Toxicants in Food Packaging and Household Plastics

Exposure and Health Risks to Consumers
Molecular and Integrative Toxicology

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Suzanne M. Snedeker
Editor

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Humana Press
Preface

The purpose of this book is to provide a comprehensive resource on what is known and what we need to know about toxicants present in food packaging materials and household plastics. This includes identifying human exposure scenarios for consumers, summarizing relevant known and emerging health effects, and recommending additional research needed to address data gaps that will allow for improved risk assessment for human populations. This book is meant to be a resource across disciplines and should be useful to toxicologists, environmental health scientists, food scientists, and regulators in the areas of food safety and environmental health sciences.

This book is unique in several ways:

**Format:** Each chapter starts with a bulleted list of **Key Take Home Points** and ends with a section on research needed to address data gaps.

**Breadth:** The toxicants included in the book range from more widely known chemicals such as bisphenol A (Chap. 1), various phthalates (Chap. 2), brominated flame retardants (Chap. 3), perfluorinated compounds (Chap. 7), and the heavy metals lead (Chap. 9), and cadmium (Chap. 10), to chemicals that are just starting to emerge as potential toxicants from food packaging and household plastics, as well as chemicals that will be entering use in the food packaging industry. This includes the alkylphenols nonylphenol and octylphenol that have been identified in food packaging and foodstuff (Chap. 5), chemicals used in UV-cured print inks (benzophenone and 4-methylbenzophenone) that can migrate through porous printed cartonboard and most secondary packaging to foods (Chap. 6), the metal antimony used as a catalyst in the manufacturing of PET-single-use beverage bottles (Chap. 8), methylnaphthalene detected in breakfast cereal box liners (Chap. 10), and nanoparticles (Chap. 4) that will be used in polymer food packaging in future and present emerging toxicological concerns. Several chapters also provide information on the challenges of the use of replacement chemicals, especially for the phthalates (Chap. 2), and the Brominated flame retardant (BFR) (Chap. 3).

**International Focus on Exposure:** Authors have been encouraged, whenever possible, to include international data on chemical exposure. This includes identification of data gaps where information on a chemical’s level in products or biomonitoring data may be limited to one or only a few geographic locations. This is especially important because of the global nature of our food supply and household consumer goods.
**Inclusion of Emerging Toxicological Endpoints:** Chapters that include Health Effects sections for chemicals have drawn on studies with a wide range of relevant toxicological endpoints, including not only traditional cancer and reproductive endpoints, but when appropriate, emerging research on endocrine disruption, cardiovascular disease, diabetes and obesity, immune function, neurological function and behavior, and transgenerational effects.

**Regulatory Approaches and Challenges in the United States and Europe:** One of the most unique aspects of this book is the inclusion of information to educate the reader on current approaches and practices used to monitor and evaluate the risk of chemicals that are present as intentional or unintentional substances in food processing and packaging (food contact materials). An overview of the use and functions of food packaging is presented in Chap. 4, Sect. 4.3, and a summary the U.S. Food and Drug Administration’s (FDA) approach to address the migration of substances from food contact materials is presented in Sect. 4.5. The final chapter of this book (Chap. 11) provides an overview of several areas, including the use, safety, and exposure to chemicals used in food contact materials, and a comparison of current regulations and risk assessment approaches used by agencies in the U.S. and Europe. Current challenges faced in evaluating chemical risk arising from use of food contact materials are highlighted, including interpreting low-dose effects (non-monotonic dose responses), mixture effects, developmental origins of disease, and transgenerational effects.

**New Approaches:** This book focuses on a small number of the chemicals used in food packaging and in the manufacturing of household plastics. For thousands of other chemicals, we lack basic toxicological risk information. Realistically, new approaches will be needed, including high-throughput screening, to better identify and assess the toxicological risk of chemicals that are present in household plastics and food packaging materials. Some of these approaches are outlined in Chap. 11, Sect. 11.5.6.

In closing, I would like to thank all the contributing authors for their most precious resource, their time, in developing the concepts and content of their chapters. Their efforts have been outstanding. I thank them for developing carefully thought out and researched chapters that truly make a significant contribution to our understanding of exposure and health risks of toxicants associated with food packaging and household plastics, how they are regulated, and the new avenues that need to be pursued to address what we still need to know about exposure and health effects in human populations.

Suzanne M. Snedeker
## Contents

1. **Human Health Effects of Bisphenol A**
   Thaddeus T. Schug and Linda S. Birnbaum

2. **Phthalates in Food Packaging, Consumer Products, and Indoor Environments**
   Kathryn M. Rodgers, Ruthann A. Rudel and Allan C. Just

3. **Brominated Flame Retardants and Their Replacements in Food Packaging and Household Products: Uses, Human Exposure, and Health Effects**
   Susan D. Shaw, Jennifer H. Harris, Michelle L. Berger, Bikram Subedi and Kurunthachalam Kannan

4. **Nanoparticles in Polymer Nanocomposite Food Contact Materials: Uses, Potential Release, and Emerging Toxicological Concerns**
   Karthik V. Pillai, Piper R. Hunt and Timothy V. Duncan

5. **The Alkylphenols Nonylphenol and Octylphenol in Food Contact Materials and Household Items: Exposure and Health Risk Considerations**
   Suzanne M. Snedeker and Anthony G. Hay

6. **Benzophenone UV-Photoinitiators Used in Food Packaging: Potential for Human Exposure and Health Risk Considerations**
   Suzanne M. Snedeker

7. **Perfluorinated Compounds in Food Contact Materials**
   Penelope A. Rice, Omari J. Bandele and Paul Honigfort

8. **Antimony in Food Contact Materials and Household Plastics: Uses, Exposure, and Health Risk Considerations**
   Suzanne M. Snedeker
9 Lead in Household Products ........................................ 231
Joseph Laquatra

10 Methylnaphthalene in Food Packaging and Cadmium in Food
Packaging and Household Items: Overview of Exposure,
Toxicology, Regulatory Aspects, and Research Needs. ........... 245
Suzanne M. Snedeker

11 Food Contact Materials: Practices, Agencies and Challenges ... 265
Jane Muncke

Editor Biography ............................................................ 299

Index .................................................................................. 301
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Chapter 1

Human Health Effects of Bisphenol A

Thaddeus T. Schug and Linda S. Birnbaum

Abstract  Bisphenol A (BPA) is a high production endocrine disrupting chemical found in numerous consumer products. BPA has been used commercially since 1957 to make hard polycarbonate plastics and epoxy resins used in food-can linings, cash-register receipts, and dental resins. The ubiquity of BPA in our environment results in exposure to this chemical daily in human populations. But controversy remains regarding how much BPA humans actually ingest or otherwise encounter. Many laboratory animal and human studies have linked exposures to BPA, a hormone mimicking chemical, to adverse health effects, including altered behavior and obesity in children, reproductive abnormalities, cardiovascular changes, and various cancers. However, there have been considerable inconsistencies in the outcomes from these studies with respect to the nature of the adverse health effects observed, and questions as to whether the BPA dose at which they occur are within the range of non-occupational human exposures. This chapter reviews the latest research on BPA, focusing on human exposure, discussions of biomonitoring studies and toxicokinetic models, human health effects, and research needs. We also include illustrative examples of animal models that address whether BPA-exposure is associated with changes in certain health endpoints.
**Keywords** Bisphenol A · Endocrine disruption · Developmental toxicity · Pharmacokinetics · Biomonitoring

### 1.1 Key Take Home Points

- Bisphenol A exposure is ubiquitous in our environment and it is found in our bodies.
- Bisphenol A has estrogenic and other properties and is considered to be an endocrine disrupting chemical.
- Bisphenol A is a non-persistent chemical and is quickly metabolized by the body.
- Bisphenol A exposure has been tied to many adverse health effects in animal models and humans including: prostate cancer, breast cancer, obesity, diabetes, cardiovascular problems, some neurobehavioral effects, including anxiety, as well as reproductive effects.
- Enhanced biomonitoring studies are needed to better evaluate bisphenol A exposure and health outcomes in humans.

### 1.2 Introduction

Manufacturers produce more than 8 billion pounds of BPA every year, making it one of the most common industrial chemicals produced worldwide (Rubin 2011). Plastics made with BPA are used in many consumer products, including food and beverage containers, toys, eyeglasses, computers, kitchen appliances, and medical equipment. Epoxy resins containing the chemical are used in dental work and in metal coatings for food cans, pipes, cars, dairy equipment, office equipment, and other metal products. BPA and its derivatives are also used in flame retardants (tetrabromobisphenol A), in engineering applications such as laminates for printed circuit boards, and as color developers in thermal receipt paper (Birnbaum et al. 2012). Some, but not all, plastics that are marked with recycle codes “3” or “7” may be made with BPA.

BPA has been detected in air, soil, water, landfill leachate, and the human body. The chemical has been shown to leach into foods and beverages from some types of food packaging (e.g., polycarbonate containers and epoxy lining of metal cans) and reusable containers (von Goetz et al. 2010). People also may be exposed to BPA through skin contact, inhalation, dental fillings, and occupational exposures. BPA has been found in human serum, milk, saliva, urine, and amniotic fluid (Vandenberg et al. 2009, 2010, 2012).
The ubiquity of BPA in the environment and in the human body has led to concerns about potential adverse health effects. BPA’s chemical structure allows it to fit in the estrogen receptor (ER) binding pocket, and BPA is considered to act as an endocrine disruptor. BPA binds to both nuclear and cell membrane ERs; at higher levels, BPA acts as an androgen receptor (AR) antagonist, interacts with the thyroid receptor (Vandenberg et al. 2009) and induces the peroxisome proliferator-activated receptor gamma (PPARγ) (Kwintkiewicz et al. 2010; Wang et al. 2012). Animal and human research has associated BPA with many health problems including infertility, weight gain, behavioral changes, early-onset puberty, prostate and mammary gland cancers, cardiovascular effects, obesity, and diabetes (Birnbaum et al. 2012; Schug et al. 2012).

1.3 Chemical and Biological Properties of Bisphenol A

BPA (C₁₅H₁₆O₂; CAS No. 80-05-7) is one of the most common industrial chemicals produced worldwide. BPA was first synthesized by the Russian chemist A.P. Dianin in 1891. The compound consists of two conjoined phenol functional groups, and is synthesized by the condensation of acetone (hence the suffix A in the name) with two equivalents of phenol (Fig. 1.1). BPA is used in polycarbonate plastic to enhance product strength, durability, and transparency. BPA is used in epoxy resins to extend the shelf-life of canned foods as well as in dental composite resins used to fill most cavities (Kingman et al. 2012). BPA also functions as a color developer in carbonless thermal receipt paper.

1.3.1 Endocrine Disrupting Properties of Bisphenol A

By virtue of its binding ability to steroid receptors, BPA was hypothesized to be estrogenic. These properties of BPA were first demonstrated in studies using ovariectomized rats in the 1930s during a search for synthetic estrogens. However, BPA was abandoned for pharmaceutical use when diethylstilbestrol (DES) was determined to be a much more potent estrogen (Vandenberg et al. 2010). Biochemical assays have since shown that BPA does fit within the ER binding pocket and that it binds to both ERα and ERβ, with approximately tenfold higher affinity for ERβ (Gould et al. 1998; Kuiper et al. 1998). However, the binding affinity of BPA for both ER isoforms is nearly 10,000-fold weaker than that of estradiol (EC₅₀ 2–7 × 10⁻⁷ vs. 1–6 × 10⁻¹³ M for estradiol) (Andersen et al. 1999; Kuiper et al. 1998). A recent study suggests that BPA can function as an ER agonist at higher concentrations [≥10 nanomolar (nM)] and as antagonist at lower concentrations (≤10 nM). These paradoxical actions are likely cell-type specific and may
be in part mediated by BPA activation of the AF-2 domain of ERα, not the classical ligand-binding domain (Li et al. 2012).

Studies have shown that BPA also binds to membrane-bound forms of the ER (mER) and with high affinity to a transmembrane ER receptor called G protein-coupled receptor 30 (GPR30) (Watson et al. 2007; Thomas and Dong 2006; Vinas and Watson 2013; Wetherill et al. 2007). In addition to its estrogenic activity, there is mounting evidence that BPA interacts with other nuclear receptors, albeit at higher concentrations. BPA, for example, binds to the thyroid hormone receptor (TR) with lower affinity than the ER (Moriyama et al. 2002). Studies also have shown that BPA binds to the ubiquitous aryl hydrocarbon receptor (AhR) (Pocar et al. 2005), which mediates toxicity through several signaling pathways (Pocar et al. 2005; Barouki et al. 2012). Other evidence suggests that BPA and its derivatives act as obesogens by inducing adipocyte differentiation and adipogenic marker genes in preadipocytes through various mechanisms (Masuno et al. 2005; Chamorro-Garcia et al. 2012).

### 1.4 Human Exposure, Biomonitoring, and Metabolism of Bisphenol A

#### 1.4.1 Human Exposure to Bisphenol A

Since the 1990s, many studies have been dedicated to determining which consumer products contain BPA, and how much is released from these products into food and beverages under normal conditions of use (von Goetz et al. 2010). In particular, studies have focused on the levels of BPA released from baby bottles, food-contact papers, and epoxy resins used both for dental sealants and the linings of metal food cans (Schug et al. 2012; Carwile et al. 2011). These studies confirm
that the majority of canned foods contain measurable levels of BPA. A wide range of concentrations were reported, leading scientists to estimate that current human exposures from canned and bottled goods could be in the nanogram per kilogram (ng/kg) range for children and adults and the low microgram per kilogram (µg/kg) range for bottle-fed infants (von Goetz et al. 2010). However, recent moves by manufacturers in the United States (U.S.) and Europe to remove BPA from baby bottles and infant feeding cups have reduced the risks of exposure to infants. Other recent studies have shown that thermal papers (Geens et al. 2012) and dental procedures (Kingman et al. 2012) can contribute to human exposures.

1.4.2 Biomonitoring of Bisphenol A

The ability to accurately measure exposure to BPA is critical to assessing the chemical’s health effects. Measuring BPA in urine is generally considered the most reliable indicator of BPA exposure because it integrates exposure over a recent time period, whereas BPA concentrations in blood are thought to reflect only current exposures due to the chemical’s short half-life and evidence that BPA does not bioaccumulate. However, serum measurements are currently the most meaningful way to assess single point in time levels of unconjugated BPA, also known as free BPA, which is the form that is considered to be more biologically active because it can bind to ER and other nuclear receptors (Ye et al. 2011). This is an area that requires further investigation because some posit that rapid processing of BPA in the gastrointestinal tract and the liver during first pass metabolism results in very low levels of circulating parent (and thus biologically active) BPA entering the bloodstream, precluding BPA from causing disease. However, more than 30 reports have shown human blood levels of BPA in the range of 0.1–4.0 ng per milliliter (ml) (Taylor et al. 2011; Vandenberg et al. 2010). Although in some cases consistent results have been reported across studies, these findings have spurred debate in the scientific community about the likelihood that free BPA blood measurements are compromised by contamination (Calafat 2010; Ye et al. 2012). For example, small amounts of BPA may leach into samples from syringes, containers, tubing, or even water used in experiments. In addition, instruments used to measure levels of BPA may be incorrectly calibrated. The National Institute of Environmental Health Sciences (NIEHS) is currently leading a multi-agency effort to improve measurement procedures for detection of BPA in blood (Birnbaum et al. 2012).

While the National Health and Nutrition Examination Survey (NHANES) (Stahlhut et al. 2009; Calafat et al. 2008), a statistically-based sampling of the U.S. population conducted every 2 years, and several birth cohorts, such as the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study cohort (Castorina et al. 2010), have contributed useful data on BPA exposure