



Second Edition

# Reproductive and Developmental Toxicology

Edited by Ramesh C. Gupta





# REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

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SECOND EDITION

*Edited by*

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S E C T I O N I

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GENERAL



# Introduction

*Ramesh C. Gupta*

Unsuccessful conception and adverse pregnancy outcomes have occurred since the inception of life. The etiology of such disappointing events can often be attributed to common factors such as malnutrition, hyperthermia, or a stressful environment at home or at the workplace. In addition, exposure to biotoxins, chemical toxicants, or radiation seems to be involved in infertility, miscarriage, and birth defects. A single factor or a combination of these factors can exert deleterious effects on male and/or female reproductive performance and on the mother, placenta, or conceptus. Homeostatic maintenance of human and animal/wildlife species requires proper function of the male and female reproductive systems, and normal development of offspring.

Reproductive and developmental toxicology is a very complex subject because of continuous changes taking place in the mother, placenta, and the unborn. The complexity of reproductive and developmental toxicity involves many variables, including species, gender, developmental stage, diet, genetic polymorphisms, environmental, and many other factors. Pregnant women, the unborn, infants, and toddlers constitute unique populations with greater vulnerability in terms of sensitivity to chemicals and biotoxins. Even foods such as black tea and coffee can cause developmental effects if consumed in excess during gestation.

Exposure of the developing organism to chemicals can occur in utero or through the mother's milk or contaminated food. In general, it is believed that developing organisms are more sensitive than adults to the toxic effects of chemicals because of limited defense and detoxifying mechanisms. In particular, the nervous and reproductive systems may be more vulnerable to the toxic insult of chemicals due to incomplete blood–brain and blood–testes barriers. Compelling evidence suggests that in utero or early postnatal exposure to chemicals not only damages the developing organism, but can also predispose an individual to development of devastating diseases like diabetes, metabolic syndrome, Alzheimer's disease, or Parkinson's disease later in life.

Toxicological problems related to reproductive and developmental systems have been recognized for centuries, but this area of toxicology has received enormous attention since the thalidomide incident. From 1957 to 1961, thousands of pregnant women around the world received thalidomide for morning sickness. More than 10,000 children, exposed in utero to thalidomide during the first trimester of gestation, were born with a variety of severe birth defects, mainly phocomelia and amelia. Other anomalies related to thalidomide syndrome involved eyes, ears, and the central nervous system. From this tragedy, with exhaustive efforts over half a century, scientists learned that: (1) wide species differences exist due to unknown factors, (2) the period of exposure is crucial for expression of teratogenicity, and (3) thalidomide exerts a variety of effects through multiple mechanisms, although we are still far from understanding the exact mechanism of teratogenicity. Presently, thalidomide and its analogs are available on the market for indications in leprosy, Crohn's disease, human immunodeficiency virus infection, multiple myeloma, and vascular disorder; however, they are not prescribed for women who are pregnant or trying to get pregnant.

In another incident, methylmercury was involved in Minamata disease in Japan, affecting approximately 3000 people after consumption of contaminated fish, from the late 1950s to the mid-1960s. In the early 1970s, more than 10,000 people died and 100,000 suffered permanent brain damage in Iraq by consuming "wonder wheat" imported from Mexico that was treated with methylmercury as a fungicide. In both incidents, offspring of mothers exposed to methylmercury suffered from severe malformations, cognitive impairment, and behavioral disorders, including "quiet baby syndrome." Because of the catastrophic effects of Minamata disease, the Japanese government has established the "National Institute for Minamata Disease" for bio-monitoring and surveillance of mercury exposure to avoid future cases.



Following the thalidomide tragedy, drug safety efforts were intensified throughout the world; however, only 200 of the more than 80,000 chemicals on the market have been tested for toxicity and safety. Developmental and reproductive toxicity testing in animals has been a vital component of the drug development process for humans since the late 1940s. Currently, this set of nonclinical studies in animals is required for drug approval by regulatory agencies, such as the US Food and Drug Administration (US FDA), the Organization for Economic and Cooperative Development (OECD), the Japan Pharmaceutical Manufacturers Association (JPMA), and other such agencies around the world. Currently, many associations (the Pharmaceutical Manufacturers Association, the European Federation of Pharmaceutical Industries Association, and the JPMA), professional organizations (the Society of Toxicology and its specialty section on Reproductive and Developmental Toxicology, the Teratology Society and the International Federation of Teratology Societies), and regulatory agencies (primarily from the United States, Europe, and Japan) are actively engaged in drug safety evaluation to avoid adverse reproductive and developmental effects. In this context, the International Federation of Pharmaceutical Manufacturers Association plays a pivotal role in bringing together the regulatory authorities of the United States, Europe, Japan, and elsewhere. In the United States, agencies include the Consumer Product Safety Commission, the US Environmental Protection Agency, the US FDA, the US Department of Agriculture, the Agency for Toxic Substance and Disease Registry, the National Toxicology Program, the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health, and the Occupational Safety and Health Administration. In Europe, the main agencies for safety evaluation include the OECD and REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals).

Developmental and reproductive toxicity risk assessment criteria differ from country to country, and the International Conference on Harmonization and related agencies take an active part in dealing with such disparities. The objective of all these regulatory agencies is to identify reproductive and developmental hazards and to ensure the safety of drugs and chemicals.

This book, *Reproductive and Developmental Toxicology*, provides extensive coverage of safety evaluation of new pharmaceutical compounds and risk characterization of chemicals using the guidelines of the agencies listed earlier.

It is well established that environmental and genetic factors in relation to chemical toxicity have changed significantly in the last 50 years. This is partly due to increased use of chemicals (such as therapeutic drugs,

industrial chemicals, and environmental pollutants), greenhouse gases, and global warming. Alcohol, smoke, illicit drugs, and anticonvulsants are among the most frequently encountered reproductive and developmental toxicants. These substances, along with many others, cross the placental barrier easily and can lead to a variety of effects, including intrauterine growth restriction, preterm birth, and spontaneous abortion.

Environmental contaminants, such as polychlorinated biphenyls, and brominated flame retardants, bisphenol A, phthalates, perfluorooctanoic acid, pesticides, lead in drinking water (for example, Flint, Michigan) and in toys, and cadmium and zinc in jewelry imported from China, and high levels of cadmium in drinking glasses and dinnerware, have raised serious concerns about adverse health effects in general as well as reproductive and developmental effects in particular. The current concern about "Toxic Childhood" in "Toxic America" is real and the community as a whole has no choice but to face the challenges of the 21st century to minimize chemical exposure.

Each year, approximately 3% of babies in the United States are born with life-threatening birth defects. One of the most common human birth defects is neural tube defects (NTDs), due to failure of neural tube closure, often resulting in anencephaly, exencephaly, and spina bifida. Although the etiology of NTDs is complex, chemical agents (antiepileptic drugs, thalidomide, folate antagonists, etc.), in addition to genetic and environmental factors, appear to be involved.

Today's advanced technologies allow biomonitoring of chemical (therapeutic and environmental) residues at parts per billion or parts per trillion in biological tissues and fluids. In recent investigations, 10,000 babies were examined and more than 200 chemicals were found in the umbilical cord. On the one hand, the presence of a chemical in cord blood does not prove the chemical is harmful to the unborn; on the other hand, its harmful effects cannot be ruled out unless proven safe based on toxicity testing. In essence, every chemical is safe unless proven toxic. Molecular toxicology offers novel biomarkers and sensitive end points of cellular and molecular damage (biochemical, neurochemical, or histopathological) to the fetus that are particularly useful in reproductive and developmental toxicity and safety testing (Gupta, 2014). In vitro, in vivo, and in silico models, national and international guidelines for toxicity testing, and international harmonization in risk assessment criteria are necessary for safety evaluation of chemicals and drugs. Pharmacokinetics/toxicokinetics and physiologically based pharmacokinetics of drugs/toxicants seem to differ substantially in male versus female, and more so in pregnant versus nonpregnant, as well as in young versus old; therefore, special attention should be paid when dealing with pregnancies