1 Exposure

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1.1 INTRODUCTION

In the environment, organisms including man are exposed to mixtures of chemicals rather than single compounds. Examples of mixtures are food and feedstuff, pesticide and medical products, dyes, cosmetics, and alloys. Many other commercial products, such as printing inks, contain a mixture of substances, possibly up to 60 individual chemicals in 1 formulation. Preparation of these chemicals may involve the use of several hundred other substances in upstream processes.

As a first step in the risk assessment of chemicals, it is essential to have an insight into the magnitude and duration of exposure. Following the toxicological principle that dose determines the effect, one may assume that no exposure means no risk. In the case of chemical mixtures, a proper assessment of exposure assists in adequately interpreting the interacting effects of chemicals. So, exposure assessment is an essential component of any risk assessment study of mixtures, since it can be used to reduce uncertainty and provide data.

The exposure of organisms includes man-made chemicals as well as natural compounds. Natural compounds are, for example, toxins in plants, ozone, or natural occurring metals. The total number of man-made chemicals is vast. To assess exposure, the ambient concentrations of chemicals resulting from man-made sources need to be known or estimated. Chemical Abstracts, covering more than 8000 journals since 1907, registers more than 20 million entries. This section focuses on man-made chemicals. In Europe, around 30,000 chemicals are commonly used and thereby emitted to the environment (EC 2001).

In human health risk assessment, “direct” and “indirect” methods of exposure assessment are distinguished. The direct method involves measurements of exposure at the point of contact or uptake, for instance, by monitoring chemical concentrations in humans or the environments they are exposed to (food, air, water). The indirect methods use modeling and extrapolation techniques to estimate exposure levels (Fryer et al. 2006). Also in environmental exposure assessment, these 2 ways to assess exposure may be applied.

Indirect exposure assessment, both human and environmental, starts with emission data and a prediction of the fate of chemicals in the environment and the resulting concentrations in different environmental compartments. Foster et al. (2005) outlined 5 steps in a strategy to conduct exposure assessment of complex mixtures, consisting of many different components, such as gasoline. These steps, as outlined below, are also relevant when assessing exposure to less complex mixtures.

1) Determination of mixture composition. Composition of the mixture may vary spatially and temporally. Measurements at the source (point of emission) may help in identifying (variations in) mixture composition.
2) Selection of component groups (optional). Within a mixture, different (groups of) components may be identified. These components may be grouped on the basis of properties that affect their fate in the environment.
3) Compilation of relevant property data for each group. This step consists of collecting properties relevant for predicting the fate of the different (groups of) components in the environment.
4) Assessment of the environmental fate of each group. Fate models may be used to predict environmental fate of mixture components on different spatial scales. Such models may yield a predicted distribution over air, water, soil, and sediment.
5) Assessment of environmental and human exposure. As a final step, concentrations can be calculated for each of the (groups of) mixture components in different exposure media (inhaled air, ingested water, food items) or environmental compartments (soil, sediment, air, and surface or groundwater). This information may not, however, represent the complete picture: often only part of the total concentration in an environmental compartment is biologically available for uptake by organisms. In addition, species habits and individual behavior may affect the nature of exposure. Finally, life-stage-specific aspects may be highly important in determining exposure to mixtures; this aspect is best studied for human exposure, but is also relevant to ecological assessment for some taxa.

For exposure assessment of ecosystems, direct exposure assessment involves taking field samples at the site and time of exposure and measuring chemical concentrations in these samples or in the organisms exposed at the site. Direct assessment of (potential) exposure also is possible by performing bioassays in which selected test organisms are exposed to the environmental sample, in the laboratory or in the field. The latter approach is discussed in more detail in Chapter 4.

In this chapter, the different steps in the assessment of mixture exposure are discussed. The chapter starts from emission scenarios and subsequently discusses transformation processes taking place in the environment and their effects on mixture composition. Next, bioavailability is discussed, and exposure scenarios for both humans and biota in the environment are described. These descriptions also consider methods to assess exposure to mixtures. Most data available on mixture exposure are restricted to North America and Europe, but we recognize that there are emerging problems in other regions of the world. We restrict our discussion to man-made chemicals and those natural chemicals subject to regulation (metals, polycyclic aromatic hydrocarbons (PAHs)), because these represent the most well-studied group and the current priorities for risk assessment.

1.2 EMISSION SCENARIOS

An emission is defined as the amount of chemical discharged or transferred per unit time, or it is the amount of chemical per unit volume of gas or liquid emitted. The emission can be characterized by the following attributes (OECD 2006):

1) Pollutant type
2) Release medium
3) Source type
4) Spatial scale
5) Temporal scale

Normally, an emission assessment deals with a single chemical or a group of chemicals, which have similar properties, such as PAHs, metals, ozone-depleting substances, or chlorinated biphenyls. In the environment, organisms and man are exposed to mixtures of chemicals with different properties rather than single chemicals or chemicals with similar properties. As an example, many commercial products (e.g., inks, oils, lubricants) contain a mixture of substances in a single formulation and so may be released simultaneously to environmental media, including land, surface water, groundwater, and indoor and outdoor air.

1.2.1 Major Emission Sources

Emission sources are generally divided between point, diffuse, and mobile sources (OECD 2006). Point sources, such as industrial plants, power stations, waste incinerators, and sewage treatment plants, may play a major role as sources of mixtures of chemicals. Emissions from such sources are frequently of multiple chemicals; even in cases where the emission is dominated by a single chemical, overlap of plumes from other nearby point sources for different chemicals means that the surrounding areas are subject to combined exposure. Diffuse emissions from the application of pesticides and biocides and the domestic and widespread commercial use of chemicals can make a major contribution to the release of chemical mixtures into air, soils, and waters. In the case of pesticides, these biologically active compounds are applied as mixtures, or the application is repeated with other types of active ingredients within a short period, so that more than 1 chemical is present. As for local sources, even when there is not deliberate combined release, overlapping release and transport mechanisms in the atmospheric and the aquatic environments result in the widespread presence of chemical mixtures in different environmental compartments. Emissions from mobile sources, such as vehicles, may be regarded in effect as diffuse emission and in the same way can contribute to the widespread contamination of the environment with chemical mixtures. Thus, diffuse emission can comprise contributions from several emission sources and product emissions. In addition to exposure through environmental media, such as air, soil, and water, the indoor conditions of private households can be relevant for many airborne mixtures in relation to human health due to a large variety of products that are used indoors, where the ventilation can be limited. Also, food intake can be considered

for potential relevant mixture exposures for humans and for species in the higher tier of ecological food webs.

For the terrestrial environment, waste sites may act as major emission sources of mixtures. In the United States, the Agency for Toxic Substances and Disease Registry (ATSDR) has performed a trend analysis to identify priority chemical mixtures associated with hazardous waste sites (De Rosa et al. 2001, 2004; Fay 2005). The information was extracted from the Hazardous Substance Release/Health Effects Database (HazDat) (ATSDR 1997). The HazDat contains data from hundreds of hazardous waste sites in the United States. A trend analysis was completed for frequently co-occurring chemicals in binary or ternary combinations found in air, water, and soil at or around hazardous waste sites (Fay and Mumtaz 1996; De Rosa et al. 2001, 2004). Table 1.1 gives an overview of frequently occurring substances at hazardous waste sites in the United States.

1.2.2 Emission Estimation Methods

In the work of OECD (2006) on assessment of emissions, a distinction is made between Emission Scenario Documents (ESDs) and Pollution Release and Transfer Registers (PRTRs). An ESD provides a description of activities related to emissions and methods to estimate these emissions. A PRTR is an environmental database of potentially harmful chemicals released to air, water, and soil (on-site releases) and transported to treatment and disposal sites (off-site transfers). PRTRs contain data on releases or transfers, by source, and are publicly available in many countries, including Australia, Canada, Japan, several European countries, and the United States. An OECD study identified the similarities and differences between the emission estimation methods used in ESDs and PRTRs, showing that PRTR mass balance and emission factor methods yielded more conservative estimates than the ESD fixation-based method (OECD 2006). The PRTR mass balance method was found to account for a more thorough analysis of parameters, such as substance sources and recycles, which could impact emissions. Both ESD and PRTR methods might be applied to complex chemical mixtures, although no studies are available at present.

The emission estimation methods of the PRTR approach are described by OECD (2002a, 2002b, 2002c) and include direct monitoring, mass balance, emission factor, and engineering calculations and judgment. These methods are all feasible for the estimation of mixture emissions. The mass balance approach is based on the principle of mass conservation. Emissions from a system can be estimated by knowing the amount of a substance going into the system and the amount that is created or removed (dissipated or released to other compartments, degraded, transformed, or bound):

$$\Sigma(\text{output}) = \Sigma(\text{input}) - \Sigma(\text{removed}) + \Sigma(\text{generated})$$

For mixtures of chemicals, this equation should be used to estimate the concentration of each component under steady-state conditions, or under dynamic conditions when data are available to describe temporal conditions. These calculations lead to the (constant or varying) composition of the mixture over time.

Table 1.1 Frequencies of single substances and combination of substances at hazardous waste sites in the United States

Rank	Percent of sites	Single substance	Percent of sites	Binary combination		Percent of sites	Ternary (tertiary) combinations		
Water									
1	42.4	TCE	23.5	TCE	Perc	11.6	1,1,1-TCA	TCE	Perc
2	38.4	Lead	18.9	Lead	Chromium	10.6	Benzene	TCE	Perc
3	27.3	Perc	17.9	1,1,1-TCA	TCE	10.6	Lead	Cadmium	Chromium
4	25.8	Benzene	17.3	TCE	Lead	9.8	1,1,1-TCA	1,1-DCA	TCE
5	25.8	Chromium	17.3	Lead	Cadmium	9.7	Lead	Arsenic	Cadmium
6	23.9	Arsenic	17.0	Benzene	TCE	9.7	TCE	Perc	Lead
7	20.8	1,1,1-TCA	16.3	Lead	Arsenic	9.6	Lead	Arsenic	Chromium
8	20.3	Toluene	14.5	TCE	Trans-1,2-DCE	9.4	Benzene	TCE	Toluene
9	19.8	Cadmium	13.6	TCE	Toluene	9.3	TCE	Perc	Trans-1,2-DCE
10	17.7	MeCl	13.5	Benzene	Lead	9.1	TCE	Lead	Chromium
Soil									
1	37.7	Lead	20.5	Lead	Chromium	12.0	Lead	Cadmium	Chromium
2	25.3	Chromium	17.8	Lead	Arsenic	11.6	Lead	Arsenic	Chromium
3	23.0	Arsenic	17.6	Lead	Cadmium	10.9	Lead	Arsenic	Cadmium
4	19.7	Cadmium	13.3	Arsenic	Chromium	8.4	Arsenic	Cadmium	Chromium
5	19.1	TCE	12.9	Cadmium	Chromium	8.1	Lead	Nickel	Chromium
6	16.0	Toluene	11.6	Arsenic	Cadmium	7.9	Lead	Chromium	Zinc
7	14.8	Perc	10.9	TCE	Perc	7.7	Lead	Copper	Zinc
8	13.6	PCBs	10.9	Lead	Zinc	7.6	Toluene	Lead	Chromium
9	13.0	Xylenes	10.4	Ethylbenzene	Toluene	7.5	Ethylbenzene	Toluene	Xylenes
10	12.8	Ethylbenzene	10.4	Lead	Nickel	7.5	Lead	Nickel	Cadmium

Air									
1	6.0	Benzene	3.5	Benzene	Toluene	2.2	Benzene	TCE	Perc
2	4.7	Toluene	2.7	Benzene	TCE	1.9	Benzene	Ethylbenzene	Toluene
3	3.8	TCE	2.6	Benzene	Perc	1.8	Benzene	Toluene	Perc
4	3.4	Perc	2.6	TCE	Perc	1.8	Benzene	TCE	Toluene
5	3.1	1,1,1-TCA	2.3	Toluene	Perc	1.8	TCE	Toluene	Perc
6	2.6	Lead	2.1	Ethylbenzene	Toluene	1.4	1,1,1-TCA	Toluene	Perc
7	2.5	Ethylbenzene	2.1	TCE	Toluene	1.4	1,1,1-TCA	TCE	Perc
8	2.4	MeCl	1.9	1,1,1-TCA	TCE	1.3	Benzene	1,1,1-TCA	Perc
9	2.4	Xylenes	1.9	Toluene	Xylenes	1.3	Benzene	Toluene	Xylenes
10	1.8	Chloroform	1.9	1,1,1-TCA	Perc	1.3	1,1,1-TCA	TCE	Toluene

Source: Adapted from De Rosa CT, El-Masri HE, Pohl H, Cibulas W, Mumtaz MM. 2004. J. Toxicol. Environ. Health 7:339–350.

Note: MeCl = methylene chloride, PCBs = polychlorinated biphenyls, Perc = perchloroethylene (tetrachloroethylene), 1,1,1-TCA = 1,1,1-trichloroethane, TCE = trichloroethylene, Trans-1,2-DCE = trans-1,2-dichloroethylene, 1,1-DCA = 1,1-dichloroethane.

An emission factor is defined as a constant that relates the intensity of an activity to an emission (OECD 2002a). Emission factors can be used to estimate releases from nearly any source that generates emissions with a strong proportional dependence on the extent. Emission factors are used for specific cases where no release information is available, or if the release is only given for 1 specific compartment. The complementary release estimates can be obtained using the OECD approach or from the European Technical Guidance Document (ECB 2003a). The release of a chemical to an environmental compartment *a* is calculated as

$$\text{Release}_a = F_a \times \text{Prodvol}$$

That is, the release to the compartment (e.g., freshwater or air) is equal to the product of the fraction of the produced volume released, F_a, for example, during production, and the produced volume of the chemical (Prodvol). F_a is the emission factor. Emission factors can be applied to essentially any pollution or source (OECD 2006). They may be derived by many different techniques, but often are developed by taking the average emission rate during a representative time interval and relating it to the extent of the activity in question (OECD 1999). Emission factors can be used to estimate emissions of mixtures when data on the components are available. If the ratio between concentrations of different chemicals in the emission is stable, periodic monitoring of certain pollutants can be used to represent other pollutants by applying average ratios (OECD 2006).

More complex calculations can be made based on mathematical relationships between variables within a system, the outcome being dependent on the quality of data and the validity of assumptions. No specific models are available for chemical mixtures; however, modeling tools might be useful to estimate the varying composition of mixtures in time and space.

In Europe, ESDs are commonly used to facilitate the risk assessment of single substances, and they often deal with groups of chemicals. The methods used in ESDs are designed to deal with broader emissions than those used in PRTRs by dealing with emissions from clusters of facilities. This provides information on data on a local or regional basis. Although the ESDs are directed toward single chemicals, they may provide data for estimation of the emission of mixtures. Recently such information on emissions of single chemicals has been collected by the European Chemicals Bureau (ECB 2003b). The data are currently available for the different industrial categories (ICs) and biocidal product types. This documentation has been developed by different competent authorities and by industry. In most cases the documents are based on in-depth studies of the environmental release of substances used in different industrial categories and of different biocidal product types. Some documents describe environmental releases from specific use categories under an industrial category. Data are not available for all industrial categories and biocidal product types; some documents are still under preparation. It is anticipated that this set of emission scenario documents will be expanded continuously in the future. For industrial chemicals 9 areas have been developed so far: chemical, leather processing, metal extraction, photographic, textile processing, rubber, and paint industries, as well as personal or domestic and public domains.

Data on the emission of (mixtures of) chemicals may also be obtained from the European Pollutant Emission Register (EPER), which is the first European-wide register of industrial emissions into air and water (http://eper.ec.europa.eu/ (last accessed November 2009)). EPER gives access to information on the annual emissions of approximately 9200 industrial facilities in the member states of the European Union as well as Norway mostly for the year 2001, and approximately 12,000 facilities for the year 2004. It has the option to group information by pollutant, activity (sector), air and water (direct or via a sewerage system), or country, and even gives access to data on individual facilities. Such information thus has value for developing realistic emission scenarios for diffuse release and also at the local scale.

Prediction of the composition of a chemical mixture that organisms are exposed to in a certain area requires considering all emission sources in that area or contributing to the input of chemicals in that area. The European Chemicals Bureau has described the relevant factors for estimating the release or emission of chemicals, including their intermediates and degradation products (ECB 2003a):

- the emission factor (release fraction) for processing of the intermediate,
- local production volume per time unit,
- the emission factor (release fraction) for production of the intermediate,
- the elimination in on-site treatment facilities, and
- the elimination in biological wastewater treatment facilities.

As an example, emission to surface water (in g/s) was estimated in a German scenario. The local concentration in rivers was calculated from that emission and the river flow (in m^3/s), taking into account adsorption processes in the surface water. This approach was based on a statistically evaluated database. Volumes of wastewater flows from the production or processing facility were not taken into account. Although for the time being the database is restricted to a set of 29 substances and to German conditions, it can be regarded as a realistic worst-case situation since it combines two 90th percentiles (discharge × river flow) (ECB 2003a).

1.2.3 Prioritization

As described, living organisms are constantly exposed to vast amounts of chemicals, that is, to 1 big chemical mixture. We lack the information on how to properly capture the entire exposure, on how to address the toxicity, and how to evaluate the associated risk. Therefore, the initial approach is to properly define mixtures on a smaller scale. These are the "mixtures of concern" and are usually associated with a specific exposure scenario and possible health implications. Exposures to chemical mixtures of concern can range from simple and well-defined mixtures to complex and poorly defined mixtures. For example, morphine in combination with other epidural anesthetics is used in hospital settings for pain relief. The mixture can be characterized as simple (<10 chemicals), and in some cases such mixtures can be well defined because it is easier to identify the chemicals involved and know their dose, toxicity, and potential interactions. In contrast, complex mixtures are composed of many (>10) chemicals. Their composition may be largely known or at least reproducible (e.g.,

fumes from a specific paint), or the mixture may not be fully characterized either qualitatively or quantitatively, and may even vary from one similar exposure scenario to another (e.g., diesel fuels or gasoline from different sources). The sheer number of interactions means that the complete set of individual and interactive effects can never be established. Such cases thus present a particular challenge, and Chapter 4 discusses tools available to assessing the toxicity of such complex mixtures.

In the prioritization of chemicals for setting scenarios that are the most realistic and probable for chemical mixtures, tools are needed to overcome the almost infinite number of chemicals or combinations of chemicals and of differing concentrations in emissions. The global production of chemicals has increased from 1 million tons in 1930 to 400 million tons today. There are about 100,000 different substances registered in the EU market, of which 10,000 are marketed in volumes of more than 10 tons (produced per manufacturer or imported per importer per annum), and a further 20,000 are marketed at 1 to 10 tons (EC 2001). In the selection of chemicals for mixture scenarios, the volume of marketing is an important parameter; however, other factors, such as emission pattern (spatial and temporal), degradation, and toxicity, are also very important.

1.2.4 Validation Studies

In many countries, emissions are determined by direct monitoring. In these cases the measurements should be subject to quality assessment, and the sampling plan should be evaluated to estimate the uncertainty in all steps of the procedure. To assess emissions of mixtures of chemicals, concentrations of chemicals should be measured simultaneously, but the validation procedures would be the same as for single chemicals. When emissions are estimated from data on produced, processed, or used amounts of the individual chemicals in mixtures, the calculations should be validated by measurements in the field.

1.3 INTERACTIONS AFFECTING AVAILABILITY AND EXPOSURE TO CHEMICAL MIXTURES

1.3.1 Characteristics of the Major Environmental Compartments

Identification of the most probable mixture exposure scenarios is a first step to establishing the nature of multiple chemical exposures, but even when such information is available, the interaction of the chemical constituents of the mixture with the environment needs to be considered. The physical and chemical nature of different environmental compartments has a large influence on the magnitude, duration, and stability of exposure (Table 1.2). On the one hand, chemicals in air are highly mobile and can travel over long distances, but also can be subject to rapid dilution through mixing. On the other hand, soils and sediments are immobile, and so the chemical released into these media can remain patchily distributed and dilution through mixing (e.g., by bioturbation) occurs at a very slow rate. In soils, sediments, and waters, the chemical properties of the media (such as pH, percentage of total and dissolved organic matter, cation exchange capacity, and concentrations of some ionic species) can have a large

Table 1.2 Physical characteristics influencing the duration and magnitude of exposure for the major environmental compartments

Media or compartment	Characteristics of the exposure
Soil	Immobile; hard to dilute; exposure, especially to persistent compounds, can be temporally quite constant, but spatially patchy; soil properties (pH, organic matter content, cat ion exchange capacity) have large effects on exposure (bioavailability) and can show spatial and temporal variability
Sediment	Immobile; hard to dilute; exposure, especially to persistent compounds, can be temporally quite constant, but spatially patchy; sediment characteristics can affect exposure; anoxia common and can affect exposure
Water	Mobile; can be diluted; pollutants can disperse within water column over moderate distances, pulsed exposure common; chemical characteristics can affect exposure, although these are less variable than, for example, soil
Air	Highly mobile, so pollutants can travel long distances (transboundary issues arise); composition quite stable at given altitude, and so local effect on bioavailability not such an important issue; rapid dissolution through mixing can occur; pulsed exposure common
Food chain for higher organism	The physiology of the species involved (both predator and prey) strongly influences the nature of exposure; exact exposure of an individual depends on the home range and dietary composition of the species or individual involved

influence on chemical availability. In ecotoxicology, a great deal of research effort has been focused on understanding the relationships between chemicals and soil, sediment, and water properties. The models and methods developed from this work are likely to be broadly applicable to exposure assessments for mixtures, although work is needed to validate this assumption. The importance of food chain transfer as an exposure route is greatly influenced by the properties of the chemical involved (e.g., persistence) and the physiology of the species within the particular food web. For example, Hendriks et al. (2001) modeled bioaccumulation of organic chemicals and Hendriks and Heikens (2001) modeled metal accumulation and demonstrated the need to include both chemical properties (log K_{ow} in case of organic chemicals) and species characteristics (body size, metabolic rate, trophic position, route of exposure) in order to allow for an effective assessment of bioaccumulation.

1.3.2 Environmental Fate Affecting Mixture Composition

1.3.2.1 Single Compounds as Chemical Mixtures

Once released into the environment, selected single compounds can be subject to a range of transformations that may change the chemical identity of part or the entire amount of the original chemical released. Thus over time, even release of a single compound will result in the presence of a chemical mixture. The most obvious example of cases where a single chemical release results ultimately in the presence of a complex and changing mixture is in organic molecule (especially pesticide and biocide) degradation. There is an extensive literature that describes in detail many of the catabolic processes that can transform organic molecules in the environment, and it is not realistic to include anything other than a sample of such information.

When considering how such degradation affects exposure and potential effect, it is obviously tempting to assume that degradation of biologically active molecules such as pesticides will result in a lower toxicity of the metabolite-parent compound mixture than for the parent compound alone. While this is often the case, it certainly cannot be seen as a universal law. Thus, dichlorodiphenyl trichloroethane (DDT), which is already a highly persistent and bioaccumulative insecticide, is converted in organisms into the even more stabile metabolites dichlorodiphenyl dichloroethylene (DDE) and dichlorodiphenyl dichloroethane (DDD). Thus, for this compound, the metabolite can represent an important component of the resulting mixture. The same principles apply for the pesticide aldrin, which is degraded in soil by microbial epoxidation to form the more persistent dieldrin (O'Halloran 2006). Such effects can be media specific depending on the prevalent processes. Thus, the organophosphate pesticide chlorpyrifos is degraded in air by reaction with $OH^{\bullet}$ radicals to form different products, including chlorpyrifos oxon, which has a higher toxicity than the parent compound. The oxon may subsequently be converted into other products by side chain oxidations. In water, soil, and sediment, degradation of chlorpyrifos by photolysis or hydrolysis results in the formation of 3,5,6-trichloro-pyridinol (TCP). The importance of the metabolite as a component of the mixture depends on the speed at which conversion reactions occur. In the case of water, soil, or sediment, hydrolysis of the oxon metabolite leading to the formation of TCP is expected to take place faster than that of the thiol (parent) molecule, meaning that the metabolite is only likely to be present at low concentrations, and so have only a limited contribution to overall toxicity compared to other components (Cahill et al. 2003).

As well as organic molecules, metals can also be the subject of chemical and biological transformations that can change chemical identity and result in altered toxicity. The most well-known and well-studied example of this is the conversion of mercury (Hg^0) into methylated and ionic species (such as Hg^{2+}, CH_3Hg^+, and $(CH_3)_2Hg$). Mercury is emitted to the environment from many different sources, usually as phenyl mercury, metallic mercury, and bivalent inorganic mercury. In anoxic sediments, the dominating form is sulfide (HgS), which is almost insoluble in water. Different bacteria (especially methane bacteria) as well as several species of fungi are capable of forming methyl mercury (CH_3Hg^+) and dimethyl mercury ($(CH_3)_2Hg$), which are soluble in water (Regnell 1994; King et al. 2002; Bisinoti and Jardim 2003).

These examples show that also in the case of single chemicals, such as pesticides and metals, exposure assessment should not only focus on the parent chemical but also include the metabolites and transformation products produced either in the environment or upon biotransformation in the organism.

1.3.2.2 Chemical Fate Effects on Mixture Composition

Once a mixture of chemicals is introduced into the environment, processes may take place that affect the composition of the mixture in space and time (see, e.g., Foster et al. 2005; Haws et al. 2006). When (complex) mixtures are released, differing fate properties of the individual chemicals can lead to a change in the exposure over time, and exposure in different environmental compartments and through different routes. An example is the distribution of gasoline over different environmental compartments:

depending on the compartment of first introduction and the properties of the different (groups of) components in the gasoline mixture, their distribution over the environment may differ (Foster et al. 2005). Properties of single chemicals determining their distribution and fate in the environment include physical–chemical properties, such as molar mass, boiling point, density, vapor pressure, water solubility, Henry's law constant, partition coefficients like the octanol–water partition coefficient (K_{ow}) and the octanol–air partition coefficient (K_{oa}), and degradation half-lives in different environmental compartments (air, water, soil, and sediment). In addition, bioaccumulation factors may be needed to determine partitioning in biological compartments (Foster et al. 2005).

The residence time of a compound in a mixture is not only determined by its fugacity (Mackay et al. 1992a), but also by its susceptibility for degradation. Persistency (usually indicated by its half-life) not only depends on the properties of the compound, but also on those of the environmental compartment (Haws et al. 2006). Since persistency of most organic compounds in soil, water, and sediment mainly relies on biological activity, it is important to focus on processes affecting biodegradation. It is assumed that biodegradation only takes place in the bulk aqueous phase of soil (or sediment). Processes affecting the sorption of chemicals (see above) determine the availability of chemicals in solution, and therefore play a key role in biodegradation. In addition, biological factors, such as microbial abundance and activity, and affinity for the contaminant, determine biodegradation rate. Such interactions can have both negative and positive effects on the degradation rates for particular compounds.

Two types of interaction with the potential to negatively affect degradation rates of chemicals in mixtures compared to single chemicals are competition and toxicity. When substrates are present, this can lead to the inhibition of biodegradation simply because more substrate molecules are competing for the same (and limited) number of active enzyme sites. This inhibition can be competitive in case of homologous chemicals, but also noncompetitive when 2 chemicals independently bind to the same enzyme, leading to a reduction of its overall utilization rate. It is also possible that the second chemical (inhibitor) binds to the enzyme complex but not to the free enzyme (Haws et al. 2006).[1] Toxicity to the microbial community can change biodegradation potential in cases where the species responsible for the catabolism of one compound are sensitive to the presence of another that is present in a mixture. Such interactions can potentially affect the ratio at which metabolites are formed or change the nature of degradation pathways (Haws et al. 2006).

As well as inhibition, some interactions in mixtures have the potential to stimulate degradation processes for a particular chemical. One example of an increased biodegradation rate in a mixture is as a result of increased biomass growth. This can occur, for example, when an easily metabolized substrate is present in conjunction with a more recalcitrant chemical. The rapid breakdown of the easily metabolized chemical supports the expansion of the degradative community, and this larger community is then better able to metabolize the less readily catabolized compound. This

[1] Similar principles of competitive, noncompetitive, and uncompetitive inhibition of metabolism will also be discussed in Chapter 2 in relation to toxicokinetics.

was the case with a mixture of naphthalene, phenanthrene, and pyrene. Compared to single compound studies, the mineralization rate of the easily degraded naphthalene was decreased compared to rates found for the single chemical alone, while that of the more persistent phenanthrene and pyrene was increased (Guha et al. 1999). The presence of solubilizing agents, such as biosurfactants, is a further means by which the degradation of chemicals present in combination with such chemicals may be increased. This effect has been shown for a number of PAHs (Guha et al. 1998). These biosurfactants, which enhance the bioavailability of the PAH, may, however, be toxic to the microorganisms responsible for PAH biodegradation, leading to a reduced degradation rate. This has been shown for phenanthrene (Shin et al. 2005) and demonstrates the potential complexities of the interactions that may occur.

1.3.3 Availability

1.3.3.1 Availability and Bioavailability

Bioavailability is an important issue, not only regarding the transfer of contaminants within food chains, but also for a robust effect assessment of chemical mixtures in the environment. Pathways and mechanisms on how chemicals interact with each other within a mixture, how they enter the organism, and how they accumulate under defined circumstances need to be unraveled (CSTEE 2000). It is generally accepted that the total concentration of chemicals and chemical mixtures in all environmental compartments is not enough to predict biological or ecosystem effects. Bioavailability can be defined as the fraction of a chemical compound in a specific environmental compartment that, within a given time span, is or can be made available for uptake by organisms or is made available at the site of physiological activity (cf. Peijnenburg and Jager 2003). Within the same scope other words are often used in human health issues, such as availability and bioaccessibility; the latter one usually is defined as the fraction of a chemical that is capable of being used by a living organism. These 3 concepts can be considered synonyms, and from now on in this section the word "bioavailability" is used.

For mixtures, like for single chemicals, bioavailability is a key factor governing the magnitude and duration of exposure. Processes affecting the sorption of chemicals in, for example, soils and waters are vital in determining the availability of chemicals that enter the solution phase. Physical and chemical characteristics of the sorbent (particle size, organic matter content, pH) and sorbates (K_{ow}, ionization) are the major determinants of the bioavailability of single chemicals. Additionally, in cases where mixtures of chemicals are found, the presence of other chemicals may affect bioavailability (Haws et al. 2006). Competitive sorption especially may occur when chemicals have an affinity for similar sorption sites. This has been reported for phenanthrene and pyrene, with phenanthrene desorption increasing in the presence of pyrene (White and Pignatello 1999). Also, in case of metal mixtures, competitive sorption may occur: nickel sorption to soils decreased when other cations (including H^+) were present and was highest at neutral pH (Staunton 2004). And desorption of cadmium was increased by the presence of zinc, but zinc desorption was not increased by the presence of cadmium (Van Gestel and Hensbergen 1997).

In principle, sorption of chemicals in a mixture can be predicted from isotherms for sorption of the single chemicals, but such predictions may become less accurate for mixtures with significant interactions of the chemicals (Haws et al. 2006). Another aspect hampering a proper prediction of the sorption of single chemicals, as well as of mixtures, is the fact that sorption may change with time. Due to the process of aging, sorption of organic chemicals increases with time and is stronger than expected on the basis of physical–chemical properties (such as K_{ow}) or laboratory sorption experiments (Alexander 1995; Hatzinger and Alexander 1995; Kelsey and Alexander 1997). This also is the case for metals (Smit and Van Gestel 1998; Lock and Janssen 2003). Also, in case of changing redox conditions, sorption, of especially metals may no longer be directly predictable, due to the formation of sulfides that have a very low solubility (Lee and Lee 2005).

Although the effects of chemical mixtures in the environment on humans are thought to have important health implications, they are not widely studied or especially well understood. Their potential risks, therefore, have to be considered as a crucial environmental health problem requiring clear and rigorous future investigation. Examples pertaining to human exposure to chemical mixtures can be associated with emissions from point sources and diffuse and mobile sources, although because they often represent the most severe absolute exposure concentrations, the majority of published work is focused on local scale studies associated with industrial and mining releases. One such example is the study of Pereira et al. (2004) in an abandoned mine in the southeast of Portugal (S. Domingos mine) on integrated human and environmental risk assessment. Hair samples from the scalp were analyzed for metal presence (As, Cd, Cr, Cu, Mn, and Zn) in the human population living nearby the mine. High concentrations of Cd, Cu, and As were recorded in individuals living near the mine compared to individuals that live apart. The concentrations reported in the hair of this group of people were above the reference values. It was also concluded in this study that metal concentrations were related to concentrations in soil, probably related to the consumption of milk and cheese from cattle from the region. In a further local scale study around an industrial facility, Cui et al. (2005) showed that Cd intake through vegetables was higher in samples from one village closer to a factory (500 m) than in samples from another village located at 1500 m. Cd concentration in urine and serum from residents was, however, much lower in the village closer to the factory. The authors suggested that the possible reason for this was the higher intake of Fe, Ca, and Pb from vegetables of the far-away village, suggesting also that high intake of these ions could lead to a decrease in Cd body burdens. This therefore indicates clearly that, like for environmental species, it is not the absolute concentration of a chemical that is present in the exposure medium, but rather the concentration that is actually available for uptake that is the primary determinant of exposure.

Oomen et al. (2003) defined 4 steps in the oral bioavailability of chemicals present in contaminated soils to man: soil ingestion, mobilization from soil during digestion (i.e., bioaccessibility), absorption from the intestinal lumen, and first-pass effect. An in vitro model of the human digestive system was used to study the uptake of chemicals from ingested soil. When an artificial soil, spiked

with a mixture of polychlorinated biphenyls (PCBs) and lindane, was introduced into the system, approximately 35% of PCBs and 57% of the lindane appeared to be accessible. Bioaccessibility was explained from the distribution of these chemicals over the soil solid phase, bile salt micelles, and proteins (Oomen et al. 2000). It turned out that the first step in the uptake process, the mobilization of the chemicals from soil, was most important in determining the uptake flux, and therefore the bioavailability of these contaminants in ingested soil particles (Oomen et al. 2001). Other studies demonstrated that from an artificial soil dosed at 530 mg Pb/kg, only 23% of the Pb was bioaccessible, and that only a part of the bioaccessible soil-borne lead was actually taken up (Oomen et al. 2003). These studies demonstrate that the composition of a mixture of chemicals originally present in ingested soil particles may change in the course of the uptake process, affecting exposure.

This example suggests that organisms may also affect the sorption equilibrium of chemicals in soil or sediment. Another example of that was found in the uptake of cadmium in *Hyallela azteca*. In water-only exposure, cadmium uptake and toxicity in this organism were not affected by phenanthrene. When exposed in sediment, however, cadmium uptake was increased when the animals were simultaneously exposed to phenanthrene. This most likely is a result of associated feeding, causing alterations in ingestion or digestive processes, leading to an increased cadmium uptake. So, from a toxicological point of view, the synergism seen cannot be explained from an interaction in the animals but rather is exposure related (Gust and Fleeger 2005).

1.3.3.2 Influence of Medium Physical–Chemical Properties on Chemical Availability

In case of metal mixtures in soils and sediments, bioavailability is controlled by the strength of binding of metal ions to the soil or sediment particles. The partitioning of metals to the soil or sediment reduces the availability for mobilization and uptake by plants, animals, and microbes. The binding strength depends highly on properties that control the partitioning process, such as pH, dissolved organic matter (DOM), and other organic ligands, calcium, organic matter content, inorganic ligands, and the solid-phase metal oxide (Allen 2002).

The partitioning of metal ions can be modified in the digestive track of soil-dwelling organisms or in the rhizosphere. Depending on the organism, bioavailability can be related to several key factors. In plants and microorganisms, it has been correlated to the activity of the free metal ion and its presence and diffusion in the soil pore water. Bioavailability of metals in invertebrates can be influenced by the organic matter content that is digested in their guts, and might be physiologically moderated by pH and competing cations (e.g., Ca^{2+}).

Soil or water pH is one of the most important parameters when dealing with metal bioavailability. Also for ionizable organic chemicals, like chlorophenols, pH may affect bioavailability. Changes of conditions in environmental compartments may depend on their surrounding environments and climatic changes, and pH is one of those properties that can show larger changes.

In aquatic systems, in addition to the complexation of metal ions by natural organic matter, metal bioavailability, bioaccumulation, and toxicity are highly affected by water hardness and alkalinity (Banks et al. 2003). This is also applicable to metal mixtures where complexation of metals can occur even at higher rates than when single chemical compounds are present.

Bioavailability of organic chemicals is strongly dependent on aqueous solubility. The equilibrium partitioning theory has been applied to sediment toxicity studies, and it was concluded that uptake from sediment as well as from (pore) water is possible at the same time; however, the exposure route in equilibrium is not necessarily important. For substances with log $K_{ow} < 5$, the equilibrium partitioning theory is considered acceptable to assess the risk. For substances with log $K_{ow} > 5$, a safety factor of 10 is applied, in order to include the additional uptake by sediment ingestion (Loonen et al. 1997).

Bioavailability can vary with the contact time of chemicals with soil or sediment particle constituents. Chemicals in newly deposited sediments may become more bioavailable than older buried materials. In soils the same can happen. In a study where a 70-year-old and a freshly copper-contaminated soil were compared, in the soil contaminated 70 years ago no copper toxicity to *Folsomia fimetaria* was observed for concentrations of copper as high as 2911 mg/kg. The newly spiked soil, however, caused a 10% decrease in reproduction at 337 mg Cu/kg (Scott Fordsmand et al. 2000). In the work of Smit and Van Gestel (1998), aging was also shown to be important to understanding the toxicity of Zn to *F. candida*. Within time soil pH can change, which also induces a change of Zn toxicity by altering Zn sorption to soil particles (e.g., an increase of soil pH leads to an increased Zn sorption). For chemical mixtures the same may happen due to the effect of soil characteristics on chemical adsorption to soil particles and also to chemical interactions through aging. For organic chemicals, it was suggested that molecules slowly become sequestered within the soil matrix and therefore become less available to organisms. Besides abiotic parameters, biotic interactions also may play a role. Bacteria, fungi, and soil invertebrates may alter the behavior of chemicals in soils, altering also their persistence and sorption to soil particles. These facts are crucial when evaluating soil toxicity and risk assessment for decision makers and cleanup purposes (Alexander 1995).

When exposed to mixtures, chemicals in the exposure medium may affect each other's uptake by humans in a manner that is analogous to some of the bioavailability effects outlined here for environmental species. This was, for instance, shown for the neurotoxicity of EPN (O-ethyl-O-4-nitrophenyl phenylphosphonothionate), which was enhanced by aliphatic hydrocarbons due in part to increased dermal absorption (Abou-Donia et al. 1985). It was also shown that dietary zinc inhibits some aspects of lead toxicity, which could in part be explained by decreasing dietary lead absorption (Cerklewski and Forbes 1976). Other examples of interactions of chemicals at the uptake phase in humans, which may in part be related to bioavailability interactions, are summarized in Table 1.3.

1.3.3.3 Metal Speciation Determines Bioavailability

To understand chemical exposure and bioavailability the biotic ligand model (BLM) was developed for single (cationic) metal species, assuming that the amount of a

Table 1.3 Examples of interactions of chemicals at the uptake and absorption level in humans

Antimicrobial agent	Other drug	Mechanism
Decreased absorption		
Lincomycin	Kaolin-pectin	Irreversible adsorption to kaolin-pectin
Lincomycin	Cyclamate	Possibly complexation
Ritampicin	PAS "granulates"	Adsorption to bentonite granules
Tetracycline	Sodium bicarbonate, cimetidine, bi- and trivalent metal cat ions (including anatides), atropine	Alkaline pH inhibits dissolution, probably reduced dissolution, chelation, slowed gut peristalsis
Pivampicillin PAS	Diphenhydramine	Slowed gut peristalsis
Neomycin	Digoxin	Induced malabsorption
Neomycin	Warfarin	Induced malabsorption
Neomycin	Penicillin *V*	Induced malabsorption
Increased absorption		
Tetracycline	Metoclopramine	Increased gut peristalsis
Pivampicillin	Metoclopramine	Increased gut peristalsis

Source: Based on Calabrese, EJ. 1991. Multiple Chemical interactions, Part 4: Drugs; Part 5: The drug–pollutant interface. Chelsea (MI): Lewis Publishers, p 389–578.

metal binding to a sensitive biological ligand determines its toxicity. This fraction binding to the biological membrane is considered the bioavailable fraction. In addition to metals, other cationic elements may bind to the same target sites on the biological membrane. On the other hand, concentration and activity of free metal ions is determined by the presence of organic and inorganic ligands. The BLM incorporates the competition and affinity to the site of toxic action on the organism of the free metal ion, other naturally occurring cations, and also the possible complexation by abiotic ligands (e.g., dissolved organic matter, chloride, carbonates, sulfide). On this basis, the model includes ion uptake pathways that can quantify chemical characteristics like metal affinity and capacity in vivo. In general, the greater the affinity to the binding sites, the higher the toxicity of a particular metal. The BLM was also applied to mixtures to evaluate how it would respond, using the classic toxic unit's concept of additivity. Ion competition has been included from the beginning in the BLM because cat ions like Ca^{2+} and H^{+} are known to decrease metal accumulation at the ligand (Playle 2004).

As an example, in the study of Sanchez-Dardon et al. (1999) exposure of the rainbow trout (*Oncorhynchus mykiss*) to Zn decreased Hg and Cd toxicity, probably by competition at the entry sites to gills' cells, through competition at intracellular binding sites or through induced synthesis of metallothionein. Another example is with *Daphnia magna* exposed to Zn that increased their tolerance toward Cd, probably through a competition at the ligand site in the gut or through an induction of metallothionein synthesis (Barata et al. 2002). These studies are 2 examples of possible

competition between ions to bind in the uptake and intracellular sites in organisms. See also Chapter 2 for a discussion of BLM-type interactions in relation to toxicokinetics and toxicodynamics.

1.3.3.4 Species Specificity

Bioavailability is also considered species and organ or tissue specific because what is available to one species might not be the same for the other, and the same counts for different organs or tissues inside a living organism. Barahona et al. (2005) found that physiological differences among oat, wheat, and sunflower roots, such as root waxes, might be responsible for differences in permeability for nonpolar compounds and therefore for differences in sensitivity of the root elongation process.

Another example for species-specific differences in bioavailability of chemical mixtures is the study of Loureiro et al. (2005), where avoidance behavior of earthworms and isopods was studied in 2 soils from the vicinities of an abandoned gold mine. Isopods (*Porcellionides pruinosis*) turned out to show avoidance behavior, whereas earthworms (*Eisenia andrei*) did not, suggesting isopods to be more sensitive than earthworms for these soils that contained a mixture of metals. It remains unclear which factors explain this difference, but routes of exposure and bioavailability difference may have played a role.

Since bioavailability is an integral factor in the estimation of the internal dose (or dose at target tissue) of the chemical, it is important in human studies to consider the environmental and physiological characteristics of uptake sites and their interactions since these are clearly important for defining the extent of exposure. When exposure is through food, the gastrointestinal tract and its physiology has an important effect on the amount of different chemicals that are taken up. It has been suggested, for example, that gut uptake of 2,3,7,8-tetrachlorodibenzodioxin (TCDD) and related compounds is variable, incomplete, and congener and vehicle specific, and that more lipid-soluble congeners, such as 2,3,7,8-tetrachlorodibenzofuran, are almost completely absorbed, while the extremely insoluble octachlorodibenzodioxin is less well absorbed, depending on the dosing regimen. The fact that high doses may be absorbed at a lower rate, whereas low repetitive doses may be absorbed at a greater rate, thus has the potential to alter internal exposure from the assumptions based on external exposure concentrations. To date, the only study of TCDD bioavailability in humans was reported by Poiger and Schlatter (1986) and was based on a single male in which the gastrointestinal absorption was >87% when TCDD was administered in corn oil. Laboratory data suggest that there are no major interspecies differences in the gastrointestinal absorption of dioxins and dibenzofurans. However, absorption of TCDD is dependent on conditions and characteristics of the soil medium. In animals, absorption of TCDD from different soils ranged from 0.5% (Umbreit et al. 1986a, 1986b) to 50% (Lucier et al. 1986). Absorption from a diet was 50 to 60% in rats (Fries and Marrow 1992). Therefore, exposure with food rather than with oil as a vehicle relates more closely to exposure from soil. Bioavailability has to be considered when calculating the hypothetical ingestion dose.

1.3.3.5 Formulating Agents

Another important issue on the bioavailability of chemical mixtures is the use of formulating agents for several purposes (e.g., agriculture, veterinary, human health). Some studies have been performed to compare the toxicity of pure compounds and formulations. Azadirachtin, a plant-derived extract, is often used as a repellent, antifeedant, and molt regulator for several insect species and can be applied as several formulations, like Azantin-EC, Bioneem, or Neemix. When exposed to the pure compound and 2 formulations, the cladoceran *Daphnia pulex* showed clear differences in sensitivity. LC50 values for the formulations Bioneem and Neemix were 0.07 and 0.03 µg/L, respectively, while a 50- to 100-fold higher value was found for the toxicity of the pure compound (0.382 µg/L). The higher toxicity of both formulations suggests that azadirachtin is not the only active compound in the formulations, or that the inert ingredients significantly enhanced the toxicity of azadirachtin. However, it remains unclear whether this is due to a higher bioavailability in the formulation, although it is suggested that the formulation may also affect fate (sorption, biodegradation) of azadirachtin (Goktepe and Plhak 2002).

Garcia-Ortega et al. (2006) reported conflicting results for the fate and effect of pure (Pestanal) propetamphos and its formulation Ectomort Centenary (8% active ingredient) in sediments. Sorption of propetamphos to sediments was stronger in the formulation. Biodegradation rate decreased with increasing sorption but was not affected by the formulation. Toxicity to sediment microbial communities was, however, significantly greater for the commercial formulation than for the pure compound. This cannot be explained from a higher availability of propetamphos in the formulation. Garcia-Ortega et al. (2006) therefore assume that ingredients of the formulation enhance toxicity of the active ingredient.

These studies do not confirm the effect of formulations on the bioavailability of compounds, but they do emphasize the need to test formulations (next to or instead of active ingredients) when performing a risk assessment of commercial pesticides (Garcia-Ortega et al. 2006).

1.3.3.6 Analytical–Chemical Procedures

Several methodologies have been developed for bioavailability assessment using chemical-analytical procedures. To determine the bioavailable fraction of metals or organic compounds in soils and sediments, several methods can be applied, such as extraction techniques. Usually desorption procedures are applied, using an extracting agent to desorb chemicals from the soil or sediment solid phase. An aqueous extraction might be considered the simplest alternative, although with some limitations. Deionized water has a very low ionic strength compared to natural (pore) water. That is why a weak salt extraction, for example, using 0.01 M $CaCl_2$ (Houba et al. 1996), is sometimes preferred, because it better simulates the soil solution. Such water and neutral salt extractions can be used to determine partition coefficients (K_d).

Specific extractants and sequential fractionation are also widely used procedures to estimate metal or nutrient availability to plants (see, e.g., Houba et al. 1996). Several extractants can be considered, like diethylene triamine penta acetate (DTPA), ethylene diamine tetra acetic acid (EDTA), acetic acid, HNO_3, HCl, or other

mineral acids (Allen 2002). Each reagent might be considered specific for extracting a certain fraction of metals. As an example, EDTA and DTPA are often used as extractants of exchangeable and organically bound trace metals and also to dissolve metal precipitates. These procedures can also be considered as chelating extractions, showing a correlation between water and total digestion extractions. Another technique also used for the identification of the solid phase associated with metals is an x-ray absorption fine structure methodology (EXAFS) (Manceau et al. 2003).

Recently, attempts have been made to develop biomimetic methods, simulating plant uptake of metals. An example of such a method is DGT (diffusive gradients in thin films), developed by Zhang et al. (2001), for measuring metal availability to plants. In this case, metal accumulation in a chelex layer is measured. By taking into account thickness of the diffusive layer covering the chelex layer and contact time with the soil sample, it is possible to estimate the available metal concentration in the soil solution. The DGT method may also be used to estimate metal speciation in surface water (Zhang 2004).

Similar biomimetic methods have been developed for assessing the (bio)availability of organic chemicals in water, sediments, and soil (Mayer et al. 2003; Ter Laak et al. 2006). The main advantage of these nondepletion techniques, such as the solid-phase microextraction methods (SPMEs), is that they may be used without disturbing the chemical distribution in surface water or soils or sediments.

1.3.4 Chemical–Chemical Interactions in Mixtures

Another form of interaction that may change the nature of exposure for chemicals in mixtures is through direct chemical-chemical interaction. One example is the formation of nitrosamines (which are carcinogenic) from noncarcinogenic nitrates and amines in the stomach (Klaassen 1996). The formation of N-nitrosoatrazine from atrazine and nitrite has been demonstrated in vitro in human gastric juice (pH 1.5 to 2.0) during 1.5 to 12 hours of incubation at 37 °C (Cova et al. 1996). The percent formation peaked at 3 hours, and gradually declined thereafter, due to degradation of N-nitrosoatrazine to atrazine. Peak formation of N-nitrosoatrazine was 2% from 0.05 mM atrazine and 0.5 mM nitrite, 23% from 0.05 mM atrazine and 3 mM nitrite, and 53% from 1 mM atrazine and 3 mM nitrite. The formation of N-nitrosoatrazine from atrazine and nitrite also has been demonstrated in vivo, the amount formed being dependent on the ratio of atrazine and nitrite concentrations and on pH (Krull et al. 1980).

1.4 ENVIRONMENTAL FATE MODELING

Environmental fate models make use of chemical properties to describe transfer, partitioning, and degradation (Mackay et al. 1992a; Cahill et al. 2003). For organic chemicals, quantitative structure-property relationships (QSPRs) may be used to predict partitioning from physical–chemical properties, such as K_{ow} and K_{oa}. Such properties may also allow for a prediction of the transfer of chemicals between compartments. Recently, some successful attempts have also been made to predict persistency of chemicals (Raymond et al. 2001), although this mainly concerns

degradation rate under standardized conditions (Posthumus et al. 2005). But in most cases, specific knowledge on degradation pathways is required to predict the formation of metabolites. OECD (2004) presented an overview of multimedia fate models to predict overall environmental persistence (P_{ov}) and the potential for long-range transport (LRTP) of organic chemicals. P_{ov} and LRTP derive from both chemical properties and environmental conditions. Multimedia fate models can be used during exposure assessment to identify spatial extent of exposure, environmental partitioning (media of concern), and residence time of chemicals in a certain environmental compartment. Four levels of model complexity were identified, ranging from closed systems at equilibrium to dynamic open systems. OECD (2004) identifies generic multimedia models, region-specific multimedia fate models, and multizone multimedia models (Figure 1.1). These models may be helpful in describing distribution on a global scale (Toose et al. 2004), on a regional scale (Mackay et al. 1992a), or on a smaller scale, such as in surface water (e.g., the Exposure Analysis Modeling System (EXAMS); Schramm 1990).

The input required by multimedia fate models includes properties of the chemicals (such as distribution over compartments air, water, and soil or sediment), properties of the environment or landscape receiving the contaminants, and emission patterns and mode of entry of chemicals into the environment (OECD 2004) (Figure 1.1). Fenner et al. (2005) compared the outcome of 9 multimedia fate models by applying them to a set of 3175 hypothetical chemicals covering a range of 25 half-life combinations (in water, air, or soil or sediment) and 127 combinations of partition coefficients (air-water (K_{aw}), K_{ow}, and K_{oa}). Results show great similarities between the model outputs for P_{ov} predictions, but less for LRTP. P_{ov} and, to a lesser extent,

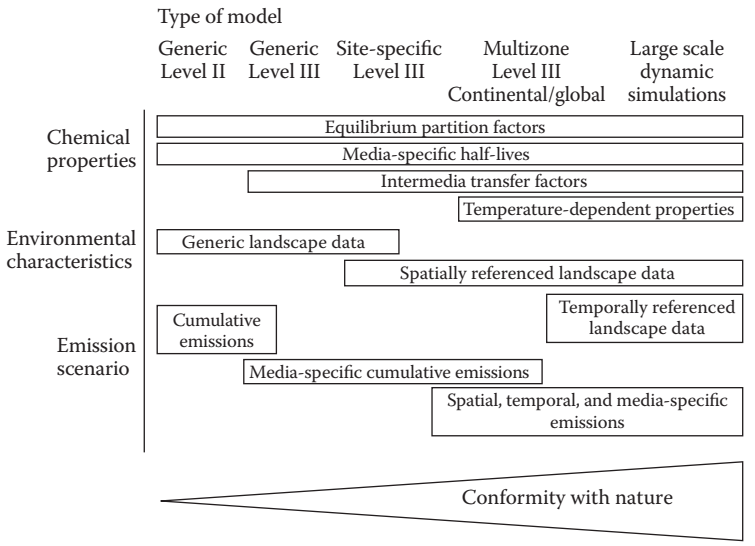

Figure 1.1 The continuum of multimedia fate models available for estimating overall persistence (P_{ov}) and potential for long-range transport of chemicals (Redrawn from OECD [2004]).

LRTP depend mainly on chemical properties. Models show significant differences in certain regions of the chemical space, with model uncertainty being higher than parameter uncertainty in case of LRTP predictions, and vice versa for P_{ov}. On the basis of this analysis, Fenner et al. (2005) conclude that it always is best to not rely on just 1 model but apply more than 1 model. Model selection is not an arbitrary task but requires careful consideration of the question and context of the assessment. Fenner et al. (2005) therefore provide guidance for selecting the most suitable model for a certain task.

So far, the main focus of multimedia fate models has been on single chemicals, but extensions may become available to include fate of transformation products. This may open the way to making the models applicable to mixtures (OECD 2004). Initially such development may simply be made through the serial analysis of the fate of individual chemicals, and from this a derivation of probable concentrations of each, assuming no interaction. Such analysis is, for example, feasible for many of the most widely used "down the drain" and is at present being extended to other product types, such as personal care chemicals and human pharmaceuticals. Such combined analysis would in fact represent a considerable step forward in addressing the nature of likely mixture exposures; however, if the interactions with the environment and between chemicals as outlined above are to be considered, then this would require a considerable effort to understand and include the major processes involved within existing models.

1.5 EXPOSURE SCENARIOS AND MONITORING

An important issue in pollution management is the identification of exposure scenarios that pose relatively high risks to humans or the environment (Thomsen et al. 2006). The regulation of these high-risk scenarios should be given priority in order to realize an effective reduction of the overall risks. An exposure scenario can be broadly defined as a set of parameters that together determine the risk level. This may include parameters such as the emission load, the emission compartment, fate parameters (persistence, biodegradability, vapor pressure), and toxic properties. The exposure scenario is thus the set of parameter values that needs to be known as a condition to estimate the risk. Thomsen et al. (2006) have described a new methodology for the identification of exposure scenarios that cause high risks for the environment or human health. They define a scenario type as the set of criteria that is considered important after analysis of a problem tree. A criterion has to be described by data, and thus empirical knowledge, before it can be taken into account as a condition for scenario selection. A data type that describes a specific criterion is denoted a descriptor. A specific scenario is defined as a combination of realistic descriptor values. In this procedure, descriptors for emission are consulted (descriptors for different product groups), as this can be seen as first screening for potential mixtures of relevance for further studies.

According to this new system, a harmful mixture consists of substances that together reach the target on 1 side and also have a toxic action that has potential to yield harmful effects. Realistic mixtures can thus be defined based on 1 of 2 principal general approaches:

1) toxicity-driven approach watching for common harmful toxicity of mixtures and thus based on the mode of action, where the combination of substances is identified that yields a high combined toxicity as a result of either additive or synergistic mixture toxicity mechanisms; and
2) exposure-driven approach watching for simultaneous exposure, where substances that can cause simultaneously exposure are investigated for combined toxicity.

It is not possible to claim one of these approaches as best because they are complementary to each other and a combination of them is ideal if possible. The method takes concentration addition (CA) as the starting point for mixture toxicity, so that the same risk descriptors can indicate toxic actions that add to each other between different substances (Thomsen et al. 2006).

1.5.1 Human Exposure

The mere presence of any single chemical or chemical mixture in the environment does not indicate that a health threat exists. An important step of mixture risk assessment is the evaluation of completed exposure pathways. Completed exposure pathways link together the source of contamination, environmental medium, point of exposure, route of exposure, and a receptor population. It means that without the potential for chemicals actually entering (or contacting) the human body, no threat is present.

Personal behavior and practices also add a further level of complexity to the estimation of individual total exposure for humans. Many publications pointed out harmful effects of high-dose alcohol consumption, smoking, drugs, or the use of mercurials in religious practices, just to name a few. All these chemicals contribute to overall exposures and may affect the toxicity of other chemicals entering the human body (Calabrese 1991). Such personal exposure patterns can also be overlaid on top of more regionally based environmental exposure resulting from diffuse environmental pollution. In this section, first, different pathways of human exposure are considered as well as life-stage-related exposures. Second, the use of monitoring data to assess mixture exposure is discussed.

1.5.1.1 Environmental Exposures Excluding Food

Environmental exposures are present through the human lifetime. However, they may vary considerably over time at the same location, for example, because of the local or global changes in emission and environmental pollution levels. Environmental exposures of humans consist of exposures outdoors and indoors as well as at workplaces; these environments may significantly differ. The exposure media include air, water, and soil and dust. Historically, research on human exposures to chemicals and associated health effects has been conducted mostly on single chemicals. In addition, several studies have dealt with complex mixtures, such as diesel fuel and gasoline, by-products from coal combustion, and tobacco smoke. A common problem of complex mixtures is that the composition may vary from one exposure to another and, as a result, the associated toxicity may vary. For a better understanding

of joint toxic action of chemicals and their effects on human health, it is important to identify combinations of chemicals that represent the most frequently occurring simple mixtures.

Some studies have attempted to address this need. For example, further analyses of the ATSDR data on mixtures at and around hazardous waste sites (see Section 1.2) considered completed exposure pathways (Table 1.4) (De Rosa et al. 2004; Fay 2005). The results show that the number of sites with mixtures in completed exposure pathways is lower than the number of sites for which only the frequency of co-occurrence was analyzed. Data from 1706 hazardous waste sites indicated that completed exposure pathways exist at 743 (44%) of the sites (Fay 2005). Of these, 588 had 2 or more chemicals in the completed exposure pathway. That means that exposure to mixtures occurred at 79% of the sites with exposure. As indicated in Table 1.4, mixtures of inorganic chemicals were found predominantly in soil, mixtures of organic chemicals were detected in air, and combinations of both in water.

A study of the US Geological Survey identified mixtures of chemicals in groundwater used for drinking water in the United States (Squillace et al. 2002). Samples were analyzed from 1255 domestic drinking water wells and 242 public supply wells between 1992 and 1999. Water in 11.6% samples did not meet current drinking water standards or human health criteria established by the US Environmental Protection Agency (USEPA). Volatile organic compounds (VOCs) were detected in 44% of the samples, pesticides in 38%, and nitrate in 28%. Many mixtures (i.e., possible combinations of chemicals) were found in the samples; however, only 402 mixtures were detected at least 15 times (>1% detection frequency). From all the samples, 47% contained at least 2 analyzed compounds and 33% contained at least 3 compounds. A list of the top 25 most frequently detected mixtures is shown in Table 1.5. Since the study was done on drinking water, human exposure can be assumed. In addition to these compounds in groundwater, drinking water may also contain a complex mixture of products resulting from disinfection, including trihalomethanes, haloacetic acids, haloacetonitriles, and bromate (Teuschler et al. 2000).

The USEPA's Total Exposure Assessment Methodology (TEAM) studies found levels of about a dozen common organic pollutants to be 2 to 5 times higher inside homes than outside, regardless of whether the homes were located in rural or highly industrial areas (USEPA 2006b). Evidence for the contribution of indoor air pollution to human exposure to mixtures of chemicals has also been obtained for other areas in the world, for instance, through the project Towards Healthy Air in Dwellings in Europe (THADE), which was sponsored by the European Union (Franchi et al. 2006). While the consumers are using products containing organic and inorganic chemicals indoors, not only can they expose themselves to high chemical concentrations, but increased concentrations can also persist in the air long after the activity is completed. Among the chemicals often found inside are carbon monoxide, nitrogen dioxide, formaldehyde, methylene chloride, and tetrachloroethylene. Carbon monoxide is generated as a product of incomplete combustion from sources, which include home furnaces and fireplaces. Similarly, nitrogen dioxide may be found in houses with poorly vented fireplaces and furnaces. Formaldehyde is found in many products used around the house, such as antiseptics, medicines, cosmetics, dishwashing liquids, fabric softeners, shoe-care agents, carpet cleaners, glues, adhesives, lacquers,

Table 1.4 Chemical mixtures in completed exposure pathways at and around hazardous waste sites in the United States

Rank	No. sites	Binary combinations		Rank	No. sites	Binary combinations	
Water							
1	120	TCE	Perc	10	45	Chloroform	TCE
2	64	1,1,1-TCA	TCE	12	42	TCE	1,2,-DCA
3	58	1,1,-DCE	TCE	13	40	1,1,1-TCA	1,2,-DCA
4	55	Benzene	TCE	13	40	1,1,1-TCA	1,2,-DCE
5	54	TCE	Lead	13	40	TCE	Trans-1,2-DCE
6	51	1,1,1-TCA	Perc	16	39	Lead	Cadmium
7	49	1,1-DCA	TCE	16	39	Perc	Lead
8	47	1,1,-DCE	Perc	18	38	Vinyl Chloride	TCE
9	46	TCE	Toluene	19	37	1,1-DCA	Perc
10	13	Lead	Arsenic	19	37	MeCl	TCE
Soil							
1	60	Lead	Arsenic	10	34	Lead	Nickel
2	56	Lead	Chromium	12	33	Copper	Zinc
3	52	Lead	Cadmium	13	32	Arsenic	Zinc
4	47	Arsenic	Chromium	13	32	PCBs	Lead
5	46	Arsenic	Cadmium	15	30	Cadmium	Copper
6	44	Lead	Zinc	16	29	Nickel	Chromium
7	39	Cadmium	Chromium	17	28	Antimony	Arsenic
8	38	Cadmium	Zinc	17	28	Arsenic	Copper
9	36	Lead	Copper	17	28	Chromium	Copper
10	34	Chromium	Zinc	27	28	Lead	Antimony
Air							
1	18	Benzene	Toluene	11	10	1,1,1-TCA	Toluene
2	16	Benzene	TCE	11	10	1,1,1-TCA	TCE
3	15	Benzene	Perc	13	9	Benzene	Xylenes
4	15	TCE	Perc	13	9	Ethylbenzene	Perc
5	14	Benzene	Ethylbenzene	15	8	1,1,1-TCA	Perc
6	13	Ethylbenzene	Toluene	15	8	Benzene	Chlorobenzene
7	12	Benzene	1,1,1-TCA	15	8	Benzene	MeCl
7	12	TCE	Toluene	15	8	Ethylbenzene	Chlorobenzene
9	11	Toluene	Perc	15	8	TCE	Ethylbenzene
10	11	Toluene	Xylenes	20	7	1,1,1-TCA	Ethylbenzene

Source: Adapted from De Rosa CT, El-Masri HE, Rohl, H, Cibulas W, Mumtaz, MM. 2004. J. Toxicol. Environ. Health 7:339–350.

Note: Binary combinations at the 1188 sites surveyed. MeCl = methylene chloride, PCBs = polychlorinated biphenyls, Perc = perchloroethylene (tetrachloroethylene), 1,1,1-TCA = 1,1,1-trichloroethane, TCE = trichloroethylene, Trans-1,2-DCE = trans-1,2-dichloroethylene, 1,1-DCA = 1,1-dichloroethane, 1,1-DCE = 1,1-dichloroethene.

Table 1.5 Top 25 most frequently detected mixtures in groundwater used for drinking water in the United States

Rank	Compounds in mixture				No. samples (out of 1497) with mixture
1	Atrazine	Deethylatrazine			284
2	Deethylatrazine	Nitrate			214
3	Atrazine	Nitrate			198
4	Atrazine	Deethylatrazine	Nitrate		179
5	Atrazine	Simazine			138
6	Deethylatrazine	Simazine			127
7	Atrazine	Deethylatrazine	Simazine		120
8	Nitrate	Simazine			111
9	Atrazine	Metolachlor			103
10	Deethylatrazine	Metolachlor			99
11	Deethylatrazine	Trichloromethane			97
12	Atrazine	Prometon			96
13	Atrazine	Deethylatrazine	Metolachlor		95
14	Atrazine	Nitrate	Simazine		92
15	Deethylatrazine	Nitrate	Simazine		92
16	Deethylatrazine	Prometon			90
17	Atrazine	Deethylatrazine	Prometon		87
18	Nitrate	Trichloromethane			86
19	Tetrachloroethene	Trichloromethane			86
20	Atrazine	Deethylatrazine	Nitrate	Simazine	86
21	Atrazine	Trichloromethane			78
22	Metolachlor	Nitrate			76
23	Nitrate	Prometon			73
24	Deethylatrazine	Metolachlor	Nitrate		71
25	Atrazine	Metolachlor	Nitrate		70

Source: Adapted from Squillace PJ, Scott JC, Moran MJ Nolan T, Koplin DW. 2002. Environ. Sci. Technol 36:1923–1930.

plastics, and some types of wood products. Methylene chloride is widely used as an industrial solvent and as a paint stripper and can also be found in certain aerosol and pesticide products, some spray paints, and automotive cleaners. Tetrachloroethylene may be found in the home environment as a result of dry cleaning of textiles. Another important group of indoor contaminants consists of pesticides. For example, chlorpyrifos, an organophosphorus insecticide, is the most widely used insecticide for indoor and outdoor residential applications in the United States (ATSDR 1997). Based on the monitoring of different outdoor and indoor media, a study indicated that indoor dust and air were the primary exposure media for the residents (Whyatt et al. 2002). Similar results were obtained in a large group of pregnant women; the chlorpyrifos body burden that did not exhibit any seasonal variations was thought to come primarily from indoor exposures (Berkowitz et al. 2003). Metals can be also found in the households; for example, lead is generated from deteriorating lead paint

and is a major concern in regards to children exposed to lead-contaminated house dust (ATSDR 1999). Further, radon can be found in many homes all over the United States (ATSDR 1998b).

1.5.1.2 Food

Another major exposure route for humans is via contaminated food. For example, North America's Great Lakes, which are the largest body of freshwater in the world, are polluted with about 362 contaminants that were found in quantifiable amounts in the water, sediment, and biota (IJC 1983; USEPA 1994). The critical pollutants were identified as PCBs, DDT, dieldrin, toxaphene, mirex, methyl mercury, benzo(*a*) pyrene, hexachlorobenzene, polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and alkylated lead. Some of these pollutants biomagnify in the aquatic food chain and can be detected in increased levels in cooked Great Lakes fish. Consequently, the blood serum levels of these chemicals are significantly increased in consumers of contaminated Great Lakes sport fish compared to people who do not eat such fish (Humphrey 1983; Fiore et al. 1989; Sonzogni et al. 1991).

Another example is human exposure to mixtures of PCDDs, PCDFs, and PCBs. The primary route of exposure for the general population is the food supply (ATSDR 1998a). When the USEPA and US Department of Agriculture (USDA) completed the first statistically designed survey of the occurrence and concentrations of PCDDs and Fs in beef fat (Ferrario et al. 1996; Winters et al. 1996), pork fat (Lorber et al. 1997), poultry fat (Ferrario et al. 1997) and US milk supply (Lorber et al. 1998), the total TEQ values[1] were the highest for pork and the lowest for chicken and milk. This exposure results in a background body burden of about 5 ng TEQ/kg body weight for a mixture of dioxin-like PCDDS, PCDFs, and PCBs (USEPA 2000a). Analysis of fish oil dietary supplements showed exceedance of the WHO-TEQ limit of 2 ng/kg for dioxins in approximately 30% of the samples. When combined with whole diet intake, exposure to dioxin-like compounds was estimated at 1.8 to 8.9 pg WHO-TEQ per kilogram body weight per day for adults and 1.4 to 14 pg WHO-TEQ per kilogram body weight per day for children (Fernandes et al. 2006).

1.5.1.3 Human Exposure in Different Life Stages

Most environmental exposures are similar for a given population at a given location and time period; however, human exposures to chemicals also have some distinctive characteristics related to the life stages (Figure 1.2).

[1] Toxicity of dioxin-like chemicals is expressed in toxicity equivalents (TEQs). TEQ is defined as the product of the concentration, C_i, of an individual "dioxin-like compound" in a complex environmental mixture and the corresponding TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) toxicity equivalency factor (TEF_i) for that compound. TEFs are based on congener-specific data. The TEF scheme compares the relative toxicity of individual dioxin-like compounds to that of TCDD, which had been traditionally assigned a toxicity of one (ATSDR 1998a). In 1998, the World Health Organization (WHO) released an updated system where a TEF of one was assigned not only to TCDD but also to 1,2,3,7,8-pentaCDD (Van den Berg et al. 1998).

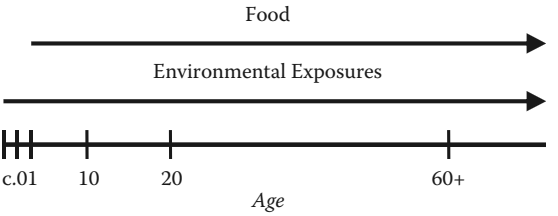

Figure 1.2 Exposures in life stages. c = conception.

1.5.1.3.1 Fetuses

In utero exposures represent the first contact of the developing organism with environmental pollutants. Less than half of all human conceptions result in the birth of a completely normal, healthy infant. For example, approximately 60% of spontaneous abortions are thought to be related to genetic, infectious, hormonal, and immunological factors (Bulletti et al. 1996). However, the role of the environment in the etiology of spontaneous abortion remains poorly understood. The placenta plays a key role in influencing fetal exposure by helping to regulate blood flow, by offering a transport barrier, and by metabolizing chemicals (Shiverick et al. 2003). However, the placenta never acts as a complete barrier; virtually any substance present in the maternal plasma is transported to some extent by the placenta. There is a distinction between direct and indirect developmental toxicants. Direct chemicals such as thalidomide and retinoids induce developmental toxicity without maternal toxicity. Indirect chemicals such as ethanol and cocaine mostly affect the fetus at levels also toxic to the mother. Epidemiological studies indicated that environmental exposures to low concentrations of some chemicals may cause subtle neurodevelopmental changes (Jacobson and Jacobson 1996) or may disrupt the endocrine system (Kavlock et al. 1996).

1.5.1.3.2 Infants

Breast-feeding is recognized as providing the developing infant the benefits of balanced nutrition and passive immunization against infections; however, exposure of infants to anthropogenic chemicals via breast milk is of concern. Many chemicals persist in the environment for a long time; they bioaccumulate in the organism and biomagnify through the food chain. Among the environmental pollutants found in breast milk are PCDDs, PCDFs, PCBs, metals, and pesticides. Considering the relatively short period of breast-feeding and relatively high daily intake, the exposure may be substantial. For example, Schecter and Gasiewicz (1987a, 1987b) estimated the daily intake of PCDDs and PCDFs in TEQs by nursing infants (10 kg) in the United States to be 83 pg TEQs/kg body weight/day. Later, Schecter et al. (1994) estimated lower intakes of 35 to 53 pg TEQs/kg body weight/day for infants (7.3 kg) (see exposure changes under Section 1.5.1.2). In contrast, intake for infants who were fed soy formula was substantially lower, ranging from 0.07 to 0.16 pg TEQ/kg body weight/day. In comparison, Schecter et al. (1994) estimated the daily intake of PCDDs and PCDFs for adults (70 kg) as 0.26 to 2.75 pg TEQs/kg body weight/day. Koppe (1995) reported that daily dietary intake of PCDDs during lactation represents only 14% of the daily secretion of PCDDs in breast milk; the rest (about

Table 1.6 Levels of various chemicals in human breast milk samples from general populations

Chemical	Range of mean or median concentrations (ng/g lipid)	Newborn intake via breast milk[a] (µg/kg/day)	Region	Reference
PCDDs and PCDFs	0.013–0.028[b]	0.00009–0.00057[c]	United States, Canada, Germany, New Zealand, Japan, Russia	Pohl and Hibbs (1996)
Mercury (total)	130–793[c]	0.922–5.625	Japan, Germany, Sweden	Abadin et al. (1997)
Hexachlorobenzene	5–63	0.035–0.447	New Zealand, Brazil, Arkansas, Australia, Canada, Mexico, Quebec Caucasians	Pohl and Tylenda (2000)
Hexachlorobenzene	100 to >1000	0.709–7.094	France, Spain, Quebec Inuits, Slovak Republic, Czech Republic	Pohl and Tylenda (2000)
p,p'-DDE	300 to >3000	2.128–21.281	New Zealand, Brazil, France, Australia, Quebec Caucasians and Inuits, Arkansas, Canada, Slovak Republic, Czech Republic, Germany, North Carolina	Pohl and Tylenda (2000), Rogan et al. (1986)
PCBs	167–1770	1.185–12.556	Japan, Quebec Caucasians and Inuits, New York, Michigan, the Netherlands, Poland, Finland, Croatia, North Carolina	DeKoning and Karmaus (2000)

Source: Adapted from Pohl HR, McClure P, De Rosa CT. 2004. Environ Toxicol Pharmacol 18: 259–266.

[a] Converted from 0.6 to 3.6 µg Hg/dL, using a conversion factor of 45.4 g lipid/10 dL milk (DeKoning and Karmaus 2000). Organic forms accounted for about 7 to 50% of total mercury (Abadin et al. 1997).

[b] Measured in 2,3,7,8-TCDD toxicity equivalents (TEQs).

[c] Calculated, based on assumptions of 3.2 kg body weight, 45.4 g fat/L milk, and 0.5 L milk/day (DeKoning and Karmaus 2000), as follows: 5 ng/g fat × 45.4 g fat/L × 0.5 L/day × 1/3.2 kg × 1 µg/1000 ng = 0.035 µg/kg/day.

86%) is derived from PCDDs stored in adipose tissue. Levels of selected chemicals found in breast milk around the world are presented in Table 1.6.

1.5.1.3.3 Children

There are many differences between children and adults. The first obvious difference is in size; children consume more food and water per kilogram of body weight, they have higher inhalation rates, and they have larger surface-area-to-volume ratios than adults. For example, Schecter and Li (1997) conducted a congener-specific analysis of PCDDs, PCDFs, and dioxin-like PCBs in US fast foods. They reported TEQ values from 0.03 to 0.28 pg/g wet weight for McDonald's big mac, 0.03 to 0.29 pg/g for Pizza Hut's personal pan supreme pizza with all toppings, 0.01 to 0.49 pg/g for Kentucky Fried Chicken's 3-piece original recipe meal, and 0.3 to 0.31 pg/g for Häagen-Dazs' chocolate–chocolate chip ice cream. Daily TEQ consumption per kilogram body weight assuming a 65 kg adult, from 1 serving of each of the fast foods tested, ranged between 0.046 and 1.556 pg/kg. The daily intake from 1 serving of each of the fast foods tested, assuming a 20 kg child (6-year-old), ranged from 0.15 to 5.05 pg TEQs/kg. A child on average consumes 3 times more TEQs on a per kilogram body weight basis than adults eating any one of the fast foods tested.

Children may also be more sensitive to harmful environmental chemicals because of differences in absorption, excretion, and metabolism (see also Chapter 2). Immaturity of some systems (e.g., immune, nervous systems) also contributes to children's vulnerability to chemicals.

Another difference between children and adults is in their behavior. Children spend more time outside and play in the dirt. Associated with this activity is soil ingestion, where hand-to-mouth ingestion has been recognized as a major exposure route (Clark et al. 1996; Hemond and Solo-Gabriele 2004). The soil ingestion value for children is based on a number of studies estimating the average soil ingestion in populations of normal children (Binder et al. 1986; Clausing et al. 1987). One of the reports suggested that an average child ingests only about 25 to 40 mg of soil daily (Gough 1991). However, about 1 to 2% of children are geophagic ("pica children") and ingest from 5 to 10 g of soil daily (USEPA 1989a). Known child-specific exposure factors have been reviewed by the USEPA (2002a).

1.5.1.3.4 Adults

Occupational exposures play an important role during adulthood. Often the exposures last for many years and exposure levels are much higher than those of the general population. Some of the common complex mixtures regulated in the workplace include coal tar pitch volatiles, mineral oil mist, petroleum distillates, and Stoddard solvent[1] (Hearl 2005). There are numerous possible combinations of chemicals found at the workplace; that is, most exposures are to chemical mixtures.

[1] Stoddard solvent is a colorless, flammable liquid that smells and tastes like kerosene. It will turn into a vapor at temperatures of 150 to 200 °C. Stoddard solvent is a petroleum mixture that is also known as dry cleaning safety solvent, petroleum solvent, and varnoline; its registered trade names are Texsolve S® and Varsol 1®. It is a chemical mixture that is similar to white spirits. Stoddard solvent is used as paint thinner; in some types of photocopier toners, printing inks, and adhesives; as a dry cleaning solvent; and as a general cleaner and degreaser.

Additive and synergistic effects of chemicals with common targets of toxicity are of great concern in occupational settings. For example, coexposure to acetone, sec-butyl acetate, and methyl ethyl ketone causes increased skin irritation; coexposure to heptane, methyl chloroform, and perchloroethylene increases central nervous system effects (Hearl 2005). In addition, personal behavior can affect the outcome of occupational exposures. For example, smoking increases the development of cancer in occupational exposures to asbestos (Selikoff et al. 1980) and to radon (Lundin et al. 1969; Archer 1985); alcohol increases liver effects of occupational exposure to hepatotoxicants such as carbon tetrachloride (Manno et al. 1996). Inadequate dietary protein enhances the toxicity of pesticides such as heptachlor (Boyd 1969; Shakman 1974). Household members, including children, can be exposed to workplace chemicals by coming into contact with contaminated work cloths (e.g., off-gassing of tetrachloroethylene).

1.5.1.3.5 Seniors

Elderly people are obviously not the only age category exposed to pharmaceuticals, but they are by far the most exposed. It is beyond the scope of this chapter to describe all the exposure scenarios and possible interactions. Interested readers are encouraged to consult other detailed literature on the topic (Calabrese 1991).

1.5.1.4 Modeling and Measuring Human Exposure

Several exposure models are available for human health risk assessment, some of which are summarized in a review by Fryer et al. (2006). They categorize exposure models according to the route of exposure:

1) environmental, distinguishing environmental concentration models (see Section 1.4) and human intake models;
2) dietary;
3) consumer product;
4) occupational;
5) aggregate, including multiple exposure pathways; and
6) cumulative, including multiple chemical exposure.

Fryer et al. (2006) conclude that the use of human exposure models still is fragmentary, with different organizations using different models for very similar exposure assessment situations. The main problem in the use of models is the lack of input data and the lack of validation of both the input data and the output of the model. They therefore recommend the development of an overall framework for human exposure (and risk) assessment.

One problem encountered when assessing exposure of human populations to contaminated land is spatial heterogeneity of pollution. To overcome this problem, Gay and Korre (2006) propose the combinations of spatial statistical methods for mapping soil concentrations, and probabilistic human health risk assessment methods. They applied geostatistical methods to map As concentrations in soil. Subsequently, an age-stratified human population was mapped across the contaminated area, and the intake of As by individuals was calculated using a modified version of the Contaminated Land Exposure Assessment (CLEA) model. This approach allowed a

determination of sites with clearly elevated human exposure, and may also be used to determine exposure to mixtures of chemicals.

Weis et al. (2005) reported the results of the ad hoc Committee on Environmental Exposure Technology Development. They identified a toolbox of methods for measuring external (environmental) and internal (biological) exposure and assessing human behaviors that influence the likelihood of exposure. The toolbox of environmental exposure methods includes environmental sensors, such as in vitro sensors, like personal dosimeters, to detect and quantify priority environmental exposure, and Geographical Information System (GIS) technology to map and link environmental and personal exposure. The latter technique may also be used to identify populations at risk. The internal exposure methods comprise biological sensors, toxicogenomic measurements, and body burden analyses. The latter also include determination of biomarkers of exposure, such as DNA adducts. All these methods may be used to determine exposure to single chemicals and mixtures.

1.5.1.5 Human Biobanks and Human Volunteer Monitoring of Exposure

Monitoring body burdens of chemicals in human populations may contribute to a better understanding of what chemicals and at what concentrations they get into the body. For chemicals with known toxicity levels, it may be possible to learn the prevalence of people with concentrations exceeding those toxicity levels. However, it should be noted that most biomonitoring studies in the general population are designed as survey studies. Many of the studies do not take into account exposure history. Therefore, the results often represent a snapshot at 1 point in time.

In the United States, the Centers for Disease Control and Prevention (CDC) released the third National Report on Human Exposure to Environmental Chemicals (CDC 2005). The report presents blood and urine levels for 148 environmental chemicals (or their metabolites) found in the general civilian US population over the 2-year period 2001–2002. The study is part of the National Health and Nutrition Examination Survey (NHANES), designed to provide an insight into the health and nutritional status of the US population. Future follow-ups are planned to encompass 2-year periods with information on trends of exposure in population groups defined by age, sex, and race. The latest report monitored 32 more chemicals than the second report, which encompassed the 2-year period from 1999 to 2000 (CDC 2003). The major chemical groups monitored included metals, phytoestrogens, PAHs, PCDDs, PCDFs, coplanar and mono-ortho-substituted biphenyls, non-dioxin-like PCBs, carbamate pesticides, organochlorine pesticides, pyrethroid pesticides (added in the third report), phthalates, organophosphate insecticides, and herbicides. Cotinine, a major metabolite of nicotine, was measured as an indicator of smoking. Urine creatinine was analyzed as a continuous variable for chemicals measured in urine to adjust for urinary dilution. Sample sizes varied under each of the categories from several hundreds to several thousands.

The large-scale monitoring studies enable researchers to track, over established time periods, trends in levels of exposure in human populations and to assess the effectiveness of public health efforts to reduce exposure to specific harmful chemicals. Aylward and Hays (2002) summarized recent trends in dioxins intake in the United States and in Western Europe. The intake estimates show clear decreases of

dioxin exposures in these countries. For example, USEPA's 2000 estimate of 0.6 pg TEQ/kg/day is 66% lower than the 1994 estimate of 1.7 pg/kg/day for PCDDs/Fs. In the United Kingdom, the intake levels for PCDDs/Fs were 4.6, 1.6, and 0.9 pg TEQ/kg/day in 1982, 1992, and 1997, respectively. Similarly, PCDDs/Fs intakes were estimated as 4.2, 1.8, and 0.5 pg TEQ/kg/day in 1978, 1984, and 1994, respectively, in the Netherlands. Similar trends were reported for PCB intakes (Aylward et al. 2002). These decreases in intake are reflected in decreases in human body burdens. A large number of studies in the general population in the United States, Canada, Germany, and France during 1972–1999 show a trend of substantial (almost 10-fold) decreases in human TCDD-only body burden over that time period (Aylward and Hays 2002). Considering the long half-life of TCDD, a 1-compartment pharmacokinetic model estimated that the decrease in intake must have been more than 95%. A recent retrospective time-trend study that analyzed levels of major halogenated aromatic hydrocarbons in human serum concluded that PCB and polybrominated biphenyl (PBB) levels are also decreasing since their phaseout in the 1970s (Sjodin et al. 2004). In contrast, concentrations of polybrominated diphenyl ethers (PBDEs) have been increasing in recent years in the United States, because of their use as flame retardants. Such a very substantial increase has not been observed in Europe, where PBDE levels in human serum are about 10 times lower than in the United States (Thomas et al. 2006).

Large-scale monitoring studies are also under way in Europe (Pohl et al. 2005). In 2003, the EU commission launched an initiative called SCALE, which stands for Science, Children, Raising Awareness, Legal Instruments, and Evaluation. The objectives are to reduce disease burden caused by environmental factors, to identify and prevent new environmental threats, and to strengthen the EU policy-making capacity. The EU commission asked for the cooperation of all stakeholders in identifying and addressing the most relevant children's environmental health issues. Biomonitoring was specifically addressed in a document that called for unified testing approaches all over Europe so that the study results are comparable (Pohl et al. 2005). From 2003 to 2005, the Robert Koch Institute monitored 18,000 children aged from <1 to 18 years at 150 different places in Germany over a 3-year period. Detailed interviews on pregnant women, parents, and children—together with medical examinations—focused on health risks in modern life, relevant environmental pollution, psychological health, and motoric development in childhood. Similarly, the Erasmus Medical Centre in Rotterdam monitors about 10,000 subjects over a 20-year period: from early fetal life until young adulthood. The project started in 2002. Physical examinations, questionnaires, interviews, and ultrasound examinations are performed; biological samples are collected as well. The focus is on pediatric growth, neurobehavioral development, pediatric diseases, and preventive health care for mother and child.

1.5.2 Exposure in Ecosystems

Estimating exposure through measurement of chemical concentrations in tissues or body fluids (e.g., blood, urine) of environmental species (or a suitable surrogate) is a long-standing concept going back many years. In recent times, interest in the

"biomonitoring" approach has grown to the point where the subject was the focus of a *Nature* editorial that looked explicitly at application in developed and developing regions (Whitfield 2001). Some current monitoring programs have been measuring residue levels of multiple chemicals in biological samples over extended periods, while others are targeted studies addressing particular sites or issues. The principal driver behind each of the studies is not usually to quantify the exact nature of multiple chemicals exposure, but instead to assess spatial and temporal changes in exposure level for particular contaminant groups of concern (e.g., metals, PCBs, organochlorine insecticides). Despite this focus, many of these monitoring schemes can provide valuable information on the nature of complex exposure scenarios, and a few even explicitly report on the potential mixture effects that may result from a multiple chemical exposure.

The nature of the different environmental compartments means that the species selected for exposure monitoring may vary between different environmental types (e.g., air, soils, sediment, freshwaters, and marine waters). Similarly, the characteristics of the chemicals being investigated (often persistent pollutants) can also influence species choice. For some environmental compartments, such as soils and sediments, it is possible to select species for monitoring that are exposed through different routes, such as via pore water or by ingestion of contaminated particulate matter. Because of the potential for pulsed exposure in mobile media such as air and running waters, sampling for exposure biomonitoring in these ecosystems may need to be repeated to avoid missing potentially significant exposures to mobile or ephemeral pollutants. In soil and sediment, which act as contaminant sinks, such temporal repetition may be less of an issue, although this depends on the persistence of the compounds being assessed. Further in these environments, spatial heterogeneity can be more of an issue. Approaches for different environmental compartments and details of the finding and outcomes of particular schemes associated with each are outlined in detail below.

1.5.2.1 Air

Exposure through air is particularly important for gases, volatile compounds and chemicals associated with the surfaces of small airborne particulates. Since plants are in intimate contact with the air through leaf cuticles and stomatal pores, this group has been most widely used for airborne contaminant monitoring. The first widespread application of plants for biomonitoring was to support policy implementation on issues relating to acidification and eutrophication (Cape et al. 1990; Bobbink et al. 1992). Building on this work on sulfur and nutrients, metals have also been the subject of numerous studies measuring both spatial and temporal aspects of accumulation in plant leaves. Burton et al. (1986) reported that many surveys involving metal analysis of lichen thalli reflected the spatial variability of metal deposition. Bargagli et al. (2002) compared metal concentrations in 2 common biomonitor species *Hypnum cupressiforme* (a moss) and *Parmelia caperata* (lichen) around an intensive mining area. While both moss and lichen were able to indicate the nature of the complex atmospheric emission occurring in the region, each accumulated different concentrations of different metals. This emphasizes the difficulty in reading across exposure scenarios between species.

This problem is, however, not unique to plants, but is in fact applicable to many taxa (Hopkin et al. 1993; Morgan and Morgan 1993; Newton et al. 1993). One area where the analysis of mosses and lichens has made a significant contribution to understanding of present and past pollution trends has been through the analysis of samples stored in herbaria. These samples provide useful information on temporal trends in deposition that can be used in the development of dynamic models to describe pollutant loading and fate in terrestrial environments (Hassanin et al. 2005). This issue may be particularly relevant in describing past exposure that may lead to current environmental and human health concerns (e.g., past carcinogen exposure).

An obvious issue regarding the use of plants for airborne pollutant biomonitoring is that they are also potentially exposed through the soil. This confounding effect is one reason why many monitoring studies of wet and dry deposition have focused on mosses and lichens, which lack roots and so rely on atmospheric deposition to surface cuticles to obtain adequate nutrients. For PAHs, and probably also for other lipophilic organic compounds, uptake from soil may also be limited by the strong adsorption to soil and lipid materials associated with root cells (Watts et al. 2006). For such compounds, therefore, air accounts for most of the burden on or in plant leaves and other aboveground tissues. This makes mosses and lichens excellent potential monitors for organic pollutants, with the physiology of the leaf, such as the presence and nature of leaf hairs and the form of any extracuticular wax present, being an important influence on the rate of uptake (Bakker et al. 1999; Jouraeva et al. 2002).

1.5.2.2 Water

The potential for sustained and pulsed exposure in riparian, lake, estuarine, and coastal systems has established biological monitoring as a potentially useful tool for characterizing the chemical status of these habitats. For monitoring contaminants in the water column, filter feeders and species with an extensive gill system are frequently favored. This is because the extensive contact between biological membranes and the water column in these species ensures that there is significant exposure. An example of the kind of coordinated approach that can be used for monitoring waterborne pollutants using a filter feeder species is the mussel watch program run by the National Center for Coastal Ocean Science in the United States. This scheme measures concentrations of over 100 contaminants in the tissues of marine mussels from almost 300 US sites covering the Atlantic, Pacific, and Gulf coasts, and also the American shores of 3 of the Great Lakes (Michigan, Huron, and Erie). Chemical groups measured include 18 elements (17 metals plus Si), over 50 PAHs, 31 PCBs, 31 organochlorinated compounds, organometals (such as butyl-tin compounds), PCDDs, and PCDFs. Major conclusions from the survey to date include evidence of a widespread, but declining exposure to multiple organochlorines; a widespread exposure to multiple PCBs that is reducing over time (but not as quickly as for the organochlorines), a widespread exposure to PAHs that has remained largely unchanged, except where there has been a specific accidental exposure (Page et al. 2005), a decreasing exposure to organo-tin compounds, and a very prominent exposure to metals that has reduced for some (e.g., lead) but remained unchanged for others (e.g., copper and zinc) (National Oceanic and Atmospheric Administration 2002).

The large-scale nature of the US mussel watch program has, of course, led to the development of many smaller-scale schemes in other countries and regions that have mirrored the use of mussel species as subjects for biological monitoring (Sole et al. 2000; Kim et al. 2002; Rainbow et al. 2004; Mendoza et al. 2006). Other schemes also used other bivalve species, such as oyster and scallop, as alternatives to mussels (Daskalakis 1996; Silva et al. 2003; Norum et al. 2005). These biomonitoring studies range from small-scale surveys of country or regional coastlines conducted for particular contaminant groups (e.g., metals, PAHs, PCBs) to major regional surveys that rival the US program (e.g., Tanabe 2000). Being also subject to the vagaries of the research funding system, it is often difficult to obtain sufficient funds to repeat surveys, meaning that in some cases, the temporal element that is so important in the mussel watch scheme is lost. The large-scale surveys set up for coastal waters in Asia are, however, beginning to generate data suitable for the derivation of temporal trends (Sudaryanto et al. 2002; Monirith et al. 2003).

A second major group of invertebrate species recommended for marine biomonitoring is crustaceans. The barnacle *Balanus improvisus* has been used as a biomonitor of the metals Cu, Zn, Cd, Fe, Pb, Mn, and Ni in the Gulf of Gdansk (Baumard et al. 1998). Insects have also been used in freshwater (Fialkowski et al. 2003). As well as invertebrates, fish have also been recommended as potential monitors of exposure to multiple contaminants. Despite particular issues with the use of fish for monitoring organic pollutants (see below), biomonitoring studies have been able to separate individuals from sampling regions (coastal sea vs. oceanic) with different levels of prevalent pollution (Stefanelli et al. 2004). Since fish are both abundant and important components of aquatic ecosystems (at intermediate to high levels within aquatic food webs), and also because fish are an important food source, monitoring of contaminant levels in fish can provide an important link between environmental exposure to multiple compounds and human exposure to the same compounds through diet (Meili et al. 2003).

While biomonitoring studies undoubtedly provide useful information of mixture exposure assessment, the presence or, more importantly, absence of a compound in a particular species does not provide the full picture. Physiology may have a major influence on the tendency of an organism to accumulate certain chemicals. For example, fish have a potential to metabolize organic molecules that is higher than in many of the invertebrate taxa that are the most common subject of invertebrate monitoring. This means that more recalcitrant persistent organic pollutants, such as PCBs and organochlorine insecticides, are accumulated at low or very low concentrations in fish, and easily biodegradable compounds, such as PAHs and chlorinated phenols, do not tend to accumulate (van der Oost et al. 2003). A further issue in water is the pulsed nature of potential exposure, particularly in rivers. In cases where conditions, such as surface flow, cause pollutant runoff (e.g., pesticides from an arable field), this exposure can cause detrimental effects to receiving stream ecosystems. Later chemical biomonitoring studies may, however, fail to identify this exposure if the compound is both degraded from stream sediment and rapidly metabolized by the chosen monitoring species. This problem can be seen as part of a wider issue with the use of biomonitoring to detect complex exposure to easily metabolized compounds, which is described later.

1.5.2.3 Sediment

As sediments act as pollutant sinks in aquatic systems, they can be important sources of exposure, and so of the entry of chemicals into aquatic food chains. Sediments are the ultimate residence location for many pollutants released to water. The widespread presence of complex mixtures of contaminants in sediment is thus likely to occur in any location where multiple localized and diffuse contaminant sources contribute to the overall chemical load within natural waters. The role of sediment in the receipt and resupply of the chemical to the water phase means that there is interest in monitoring sediment chemical pollutant load over both different spatial and temporal scales. Because the process of sediment deposition and chemical adsorption on the one hand and solubilization and resuspension on the other link the pollutant loads of the sediment and water column, many of the species that can be used to sample the environment for waterborne pollutants (e.g., filter feeders such as mussels) can also describe the pollutant load present in sediments (Baumard et al. 1998).

An alternative to the use of filter feeders as proxies for sediment exposure is to utilize fully sediment-dwelling species. Two groups have been suggested. The first are the annelids. In freshwaters, the most commonly studied is the sludge worm, *Tubifex tubifex* (Egeler et al. 1999), while in marine sediments 2 polychaetes, *Nereis diversicolor* and *Arenicola marina*, have been used as biomonitors of single and multiple chemical exposures with varying degrees of success (Kaag et al. 1998; Poirier et al. 2006). The second sediment-dwelling group used for biomonitoring is insects, and in particular chironomids (Bervoets et al. 2004; Martín-Díaz et al. 2005a). Overall, the use of sediment-dwelling species is less well established than for bivalves such as freshwater and marine mussel species and, as a result, this later group remains the preferred taxa for multiple chemical exposure assessment in aquatic systems.

1.5.2.4 Soil

As soil is an important sink for pollutants in terrestrial ecosystems, there is interest in assessing the exposure of humans and ecological species through measurement of concentrations in organisms exposed through this medium. Such measurements can reflect the direct application of chemicals to soils as pesticides or solid waste or by aerial deposition of contaminants to the soil surface (Van Brummelen et al. 1996b; Filzek et al. 2004). Unlike air and surface waters, soil is immobile and hard to dilute, so there is a potential for temporally more stable long-term exposure than in mobile media, although it is also more likely that exposure is more heterogeneous, even at relatively small spatial scales. Since true soil organisms, such as earthworms, nematodes, and springtails, have low mobility, this means that tissue residue concentrations in these species can provide a more reliable estimate of the local exposure than more active surface-dwelling species, such as beetles, centipedes, spiders, and small mammals, for which tissue residue concentrations provide a picture of the average of contaminant concentrations over the full home range. Thus, depending on the question being asked by selecting different soil species for monitoring, it is possible for direct analysis to both include and partially ignore local scale spatial heterogeneity. For example, by using earthworms as the subject species, Marinussen and Van der Zee (1996) were able to model the spatial patterns of exposure in heterogeneously

contaminated soils at an industrial facility. Such an analysis would, however, have been even more complex for very mobile species or animals with a complex life history for a single compound, let alone if multiple chemicals and their combined effects were to be considered.

Despite issues relating to chemical heterogeneity and the subsequent choice of monitoring species, the success of the mussel watch program for marine waters has prompted the initiation of schemes in soils that mirrored the marine approach. As in marine work, it is important to consider the physiology of the species when designing and interpreting the outputs of any monitoring scheme. For example, in laboratory experiments, slugs have been shown to be sensitive to metal pollution and were thus suggested to be useful for biological assessment of soil exposure (Marigomez et al. 1998). Work to assess the potential of slugs as biomonitors was, therefore, conducted at a copper-contaminated site, concluding that exposure and effect biomarkers recorded in sentinel slugs could be sensitive, quick, and cheap indices of metal pollution in soils (Marigomez et al. 1998). Similarly using woodlice, Hopkin et al. (1986) were able to conduct reliable exposure maps for the presence of multiple metals from diffuse and localized industrial sources over a medium-sized town (Reading) of 250,000 people in the United Kingdom. Jones and Hopkin (1991) also looked at the biomonitoring potential of woodlice and mollusks, concluding that both groups had potential and that each sampled exposure in a similar manner. This was indicated by the high correlation between tissue concentrations for each metal found between the different measured species. The studies outlined above have demonstrated the feasibility of using soil species to provide a picture to environmental exposure. A review of the published literature, however, shows that while this line of research was certainly the fashion 10 years ago, it is losing favor, with few recent papers focusing on this kind of spatially based tissue concentration assessments.

1.5.2.5 Monitoring of Food Chain Transfer

The potential for some chemicals to transfer through food chains has resulted in the development of a set of long-term, large-scale monitoring studies that measure exposure of top predators (predatory birds and mammals) through quantification of chemical concentrations in tissues (e.g., liver) and eggs. Monitoring of top predators arose in response, first, to recognition of the effects of organochlorine insecticides on bird populations (Newton and Wyllie 1992; Walker et al. 2001) and, second, to the realization that these pollutants have the potential to circulate across regions and ultimately around the globe (Wania and Mackay 1996; Gouin et al. 2004). The focus on top predators, which can range across large territories, means that the residue levels measured represent a cumulative exposure across the landscape, rather than the specific regions in which they were sampled. For some bird species in particular, exposure can also occur in different regions as a result of migration, and this can result in different patterns of tissue concentration depending on specific regional chemical usage patterns (Minh et al. 2002).

Although there are numerous fairly small-scale academic studies of the concentration of persistent pollutants in avian or mammalian predators (Kenntner et al. 2003a, 2003b; Berger et al. 2004; Jaspers et al. 2005; Hela et al. 2006), the 2 most

important long-term large-scale schemes for quantifying wildlife exposure through the food chain are the UK Predatory Bird Monitoring Scheme (UK-PBMS) and the Arctic Monitoring Program of the USEPA (US-AMP). To briefly summarize both schemes, the UK-PBMS has run since the mid-1960s and measured chemical concentrations in the tissues of birds collected as dead carcasses by volunteers and non-hatching (sterile) eggs collected under license from nest sites. Like many monitoring schemes, the focus has been on quantifying exposure, including spatial (Alcock et al. 2002; Broughton et al. 2003) and temporal (Newton et al. 1991, 1993) trends. Current analytes measured include organochlorines and their metabolites, PCBs, second-generation rodenticides, mercury, and in a more limited set of samples, polybrominated compounds and PAHs.

Analyses in the UK-PBMS concentrate on the use of single methods to measuring concentrations of particular subgroups of chemicals rather than on the application of diverse methods to detect the full range of residues that may be present. Reporting also focuses on trends for single chemicals in isolation. The exception to this is for PCBs, where the scheme expressly considered the combined chemical dose that is present in the tissues of the birds using the TEQ method of Ahlborg et al. (1994) and Van den Berg et al. (1998). Sum totals of concentrations may also have been reported for other chemical subgroups, such as the organochlorines and PAHs. While relatively coarse, these summed values provide a relatively simple means of defining the changes in concentrations of the measured entirety of these contaminant groups in tissue.

The US-AMP is probably the largest-scale pollutants monitoring initiative currently undertaken. The scheme focuses on measuring chemical concentrations in soils, water, and biota at higher latitudes. The focus on polar latitudes can be linked to concerns regarding the potential for movement of persistent organic pollutants (POPs) over time to higher regions of the globe (Wania and Mackay 1996). This process occurs because of the fact that warmer temperature at lower latitudes favors volatilization of POPs, while the colder temperature at higher latitudes favors deposition. Such cycles of volatilization at lower latitudes and deposition at higher latitudes (often termed global distillation) may, therefore, lead to the accumulation of higher concentrations and an increasing contribution from the more volatile compounds in polar regions.

Biota samples measured in US-AMP include arctic plants such as mosses, large terrestrial herbivores such as caribou, waterfowl, and top predators including birds of prey and mustelids (mink and marten). Aquatic invertebrates and some fish species are also measured. Like UK-PBMS, the focus in US-AMP is on the spatial and temporal trends for individual contaminant groups, rather than holistic assessments of multiple chemical exposures. Overall, schemes such as the US-AMP and UK-PBMS and similar small-scale national programs (Sørensen et al. 2004) can provide an excellent summary of mixture exposure scenarios for top predators exposed through the food chain. The databases generated by these programs could become essential data resources for further data mining for historic and current mixture exposure assessment for wildlife and possibly even humans.

While monitoring of chemical residue levels can provide a useful snapshot of the range and extent of current exposure to some compound groups, the approach does

have some limitations. Birds and mammals, like fish, have a high metabolic potential for some organic contaminants. This means that some chemicals that are subject to rapid degradation and metabolism are not easy to reliably detect. This favors measurement of more recalcitrant contaminants, such as PCBs and organochlorinated insecticides, and also some metals such as mercury and cadmium, for which modeling (Romijn et al. 1993a, 1993b, Spurgeon and Hopkin 1996) and measurements (Hunter et al. 1987, 1989; Read and Martin 1993; Kooistra et al. 2005) have indicated the potential for concentrations to reach potentially harmful levels in tissues (Nicholson et al. 1983). For organic compounds that rapidly decay or for metals that are subject to strong homeostatic regulation, analyses for top predators may provide only a limited summary of current exposure, even though such compounds may make a substantive contribution to toxic effects.

1.5.2.6 Multimedia Exposure Scenarios

The exposure scenarios detailed above focus on separate assessment using biomonitoring organisms applicable to the particular environment under consideration. This separation of exposure by environmental compartment does not reflect the true nature of exposure for many species. For example, higher plants are likely to be exposed to airborne contaminants through the leaf surface and through the soil solution; sediment-dwelling filter feeders can be exposed through the interstitial water and also through the main water column; and top predators can be exposed through air, water, and their food supply. Elucidating the principal exposure routes for different species is an extremely active area of research in both aquatic and terrestrial environments (Vink et al. 1995; Irving et al. 2003; Jager et al. 2003), and there are obvious implications for the assessment of exposure in different exposure routes, and as a result, careful consideration needs to be given to the assessment. Such assessments are likely to be specific for each taxon and need to consider the major life history and behavioral characteristics of the organism.

Even more complex than the situations of multiple exposure routes are situations where species move between different environments during different stages of the life cycles. At their simplest, such scenarios can simply be due to feeding in different places at varying times of the year. More complex scenarios occur in species that spend separate parts of their life cycle in different environments. A nice example is given by Linkov et al. (2002). In their model, PCB exposure and bioaccumulation in winter flounder is described, taking into account spatial and temporal exposure characteristics. Other examples include many species of insect (e.g., Ephemeroptera, Tricoptera, Chironomidae) that spend their larval stages fairly sedentary in water and their adult stages as mobile wide-ranging species in terrestrial ecosystems. For such species, it is difficult to establish the true complex nature of exposure, and so measurement may be the only appropriate method to evaluate the exact scenario. A promising attempt to model spatially explicit ecological exposure of terrestrial organisms, taking into account spatial, temporal, and multiple stressor interactions, and addressing landscape heterogeneity, has been described by Hope (2001, 2005). Hope (2005) identified physical (loss of habitat) and biological (lack of adequate food) stressors, in addition to chemical stressors. Other examples of studies that took into account spatial exposure

patterns by using geostatistical or GIS-based methods include Clifford et al. (1995) for dieldrin and Kooistra et al. (2005) for Cd accumulation in terrestrial food chains.

1.5.2.7 Critique on Biomonitoring Studies for Complex Exposure Assessment

Biological monitoring is one of the best ways to provide a picture of current exposure to environmental mixtures. However, monitoring programs have to be carefully designed and results reviewed with caution. Even the largest and most comprehensive studies are limited in their scope to assess the true nature of complex environmental exposure simply by the fact that it is not feasible to measure the full range of potential pollutants. In most cases schemes are designed to meet particular policy objectives (i.e., characterized predator exposure to POPs) or for particular site-specific scenarios (i.e., metal levels in mosses around a metal smelter). Even when chemicals can conceivably be measured, the potential for metabolism can present a significant problem. This relates not only to compounds that are rapidly metabolized, and so difficult to detect even after a significant exposure event, but also to interindividual variability, due, for example, to enzyme polymorphism, that may introduce variability into the system that may mask time-dependent or spatial exposure trends.

As outlined in the discussion for particular sections above, an important fact to consider when reviewing biological monitoring data is the behavioral characteristics and lifestyles of the subject species. In the simplest case, monitoring of sessile species may be useful to provide a local scale view of exposure, while measurement of highly mobile species may provide a region scale exposure summary. Even when species have broadly similar lifestyles (e.g., birds of prey), behavioral and prey differences mean that biomonitoring can show different results for different species. While direct measurement in monitoring studies can account for these differences, this presents a particular problem for reading across exposure scenarios for species with different habitats, food sources, and behavior. Only in cases where the variables and differences that have the greatest influence on the nature of exposure are known is it possible to make interspecies predictions regarding a particular exposure scenario.

1.5.2.8 Effect-Directed Assessment

A final means of assessing combined exposure is through the direct application of biological testing for effects-based assessment of complexly polluted media (e.g., effluents, soils, sediments). For the use of bioassays for direct assessment of complex mixtures, the reader is referred to Chapter 4.

Matching the development of bioassays for complex exposure assessment has been the development of the use of biomarkers. This area has been the subject of a number of detailed reviews, some wholeheartedly recommending the approach and others being more critical (Decaprio 1997; Kammenga et al. 2000; Gagne and Blaise 2004; Forbes et al. 2006). Whatever the pros and cons of biomarkers, the use of effects-based analysis clearly has an appeal in assessing exposure to mixtures and its consequences. Such approaches have already been used in human exposure monitoring. For example, metabolite monitoring is regularly used for occupational human

exposure in regulatory settings, and it is easy to envisage such approaches being used for exposure assessment in environmental species.

A final form of direct effect assessment that can be used for exposure monitoring is through monitoring the community composition for microorganisms, meso- and macrofauna, and plants. This approach is based on the fact that the exposure to specific pollution mixtures may be expected to result in the elimination of sensitive taxa and species. Physiological and community diversity-based profiling methods for microorganisms are becoming increasingly routine, and for microinvertebrates, the development of community-based monitoring systems, such as the River Invertebrate Prediction and Classification System (RIVPACS) scheme in the United Kingdom (Hawkins et al. 2000; Wright et al. 2000) and analogous schemes in other countries, is becoming increasingly widely used for assessing the ecological condition in regulatory regimes such as the EU Water Framework Directive. In these cases, the challenge lies practically in providing the required level of taxonomic resolution in "difficult taxa" and interpretationally in making causal links between the observed community change and the complex nature of the combined exposure to multiple stressors.

1.6 SUMMARY AND CONCLUSIONS

Estimation of mixture exposure requires an assessment of all steps from emission of chemicals, fate in the environment, bioavailability in different environmental compartments, and interactions at the uptake level. In addition, behavioral aspects and life-stage-specific exposures have to be considered.

Emission estimation methods are available for several sources and chemicals (or groups of chemicals), but focus is generally on single chemicals rather than on mixtures. Multimedia fate models may be used to predict or estimate the fate and distribution of chemicals in the environment. Such models are available for different scales, but the precision of the prediction usually increases with increasing level of details required. Physical–chemical properties of the chemicals and characteristics of the environment determine the composition of a mixture ending up at a certain site or in a certain place. Exposure is determined by factors affecting bioavailability of the chemical, such as binding strength to soil or sediment particles. Chemical–chemical interactions may also affect availability. In addition, individual behavior of organisms, including man, may influence exposure. Methods to determine exposure mainly include residue analysis, either in exposure media like air, water, soil, or food, or in tissues of organisms being exposed. Also, these monitoring methods usually are focusing on single chemicals rather than on mixtures. These long-term and large-scale data sets can provide essential information that can be used to validate the outcome of emission scenario and environmental fate models.

1.7 RECOMMENDATIONS

Although several emission registrations exist, these mainly focus on single (groups of) chemicals rather than on assessing mixture exposure. In addition, emission estimations or registrations seem mainly to take place on an ad hoc basis, with little international coordination.

1) Generate emission data that may help better estimate mixture exposure.
   a) Collection of data on existing chemicals should be evaluated to determine if they are fit for the purpose of mixture scenario prediction.
   b) International collaboration for exchanging emission data.
   c) There is a special need to consider emission of new and emerging chemicals, for example, nanoparticles.

One of the reasons why current emission estimation methods do not focus on mixtures might be that there are so many possible combinations of chemicals. With some guidance on the combinations of chemicals most relevant or most likely to cause problems, it would become easier to focus.

2) Prioritize approaches to emission estimation to focus on most common and most relevant mixture emission scenarios.
   a) Further development of desk-based methods for identifying most probable mixture scenarios and widespread release of modeling outcomes.
   b) Refine large-scale monitoring programs, for example, global programs, such as the Arctic Monitoring and Assessment Program (AMAP) and the European Monitoring and Evaluation Program (EMEP) to focus on inclusion of the most relevant old and new chemicals alone and in mixtures.

Although several recent studies demonstrate awareness of the fact that chemical fate processes may have a large influence on the composition of mixtures, models usually only focus on single chemicals. Nevertheless, such models may be very useful to predict composition of mixtures, but validation is needed.

3) Studies on fate in the environment should include aspects that cause a change in mixture composition from emission until exposure.
   a) Models that describe distribution of mixtures in the environment need to be validated.

Several factors and processes may lead to interactions between chemicals in the environment. Such interactions not only determine fate and transport in the environment, but may also play a role in determining uptake. More insight into such interactions is highly needed in order to enable a more accurate exposure assessment of mixtures.

4) Research on potential interactions between individual chemicals that might affect the exposure, availability, or toxicity of the mixture and inclusion of outcomes into developing multimedia fate models for mixtures.

Monitoring programs mainly focus on measuring (single) chemicals in the environment or in organisms as an indication of exposure. In many cases no additional information is provided, hampering a proper interpretation of such data.

5) Monitoring programs measuring total concentrations should include measures of parameters (environmental characteristics, for example, clay, organic carbon content, pH, dissolved organic carbon (DOC)) and physical chemical properties of compounds that help to evaluate bioavailability.

Several models have been developed to link bioavailability or uptake of chemicals in organisms to their speciation in the environment. Again, focus generally is on single chemicals, while extension for use on mixtures is desired.

6) Research is needed to assess if it is possible to extend integrated models that link exposure-toxicity (like the BLM) for use with mixtures.

Like many data, emission and exposure data are presented as constant values, often a mean with standard deviation. In environmental risk assessment, however, awareness is growing that a stochastic or probabilistic approach is more suitable to obtain insight in the possible risk of chemicals. This also requires expressing exposure data as statistical, probabilistic distributions. Also in this case, the focus should be extended to mixtures.

7) Improve methods for identification of the probabilistic distribution of short- and long-term exposure of possible chemical mixtures for ecosystems and humans.

An adequate assessment of exposure to mixtures may require development of improved tools for measurement or detection of chemicals, but also for assessing temporal aspects of exposure.

8) Generate data that may help better estimate mixture exposure.
   a) Analytical methods should be available for new high-production-volume chemicals coming onto the market (e.g., as for pesticides).
   b) Differentiate between simultaneous and subsequent exposure
      i) Long-term trends at the same locations
      ii) Spatial sampling at the same time
   c) Better understanding of routes of exposure, potential entry and exposure of humans to new chemicals, and their contribution to mixtures.

Assessing human exposure is quite complex, because exposure is dependent on life stage and may be influenced by behavioral patterns. Prediction of exposure may be improved by accounting for these aspects.

9) Improve prediction of exposure for different life stages of humans for chemical mixtures accounting for behavior patterns.

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