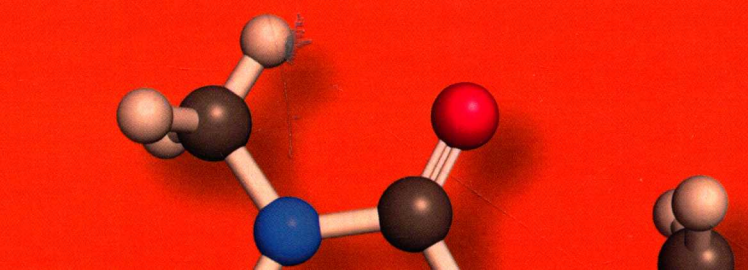
Second Edition

Reproductive and Developmental Toxicology

Edited by Ramesh C. Gupta



REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

SECOND EDITION

Edited by

RAMESH C. GUPTA, DVM, MVSc, PhD, DABT, FACT, FACN, FATS

Professor and Head, Toxicology Department

Breathitt Veterinary Center, Murray State University

Hopkinsville, KY, United States

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REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

List of Contributors

Manoj Aggarwal, BVSc, MVSc, PhD Human Health Assessment, Dow AgroSciences, European Development Centre, Abingdon, Oxon, United Kingdom

Shruti Agrawal, MS, PhD National Institute of Pharmaceutical Education and Research, Raebareli, Uttar Pradesh, India

Arturo Anadón, DVM, PhD, DipECVPT Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

Gregory J. Anger, PhD Scientific Advisor, Janssen Pharmaceuticals, Toronto, ON, Canada

Anthony E. Archibong, PhD Department of Physiology, Meharry Medical College, Nashville, TN, United States

Irma Ares Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

Michael Aschner, PhD Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, United States

Daiana S. Avila, PhD Federal Pampa University, Rio Grande do Sul, Brazil

Denise C. Bailey, BS Department of Biology, King University, Bristol, TN, United States

Nancy C. Baker, PhD Contractor to the National Center for Computational Toxicology, Durham, NC, United States

Norman J. Barlow, DVM, PhD, MBA, MLD Janssen Pharmaceutical Companies of Johnson and Johnson, Spring House, PA, United States

Sudheer Beedanagari, PhD Alkermes Inc., Waltham, MA, United States

Karyn Bischoff, DVM, MS Population Medicine and Diagnostic Sciences, Cornell University, Ithaca, NY, United States; New York State Animal Health Diagnostic Center, Cornell Unviersity, Ithaca, NY, United States

William M. Bracken, PhD, DABT Preclinical Safety, Global Pharmaceutical R&D, AbbVie, North Chicago, IL, United States

Emily Brehm, BS Department of Comparative Biosciences, University of Illinois, Urbana, IL, United States

Richard M. Breyer, PhD Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, United States

Susan Bright-Ponte, DVM, MPH Division of Veterinary Product Safety, Center for Veterinary Medicine, US Food and Drug Administration, Rockville, MD, United States

Luisa Campagnolo, MSc, PhD Department of Biomedicine and Prevention, University of Tor Vergata, Rome, Italy

Edward W. Carney[†], PhD The Dow Chemical Company, Midland, MI, United States

Victor Castellano, DVM, PhD Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

Sandrine Fleur Chebekoue, MSc Occupational and Environmental Health, School of Public Health, University of Montreal, Montreal, QC, Canada

Catheryne Chiang, MS Department of Comparative Biosciences, University of Illinois, Urbana, IL, United States

Wei-Chun Chou, PhD National Institute of Environmental Health Sciences, National Health Research Institutes, Zhunan, Taiwan

Supratim Choudhuri, PhD Division of Biotechnology and GRAS Notice Review, FDA/CFSAN/OFAS, College Park, MD, United States

Jane K. Cleal, BSc(Hons), PhD Developmental Origins of Health and Disease, School of Medicine, University of Southampton, Southampton General Hospital, Southampton, United Kingdom

Robert W. Coppock, BS, DVM, MS, PhD, DABVT Toxicologist and Associates Ltd, Vegreville, AB, United States

Lucio G. Costa, PhD, ATS Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, United States; Department of Neuroscience, University of Parma, Parma, Italy

Margarita Curras-Collazo, PhD Department of Cell Biology and Neuroscience, University of California, Riverside, CA, United States

João Batista Teixeira da Rocha, PhD Departamento de Bioquímica, Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, Brazil

Rosane S. Da Silva, PhD Laboratory of Neurochemistry and Psychopharmacology, Department of Cellular and Molecular Biology, Pontifícia Universidade Católica do Rio Grande do Sul Brazil, Porto Alegre, Brazil

T. Zane Davis, PhD Poisonous Plant Research Laboratory, Agricultural Research Service, US Department of Agriculture, Logan, UT, United States

Robin B. Doss, BS, LVT Murray State University, Hopkinsville, KY, United States

Margitta M. Dziwenka, DVM Toxicologist and Associates Ltd, Vegreville, AB, United States

[†] Deceased.

Brian Enright Preclinical Safety, Global Pharmaceutical R&D, AbbVie, North Chicago, IL, United States

Per Eriksson, PhD Department of Physiology and Developmental Biology, Environmental Toxicology, Uppsala University, Uppsala, Sweden

Carmen Estevan, PhD Unidad de Toxicología y Seguridad Química, Instituto de Bioingeniería, Universidad Miguel Hernández de Elche, Elche, Spain

Timothy J. Evans, DVM, MS, PhD, DABVT, DACT Department of Veterinary Pathobiology, Veterinary Medical Diagnostic Laboratory, College of Veterinary Medicine, University of Missouri, Columbia, MO, United States

Bengt Fadeel, MD, PhD Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Anna M. Fan, PhD, DABT Independent Researcher, Danville, CA, United States

Ali S. Faqi, DVM, PhD, DABT, Fellow ATS Developmental and Reproductive Toxicology, MPI Research Inc., Mattawan, MI, United States

Marcelo Farina, PhD Departamento de Bioquímica, Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, Brazil

Suzanne E. Fenton, PhD Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Durham, NC, United State

Maureen H. Feuston, PhD (Retired) Preclinical Safety, Sanofi R&D, Bridgewater, NJ, United States

Ayhan Filazi, DVM, PhD Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Ankara University, Ankara, Turkey

Vanessa A. Fitsanakis, PhD Department of Biology, King University, Bristol, TN, United States

John Flaskos, BSc, MSc, PhD Laboratory of Biochemistry and Toxicology, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Jodi A. Flaws, PhD Department of Comparative Biosciences, University of Illinois, Urbana, IL, United States

Swaran J.S. Flora, MS, PhD National Institute of Pharmaceutical Education and Research, Raebareli, Uttar Pradesh, India

Vekataseshu K. Ganjam, BSc, BVSc, MS, PhD, MA(Penn, hc) Departments of Biomedical Science and Veterinary Medicine and Surgery, University of Missouri, Columbia, MO, United States

Dale R. Gardner, PhD Poisonous Plant Research Laboratory, Agricultural Research Service, US Department of Agriculture, Logan, UT, United States

Nicole M. Gardner, PhD Department of Pathology, University of Iowa-Carver College of Medicine, Iowa City, IA, United States

Ramesh C. Garg, BVSc, MVSc, PhD, DABT Global Pharmaceutical R&D, AbbVie, North Chicago, IL, United States

Vincent F. Garry, MD, MS, DABT Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, MN, United States

Janee Gelineau-van Waes, PhD, DVM Department of Pharmacology, Creighton University School of Medicine, Omaha, NE, United States

Keith M. Godfrey, BM, PhD, FRCP MRC Lifecourse Epidemiology Unit and NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, United Kingdom

Consuelo Guerri, PhD Cell Pathology Laboratory, Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain

Marina Guizzetti, PhD Department of Behavioral Neuroscience, Oregon Health and Science University, Portland, OR, United States; VA Portland Health Care System, Portland, OR, United States

Kavita Gulati, MSc, PhD Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

Mary Gulumian, BSc, MSc, PhD National Institute for Occupational Health and the University of the Witwatersrand, Johannesburg, South Africa

Pawan K. Gupta, PhD, PostDoc(USA), PGDCA, HonDSc, MSc, VM & AH, BVSc, FASc AW, FST, FAEB, FACVT(USA), FNAVSc, Gold Medalist Society of Toxicology of India, Bareilly, Uttar Pradesh, India; Academy of Sciences for Animal Welfare, Bareilly, Uttar Pradesh, India

Ramesh C. Gupta, DVM, MVSc, PhD, DABT, FACT, FACN, FATS Breathitt Veterinary Center, Murray State University, Hopkinsville, KY, United States

Rekha K. Gupta, MD School of Medicine, University of Louisville, Louisville, KY, United States

Sharon M. Gwaltney-Brant, DVM, PhD, DABVT, DABT Veterinary Information Network, Mahomet, IL, United States

Jeffrey O. Hall, DVM, PhD Utah State Veterinary Diagnostic Laboratory, Utah State University, Logan, UT, United States

Deborah K. Hansen, PhD Division of Personalized Nutrition and Medicine, FDA/National Center for Toxicological Research, Jefferson, AR, United States

Alan J. Hargreaves, BSc, PhD School of Science and Technology, Nottingham Trent University, Nottingham, United Kingdom

Kenneth J. Harris, PhD Department of Biochemistry and Cancer Biology, Meharry Medical College, Nashville, TN, United States

Alan M. Hoberman, PhD, DABT, Fellow ATS Reproduction, Developmental and Juvenile Toxicology, Charles River, Horsham Research, Horsham, PA, United States

Karin S. Hougaard, BM, MSc, PhD Danish Nanosafety Centre, National Research Centre for the Working Environment, Copenhagen, Denmark; Department of Public

Health, Section for Occupational and Environmental Health, University of Copenhagen, Copenhagen, Denmark

Sinan Ince, DVM, PhD Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Afyon Kocatepe University, Afyon, Turkey

Amy L. Inselman, PhD Division of Personalized Nutrition and Medicine, FDA/National Center for Toxicological Research, Jefferson, AR, United States

Poorni Iyer, DVM, PhD, DABT Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA, United States

Nicklas R. Jacobsen, MSc, PhD Danish Nanosafety Centre, National Research Centre for the Working Environment, Copenhagen, Denmark

Valerian E. Kagan, PhD, DSc Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA, United States

Starling Kalpana, BVSc, MVSc, PhD National Research Centre on Meat, Hyderabad, Telangana, India

Kotaro Kaneko, PhD Division of Biotechnology and GRAS Notice Review, FDA/CFSAN/OFAS, College Park, MD, United States

Anumantha Kanthasamy, PhD Department of Biomedical Sciences, Iowa Center for Advanced Neurotoxicology, Iowa State University, Ames, IA, United States

Arthi Kanthasamy, PhD Department of Biomedical Sciences, Iowa Center for Advanced Neurotoxicology, Iowa State University, Ames, IA, United States

Vesa Karttunen, PhD School of Pharmacy/Toxicology, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland

Hyung Sik Kim, PhD Division of Toxicology, School of Pharmacy, Sungkyunkwan University, Suwon, Korea

Thomas B. Knudsen, PhD National Center for Computational Toxicology, US Environmental Protection Agency, Durham, NC, United States

Prasada Rao S. Kodavanti, PhD Neurotoxicology Branch, Toxicity Assessment Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Durham, NC, United States

Kannan Krishnan, PhD, DABT, FATS, FCAHS Risk Sciences International, Ottawa, ON, Canada

Shaila Kulkarni, MS Cellular Toxicology, Investigative Laboratory Sciences, Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, Kenilworth, NJ, United States

Rajiv Lall, MS Vets Plus Inc., Menomonie, WI, United States

Michelle A. Lasher, MS, LVT Murray State University, Hopkinsville, KY, United States

Scott B. Laudert, BS, MS, PhD Micronutrients, Indianapolis, IN, United States

Byung-Mu Lee, DrPH Division of Toxicology, School of Pharmacy, Sungkyunkwan University, Suwon, Korea

Jessica Legradi, PhD Department Environment and Health, VU Amsterdam, Amsterdam, The Netherlands

Maxwell C.K. Leung, PhD National Center for Computational Toxicology, US Environmental Protection Agency, Durham, NC, United States

Elise M. Lewis, PhD Developmental and Neurobehavioral Toxicology, Preclinical Services, Charles River Laboratories, Horsham, PA, United States

Rohan M. Lewis, BSc(Hons), PhD Faculty of Medicine, University of Southampton, Southampton, United Kingdom

Xin Li, BS Neuroscience Graduate Program, Vanderbilt University Medical Center, Nashville, TN, United States

Pinpin Lin, PhD, DABT National Institute of Environmental Health Sciences, National Health Research Institutes, Zhunan, Taiwan

Bommanna G. Loganathan, PhD, ACSF Department of Chemistry and Watershed Studies Institute, Murray State University, Murray, KY, United States

Jan Ludvig Lyche, CMV, PhD, European Registered Toxicologist (ERT) Department for Food Safety and Infection Biology, Norwegian University of Life Science, Oslo, Norway

Robert C. MacPhail, PhD Department of Biomedical Sciences and Pathobiology, Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, VA, United States

Brinda Mahadevan, PhD Global Preclinical Development, Innovation and Development, Established Pharmaceuticals, Abbott Laboratories, Mumbai, India

Jitendra K. Malik, BVSc & AH, MVSc, PhD Division of Pharmacology and Toxicology, Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Ana Paula Marreilha dos Santos, PhD Faculdade de Farmácia, Universidade de Lisboa, Lisbon, Portugal

Maria Aranzazu Martínez Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

Maria Rosa Martínez-Larrañaga, DSc, PhD Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

David McClary, DVM, MS, DACT Dairy Business Unit, Elanco Animal Health, Eli Lilly and Co., Greenfield, IN, United States

Fabiano P. Menezes, MSc Laboratory of Neurochemistry and Psychopharmacology, Department of Cellular and Molecular Biology, Pontifícia Universidade Católica do Rio Grande do Sul Brazil, Porto Alegre, Brazil

Jerrold S. Meyer, PhD Department of Psychological and Brain Sciences, University of Massachusetts, Amherst, MA, United States

Dejan Milatovic, PhD Independent Researcher, Charlottesville, VA, United States

Ida R. Miller Mukherjee, PhD Institute of Psychiatry and Human Behaviour, Bambolim, Goa, India

Ali Mustafa Mohammed, MSc School of Pharmacy/ Toxicology, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland

Peter Møller, MSc, DMSc, PhD Section of Occupational and Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Thomas J. Montine, MD, PhD Department of Pathology, Stanford University, Stanford, CA, United States

Mingwei Ni, MD, PhD Department of General Surgery, Mayo Clinic, Rochester, MN, United States

Efstathios Nikolaidis, DVM, PhD Laboratory of Pharmacology, Veterinary School, Aristotle University of Thessaloniki, Thessaloniki, Greece

Meliton N. Novilla, DVM, MS, PhD, DACVP, FIATP Shin Nippon Biomedical Laboratories USA, Ltd, Everett, WA, United States

Stephanie Padilla, PhD Integrated Systems Toxicology Division, Office of Research and Development, US Environmental Protection Agency, Durham, NC, United States

Carlos M. Palmeira, PhD Department of Life Sciences and Center for Neurosciences and Cell Biology, University of Coimbra, Coimbra, Portugal

David Pamies, PhD Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, United States

Kip E. Panter, PhD Poisonous Plant Research Laboratory, Agricultural Research Service, US Department of Agriculture, Logan, UT, United States

María Pascual, PhD Cell Pathology Laboratory, Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain

Claudia Pellacani Department of Neuroscience, University of Parma, Parma, Italy

Brian J. Piper, PhD, MS Department of Basic Sciences, Commonwealth Medical College, Scranton, PA, United States

Micheline Piquette-Miller, BSc Pharmacy, PhD Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada

Vadim B. Popov, PhD, DSc Research Institute of Hygiene, Occupational Pathology and Human Ecology, Federal State Unitary Enterprise, Federal Medical Biological Agency of Russia, St Petersburg, Russia

M. Margaret Pratt, PhD Integrated Risk Information System, National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Washington, DC, United States

Galina A. Protasova, PhD Research Institute of Hygiene, Occupational Pathology and Human Ecology, Federal State Unitary Enterprise, Federal Medical Biological Agency of Russia, St Petersburg, Russia

Nishant Rai Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

João Ramalho-Santos, PhD Center for Neurosciences and Cell Biology, Department of Life Sciences, University of Coimbra, Coimbra, Portugal

Aramandla Ramesh, PhD Department of Biochemistry and Cancer Biology, Meharry Medical College, Nashville, TN, United States

Arunabha Ray, PhD National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health, Bethesda, MD, United States

Kausik Ray, PhD National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health, Bethesda, MD, United States

Aiguo Ren, MD, PhD Ministry of Health Key Laboratory of Reproductive Health, Institute of Reproductive and Child Health, Peking University, Beijing, China

Stephen J. Renaud, BSc, PhD Department of Anatomy and Cell Biology, Western University, London, ON, Canada

Ronald T. Riley, PhD Toxicology and Mycotoxin Research Unit, Agricultural Research Service, US Department of Agriculture, Athens, GA, United States

Drucilla J. Roberts, MA, MD Department of Pathology, Massachusetts General Hospital, Boston, MA, United States

Lu Rongzhu, PhD Department of Preventive Medicine, School of Medical Science and Laboratory Medicine, Jiangsu University, Zhenjiang, China

Magdalini Sachana, DVM, PhD Environment, Health and Safety Division, Environment Directorate, OECD, Paris, France

Kai M. Savolainen, MD, PhD Nanosafety Research Centre, Finnish Institute of Occupational Health, Helsinki, Finland

Lilia V. Shabasheva Research Institute of Hygiene, Occupational Pathology and Human Ecology, Federal State Unitary Enterprise, Federal Medical Biological Agency of Russia, St Petersburg, Russia

Kathleen T. Shiverick, BS, PhD Department of Pharmacology and Therapeutics, University of Florida, Gainesville, FL, United States

Suresh C. Sikka, PhD Department of Urology, Tulane University School of Medicine, New Orleans, LA, United States

Miguel A. Sogorb, PhD Unidad de Toxicología y Seguridad Química, Instituto de Bioingeniería, Universidad Miguel Hernández de Elche, Elche, Spain

Offie P. Soldin, PhD Departments of Oncology, Medicine, and Physiology and Biophysics, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, United States

Chunjuan Song, MS Department of Biomedical Sciences, Iowa Center for Advanced Neurotoxicology, Iowa State University, Ames, IA, United States

Ajay Srivastava, DVM, PhD Vets Plus Inc., Menomonie, WI, United States

Szabina A. Stice, PhD Division of Biotechnology and GRAS Notice Review, FDA, College Park, MD, United States

Tammy E. Stoker, PhD National Health and Environmental Effects Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Durham, NC, United States

Jaideep S. Toor, PhD Department of Urology, Tulane University School of Medicine, New Orleans, LA, United States

Belen Tornesi Preclinical Safety, Global Pharmaceutical R&D, AbbVie, North Chicago, IL, United States

Peter Truran, BSc(Hons), MEd, PhD Minnesota Center for the Philosophy of Science, University of Minnesota, Minneapolis, MN, United States

Kirsi Vähäkangas, MD, PhD School of Pharmacy/Toxicology, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland

Joseph Valdez, BSc Neurotoxicology Branch, Toxicity Assessment Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Durham, NC, United States

Neil Vargesson, BSc, PhD School of Medicine, Medical Sciences and Nutrition, Institute of Medical Sciences, University of Aberdeen, Aberdeen, Scotland, United Kingdom

Henrik Viberg, PhD Environmental Toxicology, Uppsala University, Uppsala, Sweden

Eugenio Vilanova, PhD Unidad de Toxicología y Seguridad Química, Instituto de Bioingeniería, Universidad Miguel Hernández de Elche, Elche, Spain

Kenneth A. Voss, PhD Toxicology and Mycotoxin Research Unit, Agricultural Research Service, US Department of Agriculture, Athens, GA, United States

Suryanarayana V. Vulimiri, BVSc, MVSc, PhD, DABT National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Washington, DC, United States

Kevin D. Welch, PhD Poisonous Plant Research Laboratory, Agricultural Research Service, US Department of Agriculture, Logan, UT, United States

Daniel C. Williams, PhD Department of Biology, Coastal Carolina University, Conway, SC, United States

Moges Woldemeskel, DVM, MVSc, PhD, DACVP Department of Veterinary Pathology, Tifton Veterinary Diagnostic and Investigational Laboratory, College of Veterinary Medicine, University of Georgia, Tifton, GA, United States

Jae-Ho Yang, PhD Department of Pharmacology, School of Medicine, Catholic University of Daegu, Gyeongsan, South Korea

Zhaobao Yin, MD, PhD WY Acupuncture Clinic, PLLC, Franklin, TN, United States

Xiaoyou Ying, BE, MSc, PhD Bioimaging US, Translational In Vivo Models, Sanofi R&D, Framingham, MA, United States

Begum Yurdakok-Dikmen, DVM, PhD Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Ankara University, Ankara, Turkey

Snjezana Zaja-Milatovic, MSc Atlantic Research Group Inc., Charlottesville, VA, United States

Changqing Zhou, MS Department of Comparative Biosciences, University of Illinois, Urbana, IL, United States

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GENERAL

CHAPTER

1

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 biomonitoring and surveillance of mercury exposure to avoid future cases.

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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