

Preface

Our major objective and driving force in developing the second edition of *Nitrite and Nitrate in Human Health and Disease* is to consolidate and update all the key research and new knowledge in one volume in order to establish a framework based on the totality of evidence for nitrite and nitrate and the effects of these two anions on human health and disease. Since the publication of the first edition in 2011, more evidence has been published in human trials demonstrating the safety and efficacy of nitrite and nitrate in human disease, but also more insight has been gained into mechanisms of action. These new data are now included in the second edition. Although the biomedical science community is excited and optimistic about the potential for developing new therapeutics and perhaps regimens of disease prevention based on their ability to generate nitric oxide under appropriate conditions, epidemiologists, nutritionists, and cancer biologists have historically had cause for concern owing to the inherent nitrosative chemistry of nitrite and NO that could form potentially carcinogenic N-nitrosamines. The new data on nitrite and nitrate have even shone new light on this minimal potential risk. As a result, a risk benefit analysis for nitrite and nitrate can now be evaluated where it appears that at the right doses and routes of administration, the potential benefits far outweigh any potential risks. This is the second edition of the first book in the Springer/Humana Nutrition Series dedicated to understanding the nutritional aspects of nitrite and nitrate for human health. It is our intent to deliver a comprehensive review of nitrite and nitrate, from basic biochemistry to the complex physiology and metabolism of these two naturally occurring molecules in the human body.

Overall, the book contains well-organized and well-referenced chapters by respected scientists and physicians that covers the rich history of nitrite and nitrate, sources of exposure and physiological effects when consumed through foods containing nitrite and nitrate. The first portion of the book describes the biochemistry, metabolism, and physiology of nitrite and nitrate, and how these molecules are incorporated into the foods we eat and subsequently how they are systematically metabolized to bioactive nitric oxide. This biochemistry involves the environmental processes of nitrogen fixation and the presence of a human nitrogen cycle involving symbiotic bacteria that reside in and on the human body. The book then shifts focus to the sources of exposure to nitrite and nitrate, both environmental and dietary, as a means to quantify exposure estimates and what this may mean for human health. We also discuss the epidemiology and dietary effects on the nitric oxide pathway. This portion of the book also examines systems in nature which this pathway is exploited, including the breast milk of nursing mothers. Finally, the last section of the book discusses nitric oxide-based therapeutics and how nitrite and nitrate biochemistry can be harnessed safely and efficaciously to improve human health through the production of nitric oxide. We end with a summary of the collective body of knowledge presented in the book and what we might expect going forward. Each chapter begins with an abstract and Key Points that outline the concepts presented to assist the reader in understanding the fundamental principles presented in each chapter.

It is undisputed in the biomedical community that NO is one of the most important molecules the human body produces. If NO is such an important molecule in practically every organ system in our body, why, then, is there only a singular pathway for its production, i.e., the complex oxidation of L-arginine? Phosphorylation is another fundamental cellular process that is just as important in cell signaling, with over 500 recognized kinases and many phosphatases to regulate this biochemical process; by contrast, there is only one class of enzymes, the nitric oxide synthases, to produce NO. Most physiological systems are rich in redundancy, allowing backup systems to support the primary system. The provision of nitrate and nitrite as sources of NO may then be viewed as a system of redundancy. After all, a one-electron reduction is energetically and kinetically favorable to a five-electron oxidation.

According to the World Health Organization, cardiovascular disease is the number one killer of both men and women in the United States. These deaths represent a staggering 40 % of all deaths. Close to one million people die each year and more than six million are hospitalized due to cardiovascular disease. Therefore, developing new strategies to correct NO insufficiency and replete NO availability is of paramount importance and could potentially save millions of lives worldwide and lessen the burden on the health care system. We now appreciate that reduced or insufficient NO production or activity is a hallmark of a number of disorders, including many complex, chronic cardiovascular diseases and even Alzheimer's and diabetes mellitus. Therefore, developing new strategies to restore and replete bioactive NO is of paramount importance and could potentially lessen the burden of disease for society. Thus, understanding the biological activity of nitrite and nitrate may not only lead to novel treatments for disease but may lead to strategies to prevent disease development or progression and even the physiological basis for the benefits of certain diets such as the Mediterranean diet. To achieve this laudable goal, we must first establish the context for potential benefit while preventing unwanted risks or harm. We hope the information provided in this text will begin to help define that context, be a source of valuable information, and be useful for anyone who wants the most important and updated information about nitrate and nitrite.

We have invited the world's leading experts to share their research and perspectives, which we hope will help define the context for benefits vs. any potential risks associated with nitrite and nitrate, through either dietary ingestion or therapeutic dosing. This diverse collection of authors includes muscle biologists, physiologists, physicians, epidemiologist, cancer biologist, registered dietician, chemist, and public health experts from five countries around the world in both academia and government. This approach will provide a fair and balanced view of nitric oxide biochemistry, and nitrite and nitrate biochemistry in physiology and in the food sciences. As a result, we are indebted to these many individuals. We feel extremely honored and grateful to have many of the world's experts contribute their knowledge and perspective. We realize the time and dedication it takes to compose a book chapter on the latest body of knowledge, so we appreciate these authors' taking the time to help develop this volume. Without their creative contributions, this book would not have been possible. We also sincerely thank Springer-Humana Press for including this body of work in the Nutrition and Health Series with Dr. Adrienne Bendich as Series Editor. The Editors also wish to thank Stephanie Tribuna for her time and effort in organizing and managing this project with the Editors. This is an exciting time in NO and nitrite-based research. This has been—and we predict will continue to be—an area of intense research in the future. It is our hope that the information contained here will educate and inform scientists, physicians, health care professionals, nutritionists, dieticians, and even the general public on the effects of nitrite and nitrate in human health and disease.

Houston, TX
Boston, MA

Nathan S. Bryan
Joseph Loscalzo

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Bryan, N.S.; Loscalzo, J. (Eds.)

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