Effects of Persistent and Bioactive Organic Pollutants on Human Health

Edited by DAVID O. CARPENTER

WILEY

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CONTENTS

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Introduction: Why Should We Care about Organic Chemicals and Human Health?

DAVID O. CARPENTER

ABSTRACT

Background: The last several decades have seen an enormous increase in the development and manufacture of different organic chemicals that have proven useful for many aspects of contemporary life. The question is the degree to which some of these chemicals cause harm to human beings.

Objective: This book is directed at the goal of identifying organic chemicals that, while useful in many regards, pose risks to human health because of their biological activity and often their persistence.

Discussion: The various chapters in this book are directed at the effects of organic chemicals on the various organ systems.

Conclusions: While recognizing the wonderful benefits that have come from the development and use of many organic chemicals, serious adverse human health effects have occurred because of inadequate testing prior to use and ineffective steps to prevent release of the chemicals into air, food, water, and the environment, resulting in exposure and disease in humans. It is urgent that more effective ways be found to ensure the safety of organic chemicals, no matter how useful they may be, before they are produced and released into the environment.

Organic chemicals are a major part of everyday life in the modern world. Without question, chemicals have made our lives much easier. But at the same time, it is important to recognize that there have been some downsides to the chemical revolution. This book is focused on the downsides, but that is not to indicate that the benefits of chemicals are ignored. The use of chemicals has resulted in increased food production and safety of food, safer drinking water, improvements in life expectancy from development of pharmaceuticals and antibiotics, and greater convenience to everyone.

It is quite remarkable how much has changed in our daily lives after the development of synthetic chemicals. In the past, our carpets, draperies, and clothes were all made from natural fibers such as wool, linen, or cotton. Today, many are made from synthetic products all derived from petroleum. Most carpets, draperies, and many clothes are treated with organic flame retardants. In the past, our cookware was made of glass, pottery, and various metals. Today, we store foods in plastic, and our cookware is lined with perfluorinated compounds to prevent food from sticking. We drive in cars that may have a metal motor and frame and have glass windows, but everything else is made from plastic and petroleum products. We spray our homes with pesticides and air fresheners. We bathe our bodies with personal care products (creams, cosmetics, deodorants, perfumes, polish for nails, etc.) containing many different chemicals, and often we have no idea what they are or what they might do to alter our health, no matter how beautiful they make us look and how good they make us smell. We dye our hair with chemicals and treat our hair with shampoos and conditioners that contain a variety of chemicals, often not even identified on the bottle because the mixture is proprietary.

We eat food that is often raised at distant places and depend on fossil fuels to get them to our local supermarket. Because we all like our fruits and vegetables to look perfect, they must be grown heavily treated with pesticides and fungicides, with herbicides added to keep the weeds under control. Since foods spoil over time, many fresh foods are treated with preservatives to make them look fresh even if they are not. Food additives are in almost every prepared product to reduce rate of spoilage and to improve color and flavor. There are some 3000 food additives in common usage. While our canned foods used to be in bare aluminum cans, we now line these cans with bisphenol A to avoid any metallic taste, assuming that the bisphenol A stays on the can. When we freeze our foods, we almost always place them in plastic, and we drink from plastic bottles and cups and assume that the plasticizers there, usually various phthalates or bisphenol A, do not leach into the food or drink.

It is not just fruits and vegetables that now contain chemicals that were not in them in earlier times. Now our meats come from animals treated with antibiotics and growth hormones. Our fish come from waters contaminated with persistent organic pollutants, such as bis[p-chlorophenyl]-1,1,1-trichloroethane (DDT) and its breakdown product, 2,2-bis(p-chlorophenyl)-1,1-dichloroethylene (DDE), other pesticides, polychlorinated biphenyls (PCBs), methyl mercury, and even pharmaceuticals that are discharged into the waste water through

human excretion and deposition of unused pharmaceuticals down the toilet. Many of the fish we eat come from fish farms, where fish are caged and fed food that often is contaminated with chemicals (Hites et al. 2004). In addition, in order to prevent infectious and fungal diseases in the enclosed, concentrated environment, antibiotics and fungicides must be used. Even the wild fish from lakes, streams, and the ocean contain organic chemicals, especially those that are lipophilic and persistent. The same contaminants, albeit usually at a lower concentration, are in our meats, eggs, and dairy products as a result of the contemporary practice of adding waste animal fats and products into the food fed to domestic farm animals. The feeding of waste animal fats to domestic animals that are not naturally carnivorous has resulted in the recycling of dangerous persistent chemicals like DDT and PCBs, which have not been produced in developed countries for more than 30 years, back into our food supply (IOM 2003).

Most people assume that the chemicals in carpets, in plastic food containers, and in drink bottles, and those sprayed under the kitchen sink to deal with insects stay put. However, it is clear that this is often not the case. Furthermore, most people assume that governments would not allow chemicals that might pose a hazard to health to be used. However, this also is often not the case. Unfortunately, chemicals volatilize from carpets and under-the-sink pesticide applications. They leach out of food and drink containers. Even before reaching the kitchen, there are chemicals in the food reflecting what the food animal ate or was treated with, and there are chemicals on the fruits and vegetables that are only partially removed by washing. So, a variety of organic chemicals are in the food and water we eat and drink and in the air we breathe, and are also absorbed through our skin.

Because infants and children are particularly vulnerable to harm from exposure to contaminants, there is special concern about the impact of pesticides in the diets of infants and children (NRC 1993). However, the mother's body is the first environment for the child, and the contaminants in the mother's body are passed to the fetus. Thus, efforts to reduce exposure to dangerous organics should focus on all women of reproductive age, not just infants and children.

Governments struggle to balance the promotion of new chemicals that will be useful to humankind with the protection of the public from hazards. The development and marketing of organic chemicals has increased enormously in a relatively brief period of time after World War II. In the United States, the Toxic Substance Control Act of 1976 (TSCA) is the law that presently regulates new chemicals. At present, there are more than 84,000 chemicals in this inventory, most of them organics. When the law was passed, most existing chemicals (62,000) were grandfathered into the inventory and were allowed to remain on the market without further study. Some chemicals were specifically identified to no longer be manufactured and used, as was the case with PCBs. New chemicals continue to be added to the inventory, but most of the testing of safety is dependent on the manufacturer. Figure 1.1 shows the

Industrial Chemicals:
~ 82,000

Pharmaceuticals:
~ 1,000

Pesticides: ~1,000

Food Additives: ~3,000

Cosmetics and Additives:
~ 6,000
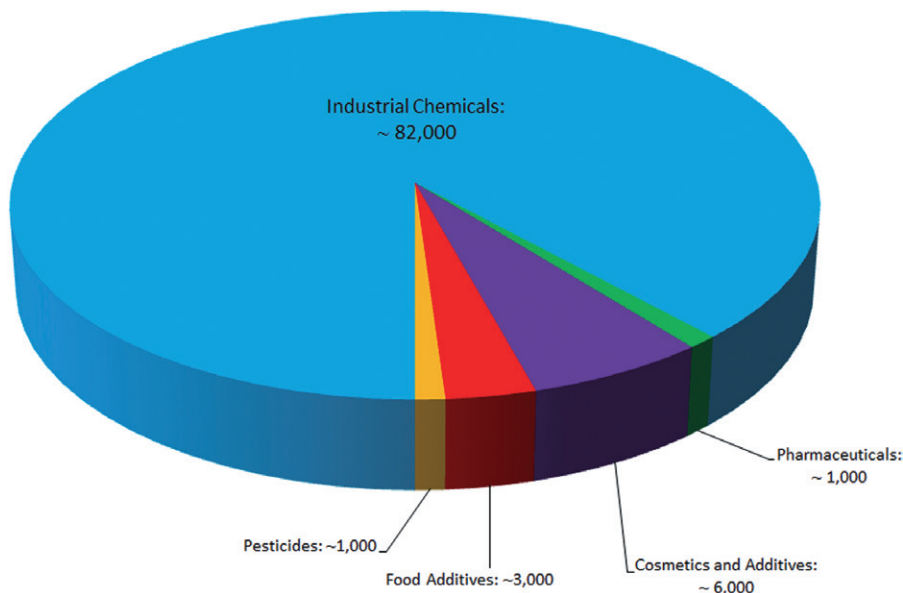
Figure 1.1. Approximately 100,000 individual chemicals have been registered for commercial use in the United States over the past 30 years. Chemical classes that receive the majority of public attention (e.g., pharmaceuticals, cosmetics and food additives, and pesticides) constitute only a small percentage of this inventory. Analytical methodologies are currently limited to several hundred of these nonregulated chemicals. Adapted from Muir and Howard (2006) with permission.

distribution of chemicals currently on the market. Most are organics, although there are also some metals. To date, only about 250 chemicals have been rigorously tested independent of the industry by the Environmental Protection Agency (EPA), and only 5 have been regulated. In addition, TSCA (and thus EPA) does not have regulatory authority over pesticides, tobacco and tobacco products, radioactive materials, foods, food additives, drugs, and cosmetics, all of which are regulated by different government agencies. While new legislation is needed, a number of steps have been taken to prioritize chemicals of high use and those that are the most worrisome in terms of impacts on public health.

In 1999, the Canadian government implemented a tiered approach to address chemicals of concern in their inventory under the Canadian Environmental Protection Act. They evaluated 23,000 chemicals with a screen including physicochemical properties that might relate to persistence and bioaccumulation, measures of toxicity to various organ systems with consideration of acute, subchronic, and chronic endpoints. They identified 500 chemicals of high priority and 193 that required regulatory action. The government is continually reviewing the high-priority chemicals.

In late 2008, the European Chemical Agency, in preparation for the implementation of Registration, Evaluation, and Authorization of Chemicals (REACH), preregistered about 150,000 substances (http://www.echa.europa.eu/). The stated goal of REACH is "to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances." It gives greater responsibility to industry to manage risks from chemicals and to provide safety information. It also has a goal of obtaining progressive substitution of the most dangerous chemicals when less dangerous alternatives are available. The provisions of REACH are to be phased in over a period of 11 years.

These actions by various governments are all intended to prevent chemicals, especially organic chemicals, from being produced and used before it is certain that they will not escape into the environment, lead to exposure to animals and people, and pose significant hazards to human health. However, the reality is that to do so is very difficult. Premarket tests usually look at acute lethality in animal models or study animal or human cells in culture. Investigation of the subtle effects on the nervous or immune systems and the delayed elevated risk of developing cancer is much more difficult and much more expensive. Even if this long-term testing is done in animal models, there is no certainty that humans will respond exactly the same. Thus, we all become guinea pigs for the effects of exposure to chemicals.

Another major problem is that most testing and understanding of the hazardous effects of chemicals in animal and cellular models are done one chemical at a time. But in the real world, each of us is constantly exposed to a very great mixture of chemicals. There is a mixture of chemicals in the air we breathe, a different mixture in the water or other fluids we drink, yet a different mixture in the food we eat and then we put yet other chemicals on or in our body through medications, lotions, shampoos, and other personal care products. However, interactions between the effects of two or more chemicals have been very poorly studied. There are three major possibilities—the effects of two chemicals may be additive, less than additive, or synergistic (Carpenter et al. 1998). Of particular concern is when there are synergistic effects.

To make things even more complex, the above-mentioned discussion assumes that one chemical has only one site of action. DDT, for example, kills insects by blocking the action potential in insect nerves and causing paralysis. This is the mechanism of action that kills pests. However, in humans, DDT does not block action potentials but increases the risk of a great variety of human diseases, including cancer, cardiovascular disease, diabetes, nervous systems effects, and changes in immune system function (detailed in the various chapters in this book). These different effects are certainly not mediated by actions at the neuronal sodium channel! And it is very unlikely that the effects on the different organ systems are mediated by the same mechanisms. This may involve different receptor binding sites or induction of different genes. Kiyosawa et al. (2008b) found that technical-grade DDT in

rats induced genes associated with drug metabolism, cell proliferation and oxidative stress, and the nuclear receptors constitutive androstane receptor and pregnane X receptor. In another study, Kiyosawa et al. (2008a) reported that the pattern of gene induction in the mouse was significantly different from that in the rat to the same exposure. So one must conclude that any chemical that can induce genes regulating many different physiological functions has the potential to cause a great variety of different effects, but that there may be significant species differences which make extrapolation from animals to humans subject to errors.

These actions at different receptors and induction of a great variety of different genes likely explain the increasing frequency of demonstration of low-dose effects, nonlinear dose–response curves and what is commonly called "hormesis" (Calabrese 2008; Lee et al. 2010; Welshons et al. 2003). It has always been a tenant of toxicology that "the poison is in the dose." This may well be true if the poison has a single binding site that leads to a single action, but it is clearly not true for the actions of many organics that have both multiple binding sites in different organ systems and also induce genes that alter many different physiological functions.

One book cannot hope to cover all organic chemicals or all possible biological effects. However, in this book, we have tried to consider effects on the major organ systems and the actions of representative chemicals for which there is at least some information. In many cases, the focus is on the persistent organic pollutants for the very practical reason that, because of their persistence, we have better exposure assessment and more information than is available for less persistent organics. As will be clear, our knowledge on the range of human health effects of organic chemicals is incomplete and much more research is needed.

REFERENCES

Calabrese EF. 2008. Hormesis: 2008. Why it is important to toxicology and toxicologists. Environ Toxicol Chem 27:1451–1474.

Carpenter DO, Arcaro KF, Bush B, Niemi WD, Pang S, Vakharia DD. 1998. Human health and chemical mixtures: An overview. Environ Health Perspect 106 (Suppl 6):1263–1270.

Hites RA, Foran JA, Carpenter DO, Hamilton MC, Knuth BA, Schwager SJ. 2004. Global assessment of organic contaminants in farmed salmon. Science 303: 226–229.

IOM (Institute of Medicine). 2003. Dioxins and Dioxin-Like Compounds in the Food Supply: Strategies to Decrease Exposure. Washington, DC: National Academies Press.

Kiyosawa N, Kwekel JC, Burgoon LD, Dere E, Williams KJ, Tashiro C, et al. 2008a. Species-specific regulation of PXR/CAR/ER-target genes in the mouse and rat liver elicited by o,p′-DDT. BMC Genomics 9:487.

Kiyosawa N, Kwekel JC, Burgoon LD, Williams KJ, Tashiro C, Chittim B, et al. 2008b. o,p′-DDT elicits PXR/CAR-, not ER-, mediated responses in the immature ovariectomized rat liver. Toxicol Sci 101:350–363.

Lee DH, Steffes MW, Sjödin A, Jones RS, Needham LL, Jacobs DR, Jr. 2010. Low dose of some persistent organic pollutants predicts type 2 diabetes: A nested case-control study. Environ Health Perspect 118:1235–1242.

Muir DC, Howard PH. 2006. Are there other persistent organic pollutants? A challenge for environmental chemists. Environ Sci Technol 40:7157–7166.

NRC (National Research Council). 1993. Pesticides in the Diets of Infants and Children. Washington, DC: National Academies Press.

Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. 2003. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ Health Perspect 111:994–1006.

Sources of Human Exposure

MARTÍ NADAL and JOSÉ L. DOMINGO

ABSTRACT

Background: Persistent and bioactive organic pollutants may reach the human body through different pathways, which usually determine subsequent health effects. Although occupational exposure has a prominent role, the environmental/dietary contact with these substances may be also very important. Therefore, it is critical not only to identify but also to estimate the contribution of each one of the exposure pathways.

Objectives: This chapter presents current calculation methods to estimate the main pathways of exposure to organic pollutants. Information regarding a few chemicals (persistent organic pollutants, pesticides, benzene, and perfluoroalkyl substances) is also summarized.

Discussion: Direct (or nondietary) exposure can be estimated as the sum of pollutant intake through air inhalation (air concentration related), as well as soil ingestion and dermal absorption (both dependent of soil concentration). In turn, dietary exposure can be calculated by considering food intake and water consumption. Dietary intake seems to be the main human exposure route to organic contaminants such as POPs or pesticides, with only a few exceptions. To a lesser extent, other pathways may have some notable contribution, especially for particular subgroups of population characterized by being more vulnerable to environmental pollutants, such as children or aged people.

Conclusions: Some basic tools to perform a first-tier screening for human health risk assessment, focusing on human exposure, are provided here. Food consumption seems to be the most important contributive route to the total intake of persistent and bioactive organic pollutants.

INTRODUCTION

During normal life, people may be exposed to a broad range of chemicals through different pathways. Many contacts with those substances occur in an unconscious and/or involuntary manner during usual and daily activities. Indoor spaces are environments where the potential exposure to chemicals is especially significant. Moreover, occupational exposure to chemicals is also important for some adults during the working day. However, foodstuffs play a key role in the uptake of contaminants by humans. As it has been largely confirmed in recent years, dietary intake is the most critical pathway of exposure for many pollutant substances.

The effects of persistent and bioactive organic pollutants on human health are often dependent on the exposure routes through which those contaminants enter the human body. Therefore, it is critical to identify the main entrance pathways, as well as to estimate the contribution of each one. This information is essential to undertake actions to minimize the human exposure to organics, especially in those subpopulation groups for which the potential adverse health effects are more notable, such as children or the elderly.

This chapter is divided into two basic sections. The first one highlights current methods to estimate the main pathways of exposure to organic pollutants, while the second one compiles information for some specific chemicals, which are contemplated in subsequent chapters.

HUMAN EXPOSURE PATHWAYS

The U.S. National Research Council (NRC 1983), in its so-called Red Book, established a series of principles to be considered for human health risk assessment, defining it as a process in which information is analyzed to determine if an environmental hazard might cause harm to exposed persons and ecosystems. Human exposure was identified as a critical step in the original four-step risk assessment process. In recent years, scientists and governmental organizations have been encouraged to derive quick, easy, but robust mathematical tools to assess human exposure to environmental pollutants, considering that there exist diverse potential routes (dietary and nondietary) through which chemicals can enter the human body.

Direct or Nondietary

Air Inhalation   Inhalation occurs when chemical, radioactive, or physical pollutants enter the respiratory system, reaching the lungs. This may be a very important route of exposure, especially for some volatile chemicals and semivolatile organic compounds (SVOCs). This pathway has been found to be the most significant for volatile organic compounds (VOCs), such as benzene and formaldehyde, among others.

The U.S. Environmental Protection Agency (EPA) developed a specific methodology to assess exposure through inhalation (U.S. EPA 2009b). This approach, consistent with the inhalation dosimetry methodology, involves the estimation of exposure concentrations (ECs), instead of doses, for each receptor exposed to contaminants via inhalation in the risk assessment. ECs are time-weighted average concentrations derived from measured or modeled contaminant concentrations in air. The estimation of ECs is a prior step to the evaluation of noncancer risks (hazard quotient) or cancer risks. The recommended process for obtaining a specific EC value is the following: (1) to assess the duration of the exposure scenario, (2) to assess the exposure pattern of the exposure scenario, and (3) to estimate the scenario-specific EC. In the first step, the duration of the exposure scenario is chosen among three possibilities: acute, subchronic, or chronic. The second step entails comparing the exposure time and frequency at a site to that of a typical subchronic or chronic toxicity test. The third and final step involves estimating the EC for the specific exposure scenario based on the decisions made in steps 1 and 2. For subchronic and chronic exposures, EC is calculated according to the following equation:

$$EC = (CA \times ET \times EF \times ED)/(AT \times 365),$$

where EC is the exposure concentration (mg/m^3), CA is the concentration in air (mg/m^3), ET is the exposure time (h/day), EF is the exposure frequency (day/year), ED is the exposure duration (years), and AT is the averaging time (years). Specific values of the parameters can be obtained from the scientific literature, including U.S. EPA reports. In case of acute exposure, EC would be equivalent to CA.

Soil Ingestion   Contact with contaminated soils may become an important pathway of exposure to organic chemicals, posing large and long-lasting health risks, through different activities (e.g., through hand to mouth by young children, gardening by adults, and tracking of soil and dust into the home) (Kimbrough et al. 2010). In addition, for some classes of organic pollutants, such as persistent organic pollutants (POPs), incidental ingestion of contaminated soil has been pointed out as the major nondietary exposure pathway (Rostami and Juhasz 2011).

The U.S. EPA (1989) developed specific formulations for the estimation of the contribution of each nondietary pathway. The expression used to evaluate the exposure through ingestion (Exp$_{ing}$, in mg/kg/day) is the following:

$$Exp_{ing} = (CS \times 10^{-6} \times EF \times IFP)/(BW \times 365),$$

where CS is the concentration in soil (mg/kg), EF is the exposure frequency (day/year), IFP is the soil ingestion rate (mg/day), and BW is the body weight (kg).

Oral bioavailability is the fraction of an ingested contaminant that reaches the systemic circulation from the gastrointestinal tract. In turn, bioaccessibility, in relation to human exposure via ingestion, is defined as the fraction of a toxicant in soil that becomes soluble in the gastrointestinal tract, being then available for absorption (Guney et al. 2010). When data of bioavailability and/ or bioaccessibility are unknown, worst-case scenarios are generally considered by assuming a value of 100%. In fact, a fraction of the contaminant may only be bioavailable, and therefore, this assumption may grossly overestimate the chemical daily intake, thereby influencing risk assessment (Rostami and Juhasz 2011).

Dermal Absorption   Exposure to some indoor organic compounds through the dermal pathway is sometimes underestimated. Transdermal permeation can be substantially greater than is commonly assumed (Weschler and Naz- aroff 2012).

When assessing exposure to organic pollutants through the dermal pathway, two different subroutes must be considered, as dermal contact may be relevant for chemicals contained in both water and soil (Ferré-Huguet et al. 2009; U.S. EPA 2009a). A generic formula is given for estimating the exposure through dermal contact (Exp_{derm}, in mg/kg/day):

$$Exp_{derm} = (CS \times 10^{-6} \times AF \times ABS \times EF \times SA)/(BW \times 365),$$

where CS is the concentration in soil (mg/kg), AF is the adherence factor soil (mg/cm), ABS is the dermal absorption fraction (unitless), EF is the exposure frequency (day/year), SA is the surface area (cm^2/day), and BW is the body weight (kg).

A summary of calculation equations to assess the human exposure through nondietary pathways is shown in Figure 2.1.

Dietary

Food   A number of studies have shown that dietary intake is the main entrance route of POPs and other organic chemicals to the human body (Cornelis et al. 2012; Domingo 2012b; Martí-Cid et al. 2008a; Perelló et al. 2012b), accounting for more than 90% of the total exposure (Linares et al. 2010; Noorlander et al. 2011). Therefore, the calculation of the total ingestion of pollutants through food consumption is essential to estimate the total amount of chemicals to which humans are exposed.

The ingestion of pollutants (Exp_{diet}, in mg/kg/day) through food consump- tion is generally calculated as follows:

$$Exp_{diet} = \sum FIR \times CF/BW,$$

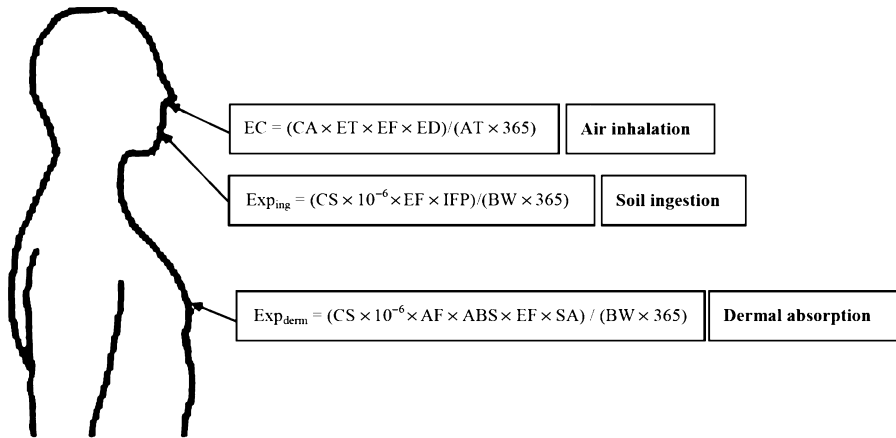|	
$EC = (CA \times ET \times EF \times ED)/(AT \times 365)$	**Air inhalation**
$Exp_{ing} = (CS \times 10^{-6} \times EF \times IFP)/(BW \times 365)$	**Soil ingestion**
$Exp_{derm} = (CS \times 10^{-6} \times AF \times ABS \times EF \times SA) / (BW \times 365)$	**Dermal absorption**

Figure 2.1. Main nondietary exposure pathway routes to persistent and bioactive organic pollutants. Calculation equations.

where FIR is the food ingestion rate (in kg/day), CF is the concentration in food (mg/kg), and BW is the body weight (kg). Thus, the daily intake of a chemical by a food group is estimated by multiplying the average concentration by the daily consumption of the food group. Finally, the estimated total dietary intake of each chemical is obtained by summing the respective intakes from each food group and dividing by the body weight.

Water   Indoor exposure through the use of contaminated tap water is an issue of great concern (López et al. 2008). For certain chemicals, the water pathway may be especially significant, considering that adults may consume more than 2 L daily. Furthermore, water is a part of the nutritional basis of food ingestion by babies, as many baby foods are prepared by using drinking water, either tap or bottled. In any case, exposure to organic substances through water consumption must not be underestimated.

Similar to food, the intake of chemicals through water ingestion (Exp_{water}, in mg/kg/day) is calculated by applying the following equation:

$$Exp_{water} = \sum WIR \times CW/BW,$$

where WIR is the water ingestion rate (L/day), CF is the concentration in water (mg/L), and BW is the body weight (kg).

CHEMICALS OF CONCERN

POPs

POPs are organic substances that may persist a long time in the environment, may present a high bioaccumulation potential through the food web, and may

pose a high degree of toxicity for human health and the environment. Furthermore, POPs are characterized by their long-range transport capacity (LRTC); that is to say, they are able to travel long distances and to be deposited in territories where they have never been used or produced, posing then an important risk for the global community. Under the framework of the Stockholm Convention on POPs signed in 2001, a list of chemicals whose production, use, and storage must be eliminated, or seriously restricted, was developed. Among these, polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) and polychlorinated biphenyls (PCBs) were included in the initial list of chemicals, commonly known as the "dirty dozen." However, in recent years, a number of other chemicals have also been catalogued as POPs, enlarging that list, while pollutants such as polychlorinated naphthalenes (PCNs) or polycyclic aromatic hydrocarbons (PAHs), already listed in the United Nations Economic Commission for Europe (UNECE) Protocol, have been also proposed (Nadal et al. 2011). Given that the treaty has been entering into force in many countries in the course of the 2000 decade, the number of studies to monitor the environmental levels of POPs has progressively increased. Furthermore, these investigations have been used to evaluate human exposure to those organic pollutants, as well as to compare the percentage of total exposure contributed by food intake. A number of studies has identified food consumption as the most important pathway of exposure to POPs (especially PCDD/Fs and PCBs), with contributions of >95% (Linares et al. 2010). Moreover, a number of those studies were focused on rather reduced groups of foodstuffs, mainly fish and seafood (Storelli et al. 2011; Yu et al. 2010), as this was the most contributive food group (Figure 2.2). In Catalonia (northeast of Spain), a wide surveillance program focused on measuring the levels of a number of chemical contaminants (including PCDD/Fs and PCBs) in various groups of foodstuffs is being performed, as requested by the Catalan Agency of Food Safety. Three campaigns have been carried out between 2000 and 2012 (Llobet et al. 2003, 2008; Perelló et al. 2012a). In the framework of these investigations, the dietary intake of these pollutants was subsequently estimated for various age and sex groups of the population of the country using deterministic and probabilistic methodologies (Perelló et al. 2012a). An important decreasing trend in the dietary exposure to PCDD/Fs and PCBs for the population living in Catalonia was noted. The authors associated this finding with the general decreasing trend in the atmospheric PCDD/F and PCB levels, which has also been observed in a number of countries in recent years. The intake of these pollutants was generally lower in Catalonia than those recently found in various other regions and countries over the world. With respect to the health risks derived from dietary exposure to PCDD/Fs and dioxin-like polychlorinated biphenyls (dl-PCBs), it must be remarked that the current total daily intake is lower (even considering the individuals in the extreme of the exposure distribution) than the tolerable daily intake (TDI) established by international organizations. In relation to this, for comparative purposes, the tolerable intake established by the World Health Organization (WHO) for dioxin-like compounds, including PCDD/Fs and dl-PCBs is within the range 1–4 pg WHO-TEQ/kg
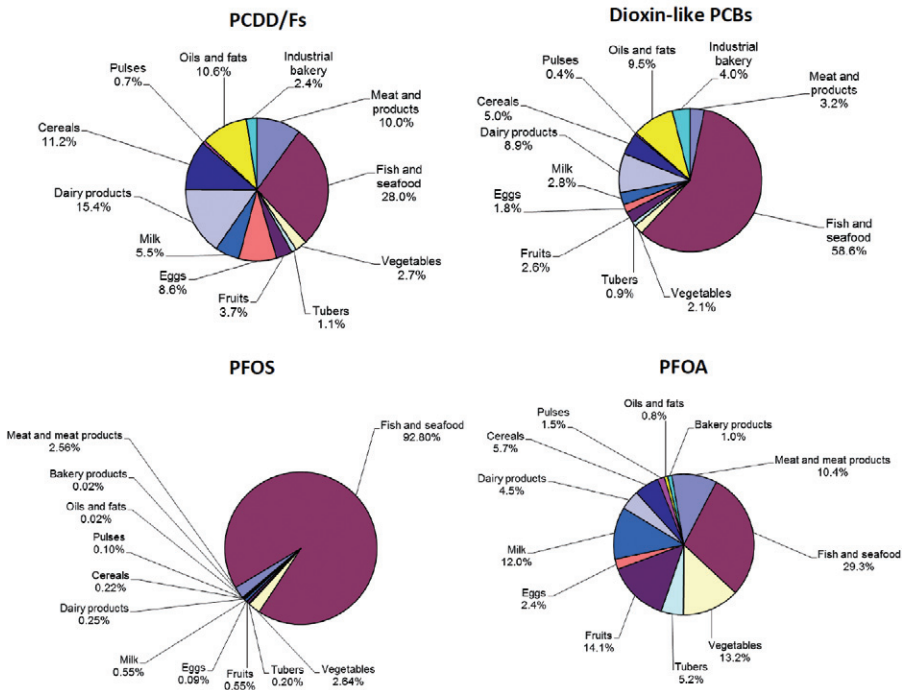
Figure 2.2. Percentages of contribution from each food group to the total dietary intake of several organic pollutants by the adult population of Catalonia (Spain).

of body weight per day (van Leeuwen et al. 2000), while the Scientific Committee on Food (SCF) of the European Commission set a value of 14 pg WHO-TEQ/kg of body weight on a weekly basis.

In parallel, the direct exposure to PCDD/Fs and PCBs by sources other than diet has been estimated for the population of Catalonia. In the most recent study (Linares et al. 2010), the direct exposure to PCDD/Fs ranged between $5.00 \cdot 10^{-6}$ and $9.69 \cdot 10^{-6}$ ng WHO-TEQ/kg·day. Dermal absorption was the main entrance route of PCDD/Fs to the human body (54%), while the lowest contribution corresponded to soil ingestion (15%). These values are in contrast with the results obtained in previous studies (59%, 28%, and 13% for inhalation, dermal contact, and soil ingestion, respectively) (Nadal et al. 2004). The decrease of importance of the inhalation route could be linked to the notable reduction of air PCDD/F levels observed in the area under evaluation, with up to 10-fold diminutions. Other investigations performed in industrial areas of Catalonia, where cement factories are operating, indicate that inhalation is still the most important route of direct contact (40–60%), compared to dermal absorption and soil ingestion (Rovira et al. 2010, 2011). Concerning other POPs, such as PAHs and PCNs, inhalation has also been pointed out as

the most contributive among the direct exposure routes (Nadal et al. 2011), but still minor in comparison to total dietary intake, whose estimative value was at least 95% of the total intake (Martí-Cid et al. 2008a,b).

Pesticides

Although several pesticides are considered as POPs (i.e., aldrin, chlordane, DDT, among others), the group of pesticides includes a longer list of chemical agents of different physicochemical characteristics. Pesticides are actually defined as "chemical substances used to prevent, destroy, repel or mitigate any pest ranging from insects (i.e., insecticides), rodents (i.e., rodenticides) and weeds (herbicides) to microorganisms (i.e., algicides, fungicides or bactericides)" (Alavanja 2009). People may be exposed to pesticides through the same pathways, being mainly dietary intake, followed by inhalation, the two most influent exposure routes. The populations at risk of developing adverse health effects associated with pesticide exposure include subjects such as farm workers, workers in the pesticide production industry, pest control workers, and individuals environmentally exposed, such as farm residents and those using household pesticides (Ndlovu et al. 2011). In fact, the potential exposure of pesticides for the agricultural sector is very important since about 1800 million people in the world are involved in agriculture, most of this population being exposed to these products (Alavanja 2009). The potential health effects of agricultural pesticide exposures are of particular interest as these chemicals are designed to have adverse biological effects on target organisms (Weichenthal et al. 2010). An increasing incidence of cancer, chronic kidney diseases, suppression of the immune system, sterility among males and females, endocrine disorders, and neurological and behavioral disorders, especially among children, has been attributed to chronic pesticide poisoning (Abhilash and Singh 2009). The application of pesticides for pest control means an important entrance route of these chemicals to the human body through the dietary intake, with fish and seafood being the group with the most significant contribution (Törnkvist et al. 2011). However, when considering long assessment periods, it has been observed that intake estimations for organochlorine pesticides have apparently decreased (Fromberg et al. 2011).

Recent findings have demonstrated that inhalation and dermal absorption of pesticides in general, and DDT in particular, may be important routes of exposure (Sereda et al. 2009). In fact, specific studies on highly exposed populations living in tropical houses where there was indoor residual spraying (IRS) estimated that inhalation could account for 70% of total exposure to DDT, 2.5 times the estimated median exposure through diet (Ritter et al. 2011). However, the general population is primarily exposed to pesticides through food intake (Beamer et al. 2012; Dirtu and Covaci 2010). In turn, the percentage contribution of nondietary exposure routes seems to be lower, especially when professional activities do not include any contact with pesticides. Ferré-Huguet et al. (2009) found that the uptake of DDTs, their

metabolites—dichlorodiphenyldichloroethylenes (DDEs) and dichlorodiphe-nyldichloroethanes (DDDs)—as well as other organochlorine compounds through soil ingestion and consumption of drinking water did not increase either noncarcinogenic nor cancer risks for the population living in the Catalan stretch of the Ebro River basin. This is an agricultural zone where industries and sewage treatment plants are of notable concern, taking into account the potential adverse impacts on water quality and local soils. The same research group also assessed the dietary intake of the same chemicals and estimated the health risks associated with food consumption (Martí-Cid et al. 2010). Although the consumption of local foods for different population age/gender groups should not mean an increase in noncancer and cancer risks, as all indices were less than the safety values, the dietary intake of DDTs, DDEs, and DDDs was found to be much higher than the environmental exposure to the same chemicals. Among the food items analyzed, fish and seafood were important contributors to the dietary exposure of DDT derivatives (DDE and DDD) in the adult population, while consumption of vegetables was especially notable for the parental compound (DDT). A review of the scientific literature indicates that ingestion of house dust may be also a major route of exposure to pesticides for infants and toddlers. The role of house dust as an exposure source is gaining more attention over the years.

However, several open questions related to health remain to be resolved. Pesticides applied outside or within the household, which are absorbed and preserved by house dust, can lead to an increased exposure through the every-day activities of children and infants. Residential exposure including house dust residues contribute to combined exposure from dietary and nondietary sources (Butte and Heinzow 2002).

Benzene

The chemical structure of benzene (C_6H_6) is a ring with six carbon atoms and a hydrogen atom attached to each carbon atom. Benzene is a natural constitu-ent of crude oil, being one of the most basic aromatic petrochemicals, together with toluene, ethylbenzene, and *m,p,o*-xylenes. It is generally accepted that benzene is a risk factor for childhood acute leukemias and breast cancer, among other adverse health effects (McNally and Parker 2006; Rennix et al. 2005).

More than 99% of the intake of benzene is through the air, where it may originate from natural sources (e.g., forest fires) or from human activities such as smoking or exhaust fumes (Van Poucke et al. 2008). Other sources of benzene are drinking water and food, both through environmental contamina-tion. Regarding inhalation, indoor air plays an important role in the total inhalation of VOCs. In addition to smoking, incense burning and emissions from consumer products are also sources of benzene and other VOCs in indoor spaces. Recently, Sarigiannis et al. (2011) reviewed bibliographic data on the occurrence of major organic compounds and evaluated cancer and

noncancer risks posed by indoor exposure in dwellings and public buildings in European Union (EU) countries. The results indicate that significant differences in indoor air quality exist within and among the countries where data were available. Another important emission source of benzene and other VOCs is municipal solid waste (MSW). Handling and treatment of MSW are known to generate benzene. Particularly, composting facilities are known to release odorous VOCs due to biodegradation of waste (Domingo and Nadal 2009). Therefore, not only individuals working at composting plants but also residents living nearby may be potentially exposed to benzene (Nadal et al. 2009; Vilavert et al. 2012). Human exposure studies are usually focused on the inhalation pathway, as this has been identified as the most contributive route (Vilavert et al. 2011).

Unlike other organic chemicals, such as POPs, food has not been identified as the leading route of exposure to VOCs in general, and benzene in particular. Since the intake of benzene from the diet is usually about 1000 times lower than that derived from heavy cigarette smoking (estimated average = 1.8 mg/ day), it is less likely that dietary sources are the major contributors to elevated levels of benzene and metabolites in the general population (Johnson et al. 2007). On the other hand, drinks can contain significant amounts of benzene, as benzoic acid is used as a preservative in some beverages and can react with ascorbic acid (vitamin C), either added or naturally occurring, to form benzene. The benzoate salts are preservatives that are added to beverages to inhibit growth of bacteria, yeasts, and mold but may also occur naturally in some fruit juices. Vitamin C may be added as a preservative, as a vitamin supplement, or may also be naturally present in some fruit juices (Haws et al. 2008). Recently, the content of pollutants, such as arsenic or benzene, is being carefully studied in baby foods, taking into consideration that infant exposure is critical for the further development of children. With respect to this, benzene has been detected not only in certain beverages and soft drinks but also in baby food, specifically in carrot juices intended for infants (Lachenmeier et al. 2010). These juices contain higher concentrations of benzene than any other beverage group, with an average content above the EU drinking water limit, which is 1 µg/L (Lachenmeier et al. 2008). In this sense, Lachenmeier et al. (2010) detected trace (µg/kg) levels of benzene in canned foods, jarred baby food, and juices containing carrots, showing that the level of exposure to benzene through food products could be currently underestimated.

Perfluoroalkyl Substances (PFASs)

PFASs are molecules made up of carbon chains to which fluorine atoms are bound. Due to the strength of the carbon/fluorine bond, these molecules are chemically very stable and are highly resistant to biological degradation, therefore being persistent in the environment (Stahl et al. 2011). Furthermore, these compounds are extremely bioaccumulative and of toxicological concern (Andersen et al. 2008; D'Hollander et al. 2010; Domingo 2012a). Because of

their chemical properties, PFASs have been widely used in a broad range of applications, such as inks, varnishes, waxes, firefighting foams, metal plating and cleaning, coating formulations, lubricants, water and oil repellents for leather, paper, and textiles (Paul et al. 2009). In recent years, a number of studies have reported a ubiquitous distribution of PFASs in human tissues (Sturm and Ahrens 2010), as well as in invertebrates, fish, reptiles, and marine mammals worldwide (Houde et al. 2011). Perfluorooctane sulfonate (PFOS) is the predominant compound detected in humans and animals, as well as in environmental samples (Jogsten et al. 2009). The industrial production of PFOS and some of its derivatives was phased out by the major producer, 3M, in 2002, while the EU banned most uses of this compound since 2008. PFOS has been very recently included in the list of priority substances in the field of water policy, which includes the chemicals identified among those presenting a significant risk to or via the aquatic environment at the EU (according to the Water Framework Directive) (EC 2012). In 2009, PFOS was included in Annex B of the Stockholm Convention list of POPs (Buck et al. 2011). Unlike other organic chemicals, PFASs do not typically accumulate in lipids. In humans, exposure levels and pathways leading to the presence of PFASs have been better characterized by monitoring these chemicals in blood. In recent years, the concentrations of various PFASs in human blood have been determined in individuals from a number of regions and countries (Fromme et al. 2009). Although the relative importance of the routes of human exposure to these compounds is not yet well established, it has been suggested that food intake and packaging, water, house dust, and air are all potentially significant exposure sources (Domingo 2012a).

Since 2006, the Laboratory of Toxicology and Environmental Health, Universitat Rovira i Virgili (Catalonia, Spain), has been performing periodical studies to find out the contribution of each pathway to total exposure to PFASs. Biomonitoring investigations included analysis of the concentrations of 13 PFASs in the blood of Catalan residents (Ericson et al. 2007). In general terms, reported values were lower than those found in human blood and serum of subjects from different countries, with PFOS showing the highest concentration of all PFASs. Breast milk samples from primiparae mothers were also collected, and the content of PFASs was determined. Milk concentrations were similar to reported levels from other countries (Kärrman et al. 2010). Finally, human liver samples were collected from subjects who had lived in different areas of Tarragona County (Catalonia, Spain). Liver samples were found to contain more PFASs above quantification limits and higher PFOS concentrations compared to reports from the scientific literature. Interestingly, perfluorooctanoic acid (PFOA) levels from Catalan males were significantly higher ($p < 0.05$) than those from females in both liver and blood (Kärrman et al. 2010). Because it is highly consumed by humans, water could be an important contributor to the exposure of PFOA, PFOS, and other PFASs (Kim et al. 2011). The concentration of the same PFASs was analyzed in water samples from Tarragona Province (Catalonia, Spain), coming from diverse origins: tap