Chapter 1

Introduction

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Background

At the beginning of the twenty-first century, the human population is in a unique, but precarious position. Economic globalization, increasingly rapid technological change, expanding industrialization, and shifting political and religious forces have provided great opportunities and challenges for the human population. Equally, we have seen rapid changes in the health of the population. In the early part of the last century, there were great advancements in health as a result of public health interventions, particularly improved water and waste sanitation, antibiotics and vaccinations. These greatly decreased the burden of acute and infectious disease in many, but not all, parts of the world and subsequently accelerated the health of the population. As infectious and acute illnesses declined, prevalence of chronic illnesses, such as heart disease and cancer, began to rise. As we move across the boundary of the twenty-first century, chronic disease in the USA and other developed countries has brought an increasing burden to the population, and other, lesser developed countries, have not been afforded the same access to or benefits of the achievements of developed countries.

We have also seen over this time period, the emergence of the importance of the environment as a determinant of health. During the mid twentieth century, environmental pollution, primarily in air and water, emerged as a concern for acute and sudden illnesses. From the "killer smogs" in Donora, Pennsylvania, and London, UK, the mercury poisoning in Minamata, Japan, the industrial chemical releases leading to the Bhopal tragedy, to the burning water of the Cuyahoga River in Ohio – these were visceral, immediate, and tragic demonstrations of the power of chemicals in our environment with immediate impact on human health. These events also motivated demand for pioneering legislative and regulatory actions by governments, which led to reductions of pollutants in air, water, and food.

However, we now find ourselves at another critical cross road. What has become clear, focused by the steady compilation of scientific findings and books on this subject, is that reproductive health and ultimately reproductive capacity of the population are under strain, and critical indicators show that we must pay attention to the warnings ahead of us [1–4]. This is reflected by a number of concerning trends in human reproductive and developmental health. There has been a 40% increase, to about 11%, in the percent of US women who report difficulty in conceiving and maintaining pregnancy [5]. In addition, between 1982 and 2002, the percent of young women under the age of 25, a peak time of fertility, reporting difficulty in conceiving and maintaining pregnancy doubled from 4.3% to 8.3% [5, 6]. There has been a decline in the age of onset of puberty, as marked by breast development and onset of menarche, for girls in the USA between the 1940s to the mid 1990s [7].

There are also negative/adverse trends related to male reproductive health. The incidence of testicular cancer, primarily a disease of young men, has increased in Europe from 1% to 6% (depending on the country) over the past 10–40 years [8]. Testicular cancer has increased by about 60% in the USA over the last 30 years [9]. In addition, there is a relatively high prevalence of abnormally low sperm counts in several Scandinavian countries (~20%) [10]. Data from three cities (Boston, USA, Copenhagen, Denmark, and Turku, Finland) demonstrate a significant secular trend decrease in serum testosterone, suggesting about a 1% per year decline for the past 40–50 years [11–13]. This decline is consistent with the reduction in sperm concentration reported by Carlsen *et al.* in 1992 [14]. Also, some of the most common birth defects today

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Table 1.1. Key definitions for environmental reproductive health.

Environmental reproductive health: Interdisciplinary study of exposures to environmental contaminants, particularly during critical periods in development (such as prior to conception and during pregnancy), and their potential effects on all aspects of future reproductive health throughout the life course, including conception, fertility, pregnancy, child and adolescent development, and adult health.
Environmental contaminants: metals and synthetic chemicals in our environment, including air, water, soil, food, consumer products, and the workplace.
Reproductive health: Ability to conceive, to carry a pregnancy, pregnancy quality and outcomes, pubertal effects and adult reproductive health disorders.

are malformations of the male reproductive system, including cryptorchidism and hypospadias [15, 16]. This constellation of adverse trends suggests an overall decrease in male reproductive function.

Furthermore, there are increasing manifestations of adverse health among infants and children. Thirty percent more babies are born prematurely, and the expected gestational age of babies delivered without medical intervention is one week earlier now than 15 years ago [17]. There are increases in certain birth defects and other adverse birth outcomes, such as gastroschisis (three fold over the last 20 years in California) and hypothyroidism (138% over the past 20 years in New York) [18, 19]. And several childhood illnesses, including certain childhood cancers and neurodevelopmental disorders, such as autism, have been reported to be increasing [20], as well. While genetics comprises one important risk factor, other external influences, periconceptually, prenatally, and early in childhood are also likely contributors.

We must pay attention to these relatively rapid changes in health endpoints over the last 30–50 years, as genetic contributions could not have evolved at the same pace, indicating other external contributors such as environment and lifestyle are playing a role.

We know over roughly the same period, starting in the mid 1940s, there has been a dramatic increase in human exposure to both natural and synthetic chemicals. For example, in the USA as of 2006, there are approximately 87 000 chemical substances in commerce, with about 3000 imported or manufactured in excess of 1 million pounds each [21]. Exposures to chemicals in the environment, which are defined here as metals and synthetic chemicals in our environment, including air, water, soil, food, consumer products, and the workplace (Table 1.1), are ubiquitous. Environmental chemicals can cause a broad spectrum of effects that depend not only on route of exposure and dose, but on the susceptibility of the individual to the compound, and timing and duration of the exposure.

We know that the health of the population can be influenced by many intrinsic and extrinsic factors [22] (Fig. 1.1), in addition to chemicals in the environment. Some external factors can increase stress on the system, such as lack of access to health care, social and racial discrimination, or poverty. Other external factors can create resiliency to competing influences on health, such as good social support networks, access to services, and stable incomes. Internal factors, such as age, gender, and genotype can also influence susceptibility to diseases and disorders. The risk from environmental exposures can be enhanced or diminished by these external and internal factors [22].

Increasing concern about the role of chemicals in our environment influencing observed increases in chronic diseases and identifying chemicals that cause harm to reproductive and/or developmental health provide an opportunity to focus on preventable risk factors. To accomplish this fully, we must expand upon the scientific basis of our understanding of the links between environmental exposures and reproductive health. Furthermore, we must work across disciplines, across sectors, with those inside and outside academia, in the community, and in the policy arena to fully realize the implications of the science and translate this information into change that results in preventing exposures to harmful chemicals for individuals and populations.

It is toward this goal that we have brought together leading scientific experts from across the relevant scientific disciplines in environmental sciences, wildlife biology, clinical research, toxicology, epidemiology, and clinical and public policy translation to provide the scientific foundation for a comprehensive understanding of the intersection of environmental contaminants and reproductive and developmental health. This book provides a review of the science in key areas of the relationship between environmental contaminants and reproductive and developmental health for students and practitioners in the fields of public health,

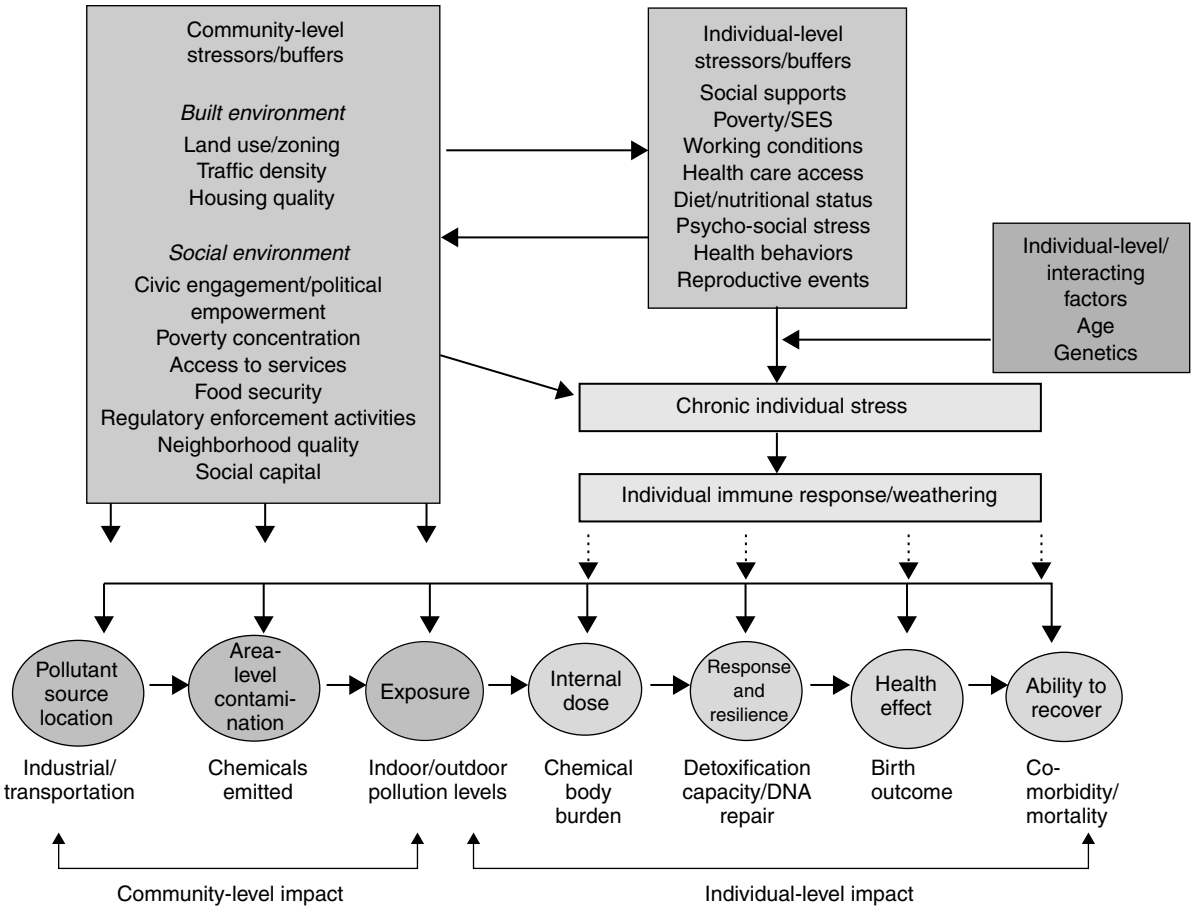

Fig. 1.1. External, both community level and individual level, and internal factors that can influence the susceptibility or resilience to disease. (Adapted from Morello-Frosch and Shenassa [22].)

environmental health and research, and medical and allied health professional training.

Scope of this book

Defining the field

Environmental reproductive health focuses on exposures to environmental contaminants (metals and synthetic chemicals), particularly during critical periods of development (such as prior to conception and during pregnancy), and their potential effects on all aspects of future reproductive health throughout the life course, including conception, fertility, pregnancy, child and adolescent development, and adult health.

Environmental contaminants

As discussed above, environmental contaminants are metals and synthetic chemicals in our environment, including air, water, soil, food, consumer products, and the workplace (Table 1.1). Common environmental pollutants include: pesticides and herbicides such as atrazine and chlorpyrifos; volatile organic compounds such as benzene, toluene and chloroform; heavy metals such as lead, mercury and arsenic; air contaminants such as carbon monoxide, ozone, particulate matter, and environmental tobacco smoke (ETS); and persistent organic pollutants, such as the dioxins, polychlorinated biphenols (PCBs), and the pesticide dichlorodiphenyltrichloroethane (DDT) and its breakdown product dichlorodiphenyldichloroethylene (DDE) (see Chapters 2 and 17).

There are many environmental contaminants that can affect reproductive health [4], and they can do so through diverse biological mechanisms. Historically, much of the scientific inquiry focused on genotoxic or mutagenic chemicals – i.e. those that can damage or

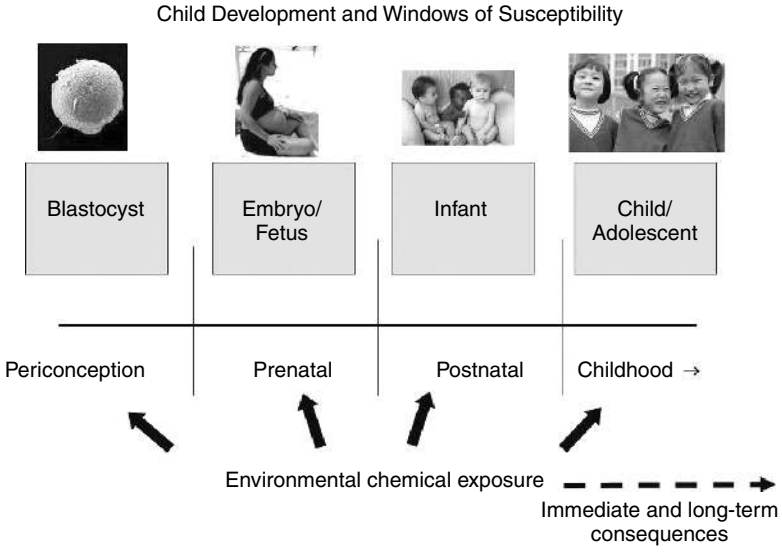

Fig. 1.2. Important developmental time periods during which perturbations, such as from exposure to environmental contaminants, can result in changes that can increase risk of subsequent immediate or long-term adverse health outcomes. (Modified from Louis *et al.* [32].)

interfere with the integrity of genetic material. While there are other mechanistic pathways that can contribute to disease, since the latter part of the twentieth century there has emerged emphasis on an important class of chemicals called endocrine-disrupting chemicals (EDCs), that interfere with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for maintenance of homeostasis and regulation of developmental processes. Some of the common EDCs discussed in this book include bisphenol-A (BPA), phthalates and certain pesticides (e.g. vinclozolin, dicofol, atrazine). Many of these compounds alter estrogen, androgen, and thyroid signaling, which are essential for normal embryonic development and reproductive activity in all vertebrates studied to date [23–25]. They can also alter hormone synthesis, storage in plasma proteins, and hepatic biotransformation and clearance [26]; disrupt neural and immune signaling pathways [27–29]; and alter the regulation of gene expression (e.g. DNA methylation, RNA stability, protein degradation) (reviewed in Edwards and Myers [30]).

Much of this book focuses on the role of/implications for/potential effects of exposure to EDCs and subsequent reproductive and developmental outcomes. It is a natural area of inquiry in this field, as EDCs can interact with the hormonal system, which regulates development and maintenance of the reproductive system. Endocrine-disrupting chemicals can also target the neuroendocrine system, which plays regulatory and homeostatic roles in the control of human physiology. As such, exposure to EDCs has broad implications for health.

Critical and sensitive periods of development and susceptibility

Another important theme throughout the book is time periods of exposure and their influence on subsequent health risks (Fig 1.2). Key developmental stages occur throughout the life course: before and around the time of conception (gamete and blastocyst stages); prenatal development (embryo and fetal stages); and infancy, childhood, and puberty [31–33].

These time periods are marked by extensive developmental changes, such as cellular proliferation and rapidly changing metabolic and hormonal capabilities. Exposures to environmental contaminants during this period may result in adverse, permanent, and irreversible effects that can manifest immediately or later in life or even in subsequent generations. For example, it has been well established that harmful exposures during the prenatal period can result in adverse birth outcomes. Exposure to thalidomide resulted in structural limb defects, excessive alcohol intake leads to fetal alcohol syndrome, and smoking can increase risk of low birthweight babies and preterm delivery. Also, we have learned that exposures during these same critical developmental periods can result in permanent alterations to physiologic systems that may not manifest until early and late adulthood, which has been labeled the fetal origin of adult disease [34, 35].

These concepts are illustrated through the tragic episode of diethylstilbestrol (DES), a synthetic estrogen and an EDC, which is discussed in several places in the book. Diethylstilbestrol was given to pregnant women in the USA between 1938 and 1971 under the erroneous assumption that it would prevent pregnancy complications. In fact, in utero exposure to DES alters the normal programming of gene families, such as *Hox* and *Wnt*, that play important roles in reproductive tract differentiation [35–38]. As a result, female offspring exposed to DES in utero are at increased risk of clear cell adenocarcinoma of the vagina and cervix, structural reproductive tract anomalies, infertility and poor pregnancy outcomes, and male offspring have an increased incidence of genital abnormalities and a possibly increased risk of prostate and testicular cancer [39]. These observed human effects have been confirmed in numerous animal models that have also provided information on the toxic mechanisms of DES. Animal experiments have also predicted changes later found in DES-exposed humans, such as oviductal malformations [40], increased incidence of uterine fibroids [41–43], and second-generational effects [44, 45] such as increased menstrual irregularities [46] and ovarian cancer [47] in DES-exposed granddaughters and increased hypospadias in DES-exposed grandsons [48, 49].

Sources of scientific information

Information about the potentially harmful effects of exposure to environmental contaminants comes from a variety of scientific sources, from wildlife studies, in vitro and in vivo toxicology studies, epidemiologic studies, and clinical evidence. Within each of these areas there are multiple types of testing methodologies and approaches that are used. Scientific data from animal studies, either within wildlife populations or controlled experimental settings, provide critical information to our understanding of the potential for environmental chemical exposure to result in adverse human health effects. The most extensive information comes from animal bioassays, and these are a preferable method for assessing the potential for human harm and for developing strategies for prevention of harmful exposures. Unlike pharmaceuticals, environmental contaminants were not intended for human use, and it is unethical to knowingly expose humans to these chemicals under experimental conditions to assess for harmful effects. Several studies of concordance between the perturbed developmental outcomes in experimental animal studies and the human clinical experience have been made [50–54]. In general, these studies conclude that there is concordance of developmental effects between animals and humans and that humans are *as sensitive* or *more sensitive* than the most sensitive animal species [55]. Given that there is general conservation of biological function across animal species, including humans, animal studies provide important insights into potential human harm.

However, there are limitations in how traditional toxicologic studies have been designed that decrease their utility for studying reproductive or developmental outcomes, such as insensitive strains or exposure periods, a focus on overt disease endpoints, and exposures to single chemicals at high doses rather than the mixture of low doses of chemicals more often seen by the public. While science continues to use animal studies to predict human harm, epidemiologic and clinical studies provide critical and complementary sources of information. This book covers both animal and human data to inform what we know about environmental chemicals and human reproductive and developmental health.

Layout of this book

The book starts with a general overview of concepts: the scope of exposures to environmental contaminants and examples of typical chemicals that will be covered in this book (Chapter 2). This is followed by an overview of female and male reproductive development (Chapters 3 and 4, respectively). Presentation of scientific concepts essential to understand the relationship between exposures to environmental contaminants and biological perturbations and eventually overt disease outcomes are discussed in Chapters 5, 6 and 7. Chapters 8 through 14 review the science evaluating exposures to environmental contaminants and adverse reproductive and developmental outcomes. The book ends with two chapters discussing the implications of the science – how current knowledge informs actions that can be taken at the personal level, such as through clinical advice, and at the population level, through changes to public policy systems.

This book brings together the core environmental health sciences that form a foundation of information from which to join with other disciplines and partners in related health, social, community, legal, and policy fields to broaden our understanding of the relationship between environmental contaminants and reproductive and developmental health. It is a critical time to

re-energize and refocus the environmental health work that was started in the latter part of the last century to meet the new environmental health challenges of the twenty-first century, by informing our actions to prevent those exposures that may harm human health, to secure the health of this and future generations.

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Chapter 2

Environmental contaminants and exposure

Mary A. Fox and Yutaka Aoki

Introduction

People come into contact with potentially hazardous chemical contaminants as part of daily life. Chemical contaminants arise from natural and anthropogenic sources. Chemical contaminants occur in the ambient environment such as outdoor air, surface water and soil, and in the air, dust on surfaces, food, water, and products found and used in indoor environments, e.g. workplaces, schools, and homes.

Contact or exposure to a hazardous chemical contaminant is necessary but not sufficient in itself to result in an adverse health effect. A sufficient amount of the chemical contaminant must be absorbed into the body and must reach the relevant site within the body where it may change or disrupt normal function. Absorption (or uptake) is influenced by properties of the body and properties of the chemical contaminant. Once inside the body the contaminant may be altered by metabolism, stored, or eliminated as waste.

This chapter reviews concepts of exposure and dose; identifies sources of contaminants; and describes the circumstances of human exposures. The range of contaminants of concern for reproductive health is discussed in Chapter 1. Selected examples highlighting exposure and dose topics are provided below.

Understanding exposure and dose

Basic definitions of exposure and dose

The following definitions are adapted from Zartarian *et al.* [1]. Exposure is defined as contact between a contaminant and the target (for our purposes the target of interest is the human body). Dose is defined as the amount of contaminant that enters the target over a specified time period by crossing a contact boundary. The contact boundary is a point or area of the body where exposure occurs. Dose as defined here is difficult to measure because a dose of contaminant at the contact boundary is then processed in the body, as discussed later. Body burden – the amount of a contaminant that enters the body and *remains inside* – can be more easily measurable and is used as a dose measure. Understanding exposure to environmental contaminants entails understanding the contaminants – their physical and chemical properties and where they are found – as well as the human activities that result in contact with contaminants. Various determinants of exposure to environmental contaminants are summarized in Table 2.1 and reviewed below. A discussion of dose follows.

Sources of contaminants and circumstances of exposure

Contaminant sources and disposition in the environment

Contaminants are introduced into outdoor and indoor environments from multiple sources such as manufacturing and energy production (contaminants used during production and retained in products or released as wastes or emissions), vehicular emissions, and consumer product use (e.g. insecticide applications to pets). The ultimate disposition of a contaminant in the environment will depend on its physical form (solid, liquid, or gas), chemical properties (e.g. solubility in water and reactivity) and its interactions with other natural processes. Some contaminants may be broken down quickly in ambient environments, while others persist.

Contaminants may be introduced into one or more media and may move between media. The chemical form of a contaminant may be changed as it moves through the environment. For example, mercury is found in the environment as metallic mercury and in

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Table 2.1. Important determinants of exposure.

Contaminants	Physical and chemical properties of contaminants Single or multiple contaminant(s) Amount or concentration of contaminants
Sources of contaminants	Naturally occurring or man-made Emissions including industrial and automotive Consumer products including foods and food containers, toys, electronics, lotions, cosmetics
Environmental media	Air Water Soil Dust Food Consumer products Multiple media
Exposure pathways/routes	Eating or drinking/ingestion Breathing/inhalation Touching/dermal absorption Combinations of pathways/routes
Exposure settings	At home At work At school In transit Indoors and outdoors
Exposure frequency and duration	Frequency: one-time, intermittent, continuous Duration: seconds or minutes up to lifetime
Population(s) of concern	Adult Adolescent Child Fetus Other special populations or individuals, such as those with underlying chronic conditions

organic and inorganic forms. Mercury changes forms as it moves through different environmental media. Conversion of inorganic mercury to methylmercury (organic form) occurs primarily in microorganisms in aquatic environments [2].

An important concept regarding movement of contaminants in the environment is bioaccumulation – where an organism retains contaminants at a concentration higher than that in its environment. Most often contaminants that bioaccumulate are lipophilic (fat-loving) and not easily broken down; they accumulate in fatty tissues. Biomagnification occurs when many species in the food chain bioaccumulate. Biomagnification may result in concentration increases by orders of magnitude, from environmental media to the top of the food chain. Contaminants released into the environment in only minute amounts may be biomagnified to be health hazards. Methylmercury is biomagnified up the food chain and contaminates food fish [2].

Multiple contaminants may be found in a given medium and may also occur in multiple media. For example, Fox *et al.* (2002) evaluated health risks for estimated concentrations of 148 hazardous air pollutants for a study area in Philadelphia [3]. The US EPA analyzes exposure to groups of related pesticides that are found in food and water (resulting from agricultural practices) and also used in and around the home [4]. Total exposure to a given contaminant must consider multiple sources, pathways, and routes of exposure. Total exposure to an individual or population must consider multiple contaminants in multiple media.

Humans and their environments

People interact with multiple environmental media every day, contacting indoor and outdoor air, surface

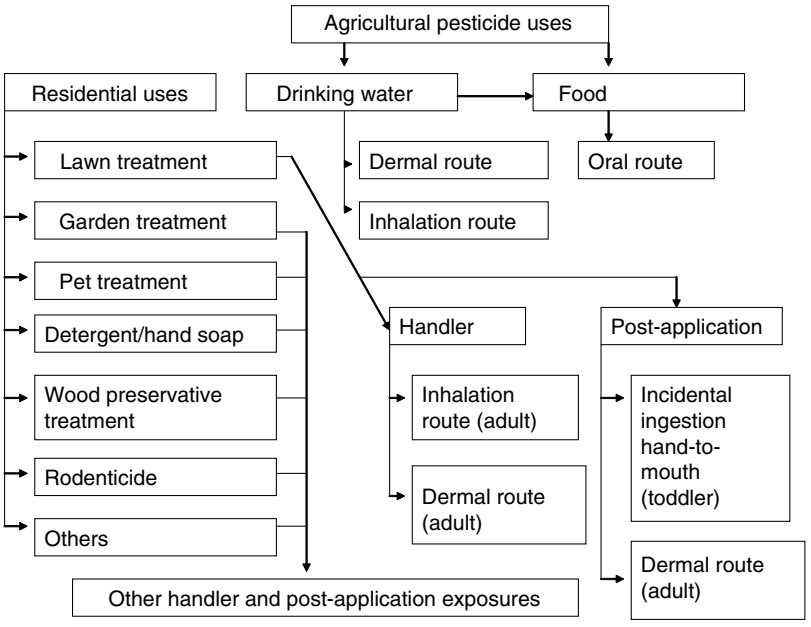

Fig. 2.1. Examples of sources, pathways, and routes of exposure to pesticides (adapted from EPA [80]).

and drinking water, soil and dust, food, and consumer products. The contaminated media people contact through breathing, eating and drinking, and touching are called exposure pathways. Exposure pathways correspond to exposure routes of inhalation, ingestion, and dermal absorption. Figure 2.1 contains some examples of exposure pathways and exposure routes resulting from agricultural and residential pesticide uses. For example, after applying a pesticide to a lawn a child playing in the grass may ingest some pesticide residue due to hand-to-mouth behavior. Exposure settings are the places where people spend time and include homes, gardens, workplaces, schools, and cars. Occurrence of contaminants will vary by setting and humans are exposed to multiple contaminants simultaneously or sequentially.

Timing of exposure: frequency and duration

Frequency and duration of exposure to environmental contaminants depends on human activities and on the occurrence of contaminants. People move through multiple exposure settings on a daily basis and will likely contact many environmental media in different geographic locations over a lifetime. Contaminants, as mentioned above, may move through multiple media and may persist in some media and not in others. Characterizing the timing of exposure requires understanding how often and how long a person is in contact with a contaminated medium and the occurrence of contaminants in that medium.

Populations of concern

Human activities and exposure settings and subsequent contaminant exposure change by age and life stage. For example, a child has greater incidental soil ingestion than an adult. A child also consumes more food and drink per unit of body weight than an adult to meet its growth and developmental needs. The workplace is an exposure setting relevant for reproductive-age adults. Table 2.2 includes information on a number of contaminants of concern for reproductive health, many of which are used in commercial production and other workplace settings. Exposures to the developing fetus through blood and amniotic fluid will depend on the mother's exposures and how the contaminants are distributed and processed in her body (more detail is given in the dose and body burden sections). In the first few months of life a breast-fed infant's exposure through food will be largely determined by its mother's body burden and a formula-fed infant will be exposed to any contaminants in the formula, in the water used to prepare its formula, or contaminants that may leach from the bottle, e.g. bisphenol-A[5]. Mouthing and crawling bring an infant into contact with contaminants in toys and house dust. Lifestyle differences such as consumption of traditional diets by indigenous populations also