective action on a specific target, a receptor or enzyme that is involved in curing a patient's disease.

This medicinal targeted toxicity results in measurable effects toward health, if all goes well. Usually drugs have a large easily quantifiable effect on a specific target (a receptor or enzyme) and the effects are usually seen over a relatively short period of time, days, weeks, and sometimes months. A rapid action is desired because diseases should ideally be cured as fast as possible for the patient's sake. If, however, medication needs to be taken over longer periods of time (e.g., asthma medication), side effects need to be at a minimum as to make this long-term medicinal exposure at all possible.

Food chemicals are different, and fortunately so. These chemicals usually do not have any drastic effects after consumption as medication does. Food constituents act on various targets and display multiple effects on our health. Unlike drugs, the actions of dietary components are mild. Looking at more detail, these effects can easily be categorized, surprisingly enough, as subtly toxic. It seems that we need to be pushed in order to stay healthy.

The health effect of food should also be tested differently compared to drug testing. The placebo-controlled double-blind randomized clinical trial (RCT) is commonly used for drugs, in which the effect of a drug is tested against a placebo without the patients and researchers knowing who gets what is not really appropriate for testing food and food constituents. The latter always are part of the diet and cannot easily be omitted for research reasons. You cannot leave out vitamins from the diet for example. Apart from the chemical complexity to actually do that, although not impossible, it would be unethical.

It is increasingly advocated that in order to investigate the effect of food, the organism is put under stress and various biomarkers that reflect the effect of the stressor are determined. The effect of food on the ability to withstand the stressor is subsequently measured. Examples of stressors are the administration a fatty, sugar containing, drink that elicits mild inflammation or smoking a few cigarettes or exhaustive exercise.

Another approach to evaluate the health effect of food is to quantify the effect on many of the physiological responses involved in a disease state. In this way a health index can be defined which takes into account multiple targets.

Doing sports (increasing our oxygen exposure) and eating well increases our endogenous protective system and thus renders protection in the long run against aging and disease.

So, the old definition of health of the WHO as a "state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" is wide off the mark. We do not live in a static world but in a dynamic one. And we behave accordingly by adapting to new situations the best we can. Health is thus *the ability to adapt*.

FOOD AND MEDICINE: THE "GOOD," THE "BAD," AND THE UNAVOIDABLE

Food is truly a complex mixture of chemicals that have all sorts of health effects. The longstanding golden rule is to diversify our daily diet and for good reasons: we hedge out bets. The wider the spread of consumed food chemicals, the smaller the chance we run afoul with health-impairing consumption habits.

A number of reasons carry this argument: (1) we reduce the chance to be exposed to the same food chemicals over and over again whereby (2) we reduce the chance of missing out on chemicals such as vitamins and minerals and antioxidants that are essential for our well-being, and (3) we reduce the chance of being exposed to chemicals we better do without such as potato alkaloids but also chemicals that are produced by molds such as the liver toxin aflatoxin.

Beneath these three arguments lies the notion that by diversifying our food intake, we train our bodies to deal with all sorts of chemicals. The potato alkaloids or the nasty courgette cucurbitacins or even the much feared mould aflatoxins can, at very small doses, trigger damage-repairing responses that in the end is beneficial for our health. As the maxim goes: what does not kill you makes you stronger.

Not that we should directly search out exposure to these compounds. That is not even required; we are exposed to such chemicals anyway. They are unavoidable. But it does show that "good" and "bad" chemicals as such do not exist: only the dose makes the poison. Even more so, traditionally classified bad chemicals actually can be a source for good for us, as long as the dosages are low enough. We have the ability to adapt, and this adaptability when trained enough will stimulate our health and longevity.

So the fear of "the chemical," our chemophobia is indeed a phobia, an anxiety disorder. We persistently fear "the chemical" in our food. This fear is narrowed down to pesticides sprayed during crop production, antibiotics used in animal rearing, food additives, and we will go to great lengths to avoid these chemicals, disproportional to the actual danger posed.

The disproportion is related to the fact that we have forgotten that food in all its naturalness carries with it all the chemistry we need to survive and thrive. From the carbohydrates, fats and protein to the vitamins and minerals and all the rest that might intoxicate us if we are not careful or might help us adapt to greater health. As human beings we are well adapted, within limits.

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