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Science and the Law: How the Communication of Science Affects Policy Development in the Environment, Food, Health, and Transport Sectors

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Science and the Law: How the Communication of Science Affects Policy Development in the Environment, Food, Health, and Transport Sectors

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Foreword

The ACS Symposium Series was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of the series is to publish timely, comprehensive books developed from the ACS sponsored symposia based on current scientific research. Occasionally, books are developed from symposia sponsored by other organizations when the topic is of keen interest to the chemistry audience.

Before agreeing to publish a book, the proposed table of contents is reviewed for appropriate and comprehensive coverage and for interest to the audience. Some papers may be excluded to better focus the book; others may be added to provide comprehensiveness. When appropriate, overview or introductory chapters are added. Drafts of chapters are peer-reviewed prior to final acceptance or rejection, and manuscripts are prepared in camera-ready format.

As a rule, only original research papers and original review papers are included in the volumes. Verbatim reproductions of previous published papers are not accepted.

ACS Books Department

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Preface

The symposium, on which this book is based, was one of a series seeking to identify areas in which science-based policy development is increasing in importance. The first symposium, held in Philadelphia, PA, in 2012, has recently been published as an ACS Symposium book (*Science and the Law: Analytical Data in Support of Regulation in Health, Food, and the Environment*, Editors: William G. Town, Judith N. Currano, Volume 1167, ISBN13: 9780841229471, eISBN: 9780841229488). This, the second symposium, set out to explore the effect of the public communication of science on the interaction between science and policy development in the regulation of the environment, food, health, and transport sectors. For example, the controversy surrounding the science behind the study of global warming and the resulting focus on the reduction of carbon dioxide emissions by international agreement and by national and international regulation is one example of such an area where science communication and policy development are inextricably intertwined. This book presents a series of case studies illustrating the impact of science communication to lawmakers and the general public in other areas of policy development, including nutrition, tobacco science, drugs, and environmental issues.

The authors have labored long and hard to present an interesting cross-section of current, hot-button issues that revolve around scientific principles, and they clearly demonstrate the extent to which accurate and appropriate communication of science influences leaders and legislation. We thank them for their efforts, without which we would not have a book at all. We also thank Rachel Ashton, for once again copy editing and formatting all the chapters, and Rachel Deary, for keeping us on task and on track. It is largely due to their efforts that we were able to complete this project on schedule. Finally, we thank our partners and families, who, despite knowing what they were in for after the experience of our first book, were still willing and happy to give us their wholehearted support with this second one.

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Editors' Biographies

William G. (Bill) Town

William G. (Bill) Town is President of the Kilmorie Consulting Division of Kilmorie Clarke Ltd. Dr. Town obtained chemistry degrees at the University of Birmingham and the University of Lancaster in the U.K. and worked at the Universities of Sheffield and Cambridge before joining the European Commission at JRC Ispra in Italy. It was here, as leader of the ECDIN and EINECS projects, that his interest in the interaction between Science and the Law was first raised. His long career has spanned chemistry, databases, software, and publishing. In 2000, he was Chair of the ACS Chemical Information Division.

Judith N. Currano

Judith N. Currano has been the head of the University of Pennsylvania's Chemistry Library since 1999. She holds a Bachelor of Arts degree in chemistry and English from the University of Rochester, where she performed undergraduate research in the lab of Robert K. Boeckman, Jr., and a Master of Science degree in library and information science from the University of Illinois at Urbana-Champaign. Her main research interests are in chemical information education and research and publication ethics, and she publishes and presents frequently on both topics. She is an editor of two books, Chemical Information for Chemists: A Primer and Science and the Law: Analytical Data in Support of Regulation in Health, Food, and the Environment. At the University of Pennsylvania, she provides chemical science researchers with a broad spectrum of library and information services, while teaching a required graduate-level course in chemical information to the Ph.D. students.

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Chapter 1

The Communication of Science and Influence on Development of Science-Based Policy

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Communication and assessment of scientific information is as important as the science itself, especially when policy-makers, politicians, and media specialists lack scientific backgrounds. Scientific advice has never been in greater demand; nor has it been more contested. A series of studies of the differences between scientists and the general public have shown differences in perspective. While recognizing the achievements of scientists, the views of scientists and citizens differ on a range of science, engineering, and technology issues. To deal with poor understanding of science, the American Association for the Advancement of Science has launched Project 2061, which is a long-term research and development initiative focused on improving science education so that all Americans can become literate in science, mathematics, and technology. In this book, we consider the many types of communication that affect science-based policy-making, either directly or indirectly.

Introduction

As I explained in the first book in this series, *Science and the Law: Analytical Data in Support of Regulation in Health, Food, and the Environment* (*1*), my personal interest in the use and communication of science in policy-making derives from the time I spent in the Joint Research Centre of the European Union (EU) in the late 1970s and early 1980s. I initially worked on designing and building a database (*2–4*) to support policy-making related to chemicals in the environment, and later on the European Inventory of Existing Commercial

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Chemical Substances (EINECS) (*5*). In the first book, as in the symposium on which it was based, it was only possible to provide a small number of case studies in a narrowly focused area (analytical chemistry) that illustrated the interaction between science and policy-making. To widen the areas covered further, more general, case studies are included in this new book. They include risk analysis approaches for establishing maximum levels of essential nutrients in fortified foods and food (dietary) supplements (chapter 9) and the importance of exposure dose in communicating the ecotoxicology of engineered nanomaterials (chapter 8). The role of regulatory science in reducing the public-health impact of tobacco use (chapter 4) and the controversy around the science of indirect land use change (chapter 7) are among the broader topics discussed.

Communication and assessment of scientific information is as important as the science itself, especially when our policy-makers, politicians, and media specialists lack scientific backgrounds. This problem was recognized as early as 1982, in the report *Technology and Government, a report of a working party of the Council for Science and Society* (*6*). As noted there, we need scientists with broad bases of scientific knowledge, communication and assessment skills, and a willingness to be involved in the political process. Equally we need policy-makers, civil servants, and politicians who have been trained in scientific methods. It is incumbent on our universities and academic societies to awaken and foster an interest in science-based policy-making.

Scientific advice has never been in greater demand; nor has it been more contested. From climate change to cyber-security, poverty to pandemics, food technologies to fracking, the questions being asked of scientists, engineers, social scientists, and other experts by policy-makers, the media, and the public continue to multiply. At the same time, in the wake of the financial crisis and controversies, such as that over the Climatic Research Unit emails, termed 'Climategate', the authority and legitimacy of those same experts are under increased scrutiny. Across Europe, scientific evidence and advice are needed to inform policies and decision-making on issues such as climate change, new technologies and environmental regulation. However, the diversity of political cultures and attitudes to expertise in different European countries can make the task of designing EU-wide advisory institutions and processes both sensitive and complex. In January, 2015, President Juncker asked Commissioner Moedas to report on options for improving scientific advice within the European Commission. In May, 2015, the new Scientific Advice Mechanism was announced, but has been widely criticized (*7*). At a time when policy issues are higher than usual on the political agenda, it is important that the cases for scientific advice and evidence-informed policy are articulated and analyzed afresh.

Two collections on scientific advice have been published by the University of Cambridge Centre for Science and Policy. *Future Directions for Scientific Advice in Whitehall*, published in April, 2013, (*8*), focuses on scientific advice in the United Kingdom, and *Future Directions for Scientific Advice in Europe*, published in April, 2015 (*9*), looks at the same topic in Europe.

In the United States, science policy is the responsibility of many organizations throughout the Federal government. Much of the large-scale policy is made through the legislative budget process of enacting the yearly Federal budget,

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although other legislative issues directly involve science, such as energy policy, climate change, and stem cell research. Further decisions are made by the various Federal agencies, which spend the funds allocated by Congress, either on in-house research or by granting funds to outside organizations and researchers. Researchers searching for ways to be effective ambassadors for science policy in the United States must learn the challenges facing Congress, according to a guide published by American Association for the Advancement of Science (AAAS) Office of Government Relations (*10*). This guide provides detailed information on congressional procedures and history and practical advice on developing and maintaining constructive relationships with law-makers, their staff members, and other science policy advisers in Washington, DC.

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The Public's and Scientists' Views on Science and Society

A series of studies of the differences between scientists and the general public have been conducted by the Pew Research Center. The surveys involved citizens of the United States and a representative sample of scientists connected to the AAAS. The findings show that, while recognizing the achievements of scientists, the views of scientists and citizens differ on a range of scientific, engineering, and technology issues. The latest report (*11*) highlights several major findings:

- Science holds an esteemed place among citizens and professionals. Americans recognize the accomplishments of scientists in key fields and, despite considerable dispute about the role of government in other realms, there is broad public support for government investment in scientific research. Simultaneously, the public and scientists are critical of the quality of science, technology, engineering, and math in grades K–12
- Despite broadly similar views about the overall place of science in the United States, citizens and scientists often have notably different points of view on science-related issues across a host of issues
- Compared with 5 years ago, citizens and scientists are less "upbeat" about the scientific enterprise. Citizens remain broadly positive about the place of the scientific achievements of the United States and their impact on society, but slightly more are negative. while the majority of scientists expressed it being a good time for science, they were less upbeat than they were five years ago. Most scientists believe that policy regulations on land use and clean air and water are not often guided by the best science.

Misconceptions of Science

To deal with poor understanding of science, the AAAS has launched Project 2061, which is a long-term research and development initiative focused on improving science education so that all Americans can become literate in science, mathematics, and technology. One of the initiatives launched by Project 2061 is the AAAS Science Assessment Website (http://assessment.aaas.org/), which

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provides support in building curricula. Science educators have easy access to more than 700 high-quality multiple-choice items for testing the understanding of middle-school and high-school students in 16 important areas of earth, life, and physical sciences, and the nature of science. The website also presents data on the state of science learning by gender and whether or not English was the students' primary language. An online testing feature lets users select items, assemble them into tests, and administer and score the tests online. These assessment items and resources will also be useful to education researchers, test developers, and anyone who is interested in the performance of middle-school and high-school students in science.

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Science Communication Channels

In this book, we consider the many types of communication that affect science-based policy-making, either directly or indirectly:

- communication of basic research in the scientific literature
- promotion of scientific articles by universities' and publishers' public and press relations departments
- dissemination of scientific press releases by scientific newswire organizations and further subsequent dissemination by internet-based news sources, print-based news sources, and television-based news sources
- public interpretation and further communication of science news
- scientific assessment and valuation of science news
- influence of lobby groups on policy development
- influence of scientists on policy development
- influence of politicians on policy development
- influence of the public on policy development
- assessment and the communication of risk (hazard labeling)
- communication of health and nutrition information to consumers
- communication of information to health professional networks

Examples of some of the communication channels in operation are considered in depth in this book in chapters 2, 3, 5, 6, and 10. Topics discussed are consumer communication of nutrition science and impact on public health; the FDA's communication of nicotine science; the effect of the communication of science on government policy in the United Kingdom; the PEPFAR government program in the United States, which is helping to keep millions alive around the world (communication with health network partners); and communicating controversial science, citing the case of tobacco harm reduction and the ethics of blanket censorship preventing communication of basic research in the scientific literature.

Each of these communication channels is prone to malfunction, or even intentional abuse by individuals or organizations with an axe to grind. Let us now consider how science communication functions in practice and where there is potential for malfunctioning.

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The Science Communication Cycle

Scientific research is mostly published initially in online and/or print journals following a process of peer review, the function of which is to ensure that the work is valid science. The results of scientific research are also communicated at scientific conferences and symposia. Such publication completes the cycle of a new idea being tested and proven or disproven by experiment, possibly leading to the generation of new concepts. The whole publication process is traditionally managed by publishers but is heavily reliant on the voluntary efforts of scientists acting as authors, peer reviewers, and/or journal editors

Other publication models are being developed, including post-publication peer review, as practiced by Science Open (https://www.scienceopen.com/home) and other publishers. Another example model is the process of peer review and publication in the interactive scientific journal *Atmospheric Chemistry and Physics*, which differs from traditional scientific journals. It is a two-stage process involving the scientific discussion forum *Atmospheric Chemistry and Physics Discussions*, and has been designed to utilize the full potential of the Internet to foster scientific discussion and enable rapid publication of scientific papers (*12*).

Scientific articles reporting the results of research are increasingly being used in assessment of the relative importance of the work of individuals and the institutions in which they work. Tenure, research funding, and capital expenditure can be influenced by the relative ranking of the published research, as assessed by the journal's Impact Factor and/or other means, such as the h-index. This system is flawed, and it results in a pressure to publish that can lead, in the worst cases, to scientific fraud or plagiarism. There have been some critiques of the use of citation statistics, impact factor, and h-index most notably, in an editorial by Jan Reedijk (*13*) and as a joint report of the International Mathematical Union, the International Council of Industrial and Applied Mathematics, and the Institute of Mathematical Statistics (*14*).

The AAAS has published an excellent overview of science (*15*). In a discussion of science ethics it states:

> *Most scientists conduct themselves according to the ethical norms of science. The strongly held traditions of accurate record keeping, openness, and replication, buttressed by the critical review of one's work by peers, serve to keep the vast majority of scientists well within the bounds of ethical professional behavior. Sometimes, however, the pressure to get credit for being the first to publish an idea or observation leads some scientists to withhold information or even to falsify their findings. Such a violation of the very nature of science impedes science. When discovered, it is strongly condemned by the scientific community and the agencies that fund research.*
>
> —American Association for the Advancement of Science

National Academies Press has also published a useful guide entitled *On Being a Scientist* (*16*), which contains much valuable advice on many aspects of the responsible conduct of research.

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The need to achieve a high profile for research results has led to the growth of a scientific public and press relations industry, which aims to ensure that research results become publishable news. Appearance of research results in news media increases the likelihood that an article will be read and subsequently cited by other scientists. It certainly impacts on the number of times an online article is downloaded and is likely to have an indirect influence on science-based policy development.

The science news cycle and some of the potential for accidental or deliberate miscommunication has recently been described in comic form (*17*). Although that overview is presented in a light-hearted manner, it shows that there is real scope for misinterpretation at every stage of the cycle. The ubiquitous lack of training in scientific knowledge and methods increases the risk at every stage and shows how modern communication methods can amplify the misinterpretation of scientific results.

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The Role of Social Media in the Communication of Science

In 2008–09, I was a member of a project team that undertook research into the uptake of Web 2.0 by chemists and economists (*18*). The chemistry results were gathered by face-to-face and telephone interviews that were conducted with 14 experts in chemistry to guide a subsequent online survey. 440 responses to the online survey were received from the chemistry community. The UK responses from chemists represented the views of 1% of the UK community of chemists and students (total approximately 40,000) but comprised over 3% of the UK community of academic chemists and students (total approximately 12,000). During the survey, the information resources mentioned most frequently by chemistry researchers were, in descending order, published journal papers, books, chemical structures, experimental and theoretical data sets, presentations, images, and working papers. At that time, there was very little reported use of Web 2.0 tools, such as blogs and discussion forums, or new formats, such as podcasts or audio and video clips. It would be interesting to repeat the survey now, some 7 years later. In the intervening period, the use of social media, such as Facebook, Twitter, WhatsApp, LinkedIn, Instagram, YouTube, and so on, has become commonplace, with the numbers of users of the most popular services measured in billions. As network speeds have improved, the delivery of online video has become ubiquitous, and online delivery of television content through services such as BBC iPlayer and YouTube has changed our viewing habits. Has this dramatic change in the social media environment had any impact on the way that science is communicated? Even without performing another survey, it is clear that the amount of scientific material available through social media is increasing rapidly, and it can be assumed that there is an audience for this material.

Many scientific journals include video interviews with the authors of research articles in which the scientists explain the significance of their work (eg, http://www.beilstein.tv/). Publishers such as Nature Publishing Group promote articles in their journals with posts on Facebook and Twitter. These article-related stories also appear on newspaper and television websites, such as BBC News,

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and which are also linked to on Facebook and Twitter. Various organizations, such as NASA and the European Southern Observatory, regularly publish videos and images relating to their astronomical and space-related work. There are a number of websites, such as http://www.iflscience.com/, that act as disseminators of scientific news, bringing together and highlighting the science news of the day. Professional organizations, such as the American Chemical Society ([ACS] www.acs.org), use their websites to deliver especially created video content, recordings of symposia national meetings, and scientific webinars. There have also been examples of lecturers delivering content remotely at physical meetings, and even of talks being delivered by Skype, such as in an ACS symposium when the speaker marooned by an unexpected snowfall. Mobile Internet is also having a big impact on the delivery of scientific information and much of the material described above is viewed on smartphones and tablets.

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Reddit Science (/r/science − The Community Discussion Platform for Science)

In a recent ACS webinar (*19*), Nathan Allen discussed science communication in the digital media age. His focus was on how services, such as Reddit, can be used to disintermediate communication between scientists and the general public and reduce the risk of distortion.

Reddit was conceived as an entertainment, social networking, and news website where registered community members could submit content, such as text posts or direct links, making it essentially an online bulletin board system. Registered users are able to vote submissions up or down to organize the posts and determine their position on the website's pages. Content entries are organized by areas of interest called subreddits.

The range of subreddit topics is large and includes news, gaming, movies, music, books, fitness, food, and photo sharing. The subreddit for science, /r/science, has over 9 million readers. It has a system of verifying accounts for commenting, which enables trained scientists, doctors and engineers to make easily identifiable and credible comments. The intent of this system is to enable the general public to distinguish between an educated opinion and a random comment without a background related to the topic. Moderators are volunteers who ensure that the subreddit stays true to its purpose by enforcing rules. Moderators have the power to approve or remove any comments or submissions made to only the subreddits they moderate. They can also issue a ban for users on the subreddits they oversee.

The Reddit Science Ask Me Anything Series

> *Our goal is to encourage discussion and facilitate outreach while helping to bridge the gap between practicing scientists and the general public (20).*

Reddit also allows submissions that do not link externally. These are called self-posts or text submissions. Many discussion-based subreddits limit

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submissions to text-only content. Scientists can make themselves available for Ask Me Anything sessions or AMA sessions, which are, essentially, a crowd-sourced interview. Anyone can submit a text submission. The title describes why it is of interest and announces "AMA!". Users may then submit comments to the post asking their questions, of which the original poster answers as many as he or she can. The /r/IAmA subreddit is dedicated to AMAs. /r/IAmA does host science-based AMAs, but it also hosts a large number on other topics, which makes it difficult for scientists to compete for attention against actors (promoting movies), musicians, television personalities, authors, and so on. /r/IAmA does not heavily moderate comments and, therefore, many inappropriate questions get through, making for a potentially unpleasant experience for inexperienced users. Individuals wishing to post an AMA need to learn the rules of Reddit, which can be difficult for those new to the community. More than 820 moderators (all with a minimum of a BS degree in a science, and of whom 300 are PhDs), work with scientists to address concerns. They host one AMA per day maximum and only for scientists. Their goal is to make science AMAs on Reddit a culturally expected step for scientists so that when they publish an important paper, they will communicate it directly to the public ("I'm going to do an AMA!"). A step-by-step guide is available for scheduling and submitting AMAs (*20*).

Reddit has partner science organizations, including American Chemical Society Webinars, Public Library of Science (PLOS) Science Wednesday (a collaboration to bring PLOS Journals authors directly to /r/science), National Oceanic and Atmospheric Administration, California Academy of Science, Columbia University, and many others.

Policy Development: Is Our Political System Corrupt?

We have discussed some of the communication channels through which the public and policy-makers are informed about scientific developments and have made the assumption that these channels are neutral and perfect. However, we must consider whether that is indeed the case, or whether the flow of information is corrupted by interest groups. Two significant publications have questioned these assumptions: *The Prostitute State* (*21*) and *Manufacturing Consent: The Political Economy of the Mass Media* (*22*).

The Prostitute State

According to McCarthy, the political systems in the United Kingdom (as well as those of the United States and the European Union) are manipulated by rich vested interests in a way that impacts negatively on our society. The effects of such interests permeate nearly every aspect of public life and are responsible for the climate and environmental crisis and the destruction of social justice.

Potential sources of corruption of the so-called four pillars of our society' have been identified by McCarthy:

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- The corrupted political system: political parties are heavily depended on corporations for donations, which means that corporations hold enormous influence over them. Individual members of parliament (MPs) can be controlled in various ways, such as bribes or being offered high paying jobs when they quit the government.

> *The resources available to UK political parties are measured in the low millions of pounds but those available to influence and manipulate them are measured in the billions. It has been estimated that for each of the UK's 646 MPs there are twenty-two full time professional political lobbyists. The £2 billion spent annually on lobbying government is the equivalent of over £3,100,000 per MP.*

- The prostituted media: most of our news media are owned by a few billionaires who control what can be printed. They can influence and control the public and bully the government.

> *Murdoch's* News of the World *scandal exposed what was long known within the political world. If any MP, minister or Prime Minister wanted to support a policy which they believed was right for the country but which was opposed by News International or the other media billionaires, they knew they would have to risk having every aspect of their private lives trashed in public for daring to do so. Their medical history, taxes, income, emails, bank-accounts, telephone conversations, police records, texts, benefits history, drug-taking and sex life would all be trawled through by those working for Murdoch, Rothermere, or Desmond. That information would then be used to destroy them politically and to demolish the policy disliked by the corporate media. As Leveson exposed, MPs would also be taking on this risk on behalf of their partners, family members, friends, employees and even neighbours!*

- The thieving tax havens: many corporations operating in the United Kingdom are registered in tax havens abroad, pay little to no tax in the country, and use their influence to stop any changes to tax laws. Estimates of how much the UK government is losing each year range from £20 billion to £100 billion in taxes, compared with an estimated £1.5 billion lost to benefit fraud. Tax paying UK registered businesses are at a massive disadvantage when competing against businesses that don't pay tax.
- The perverted academia: the 'corporate state' is controlling intellectual output by establishing and funding think-tanks, paying for academic studies, and controlling schools and universities.

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> *[The] ultra-rich and their corporations are increasingly taking over our schools, universities and think tanks, perverting their ability to be the wellsprings of independent expert knowledge, research and creativity that are so crucial to the fair and successful running of a modern democracy.*
> —Donnachadh McCarthy (*21*)

Manufacturing Consent: The Political Economy of the Mass Media

In their groundbreaking book, Herman and Chomsky (*22*) not only explained but also documented with extensive case studies how mass media and public opinion are shaped in a democracy. They argue that the mass media of the United States "are effective and powerful ideological institutions that carry out a system-supportive propaganda function by reliance on market forces, internalized assumptions, and self-censorship, and without overt coercion".

Editorial distortion is aggravated by the news media's dependence upon private and governmental news sources. If a given newspaper, television station, magazine, and so on, incurs governmental disfavor, it is subtly excluded from access to information. Consequently, it loses readers or viewers and, ultimately, advertisers. To minimize such financial danger, news media businesses editorially distort their reporting to favor government and corporate policies in order to stay in business.

Herman and Chomsky's "propaganda model" describes five editorially distorting filters applied to news reporting in mass media:

- Size, ownership, and profit orientation: the dominant mass-media outlets are large firms that are run for profit. They must, therefore, cater to the financial interest of their owners, which are often corporations or particular controlling investors. The size of the firms is a necessary consequence of the capital requirements for the technology to reach a mass audience.
- The advertising license to do business: since the majority of the revenue of major media outlets derives from advertising (not sales or subscriptions), advertisers have acquired a de facto licensing authority. Media outlets are not commercially viable without the support of advertisers. News media must, therefore, cater to the political prejudices and economic desires of their advertisers. This has weakened the working-class press, for example, and also helps explain the attrition in the number of newspapers.
- Sourcing mass media news: Herman and Chomsky argue that "the large bureaucracies of the powerful subsidize the mass media, and gain special access [to the news], by their contribution to reducing the media's costs of acquiring ... and producing, news. The large entities that provide this subsidy become 'routine' news sources and have privileged access to the gates. Non-routine sources must struggle for access, and may be ignored by the arbitrary decision of the gatekeepers."

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- Flak and the enforcers: "'Flak' refers to negative responses to a media statement or program. It may take the form of letters, telegrams, phone calls, petitions, lawsuits, speeches and bills before Congress, and other modes of complaint, threat or punitive actions. It can be organized centrally or locally, or it may consist of the entirely independent actions of individuals." Flak can be expensive to the media, either due to loss of advertising revenue, or due to the costs of legal defense or defense of the media outlet's public image. Flak can be organized by powerful, private influence groups (eg, think tanks). The prospect of eliciting flak can be a deterrent to the reporting of certain kinds of facts or opinions.
- Anti-communism as a control mechanism: this was included as a filter in the original 1988 edition of the book, but Chomsky argues that since the end of the Cold War (1991), anticommunism has been replaced by the so-called War on Terror, as the major social control mechanism.

Is Chomsky's Propaganda Model Still Valid?

In his article *Has the Internet Changed the Propaganda Model?*, Rampton (*23*) asks "Twenty years later, can the 'propaganda model' still be used to explain modern media distortions?" and considers how the internet has changed the media. He concludes that "although the specific filtering mechanisms that Herman and Chomsky describe in Manufacturing Consent may not apply in the same ways to the internet, new techniques of molding and directing public opinion are emerging along with the new media ... As new technology enters the mainstream, therefore, we can expect changes in the techniques used to influence public opinion, but institutions with wealth and power will continue to do so. Power still concedes nothing without a struggle."

Relevance to Science Communication

Although this discussion has related primarily to mass media, Chomsky (*24*) concludes that there is relevance to other forms of communication.

> *My impression is the media aren't very different from scholarship or from, say, journals of intellectual opinion—there are some extra constraints—but it's not radically different ... There is another sector of the media, the elite media, sometimes called the agenda-setting media because they are the ones with the big resources, they set the framework in which everyone else operates.* The New York Times *and CBS, that kind of thing. Their audience is mostly privileged people. The people who read the New York Times—people who are wealthy or part of what is sometimes called the political class—they are actually involved in the political system in an ongoing fashion. They are basically managers of one sort or another. They can be political managers, business managers (like corporate executives or that sort of thing), doctoral managers*

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(like university professors), or other journalists who are involved in organizing the way people think and look at things.
—Jonathan Cook (*25*)

Clearly, science communication channels, although somewhat different from the media that were the principal focus of Chomsky's original thesis, are potentially subject to the same problems and ethical concerns.

Scientific Integrity

The main ethical principle underlying the communication of science is one of scientific integrity. While government science is responsive to public concerns, it is also vulnerable to political pressures. When the scientific evidence supports policies that threaten the interests of powerful constituencies, science may be suppressed, censored, distorted, or manipulated. Abuse of science is not a new problem, but it reached new levels of pervasiveness during the first George W. Bush administration.

Although scientific input to the government is rarely the only factor in public policy decisions, this input should always be weighed from an objective and impartial perspective to avoid perilous consequences. Indeed, this principle has long been adhered to by presidents and administrations of both parties in forming and implementing policies. The administration of George W. Bush has, however, disregarded this principle. When scientific knowledge has been found to be in conflict with its political goals, the administration has often manipulated the process through which science enters into its decisions. This has been done by placing people who are professionally unqualified or who have clear conflicts of interest in official posts and on scientific advisory committees; by disbanding existing advisory committees; by censoring and suppressing reports by the government's own scientists; and by simply not seeking independent scientific advice.
—Union of Concerned Scientists (*26*)

In 2004, the Union of Concerned Scientists responded by issuing a report, *Scientific Integrity in Federal Policy Making* (*26*), and a statement signed by 62 leading United States scientists (more than 15,000 would eventually add their names) calling for an end to political interference in science. Over the following years, the Union of Concerned Scientists Scientific Integrity Program documented the problem extensively, pulling together in-depth reports, case studies, and surveys of federal scientists (*27*).

According to the United States Environmental Protection Agency Office of the Science Advisor (*28*), scientific integrity results from adherence to professional values and practices, when conducting and applying the results of science and scholarship. It ensures the following:

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- Objectivity
- Clarity
- Reproducibility
- Utility

Scientific integrity is important because it provides insulation from the following influences:

- Bias
- Fabrication
- Falsification
- Plagiarism
- Outside interference
- Censorship
- Inadequate procedural and information security

The importance of scientific integrity is recognized at the highest levels of government. President Obama promised in his inaugural address to "restore science to its rightful place," and he issued a presidential memorandum on the subject (*29*). In December, 2010, the White House Office of Science and Technology Policy provided guidance for the development of scientific integrity policies by federal agencies (*30*). The guidelines require agencies and departments to create or improve various policies:

- Foundations of scientific integrity in government
- Public communications
- Use of federal advisory committees
- Professional development of scientists and engineers

Acknowledging differences in structure and degree of regulatory responsibility, agencies and departments were given some latitude in developing their policies.

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European Group on Ethics in Science and New Technologies

Concern about scientific integrity is not limited to the United States. In the European Union a body has been established by the President of the European Commission, the European Group on Ethics in Science and New Technologies (EGE) (*31*). The EGE was set up in 1991, following a communication from the EU Commission to the European Parliament and Council entitled *Promoting the competitive environment for industrial activities based on biotechnology within the Community* (*32*). The Commission emphasized the need for ethical discussions on the development of biotechnology, thus the need for the creation an ethics body was felt.

Since 1991, the EGE has drawn up 23 opinions addressing the ethical aspects and implications of animal cloning for food supply, nanomedicine, information

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and communication technologies implants in the human body, banking of umbilical cord blood, genetic testing in the workplace, clinical research in developing countries, patenting inventions involving human stem cells, research and use of human stem cells, doping in sport, health care in the information society, research involving the use of human embryos in the context of the Fifth Framework Programme, human tissue banking, cloning techniques, patenting inventions involving elements of human origin, genetic modification of animals, prenatal diagnosis, the labelling of the food derived from modern biotechnology, gene therapy, and the use of performance-enhancers in agriculture and fisheries.

The EGE also gave an Opinion on the ethical questions arising from the European Commission's proposal for a European Council Directive for legal protection of biotechnological inventions, products derived from human blood or human plasma, and the ethics review of Fifth, Sixth, and Seventh Framework Programme research projects.

The President of the Commission decides on the EGE work program, which includes ethics reviews suggested by the EGE. The EGE's Chairperson, together with The Bureau of European Policy Advisers of the European Commission, is responsible for organizing the work of the EGE and the Secretariat.

The EGE forms a core component of a wider set of coordinated activities with two objectives: first, to embed European Union policy-making on science and new technologies in a firm ethical foundation and, second, to strengthen global cooperation on ethics. These include the Inter-service group on Ethics and European Union Policies, coordinating Commission activities in the fields of bioethics and ethics of science and new technologies; cooperation with the international organizations tasked with examining the ethical implications of science and new technologies (the United Nations and its agencies, the Organisation for Economic Co-operation and Development, and the Council of Europe); and the organization of the European Commission's International Dialogue on Bioethics, a platform bringing together the national ethics councils from 97 countries (in the European Union-G20 forum and beyond).

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Broader Aspects

To further examine aspects of how science is performed and viewed, we organized another symposium, held at the 250th ACS National Meeting, in Boston, MA, August, 2015, that addressed the topic of scientific integrity and the degree to which we can trust the scientific literature when the overwhelming pressure to publish can lead scientists into temptation. Contributions from industry, database, and journal publishers, librarians and developers of some innovative publishing platforms explored the topic from a number of different perspectives. Topics covered included: "Integrity, ethics and trust in the scientific literature", "Policy making at the American Chemical Society: developing a statement on scientific integrity", "Publishability", "…the role of peer review in protecting the integrity of scientific research", "An open, network-based solution to the reproducibility crisis", "Managing new threats to the integrity of the scientific literature", "Towards a more reproducible corpus of scientific

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literature", and "Validation and fraud in small molecule crystallography". We hope to publish a new book based on these presentations.

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Chapter 2

Impact of the Communication of Science on Government Policy – The Perspective from the United Kingdom

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Decision-making at the level of governmental policy must take into account many different factors, from public sentiment to political ideology, from legal precedent to future preparedness. Where and how science fits into this is a moveable feast. There are occasions when science is used to justify policy decisions and others where evidence is clearly ignored. This chapter looks briefly at how science has become increasingly embedded in the way policies are developed and function in the United Kingdom, from the age of enlightened thinking through to the present day. It is intended as a whistle stop tour, rather than a tour de force.

The Age of Enlightenment

It could be reasonably argued that logical thinking played only a tiny role in the formulation of governmental policies in the United Kingdom (or its individual components or forerunners) until the Age of Enlightenment. This revolutionary period of modern history featured many great thinkers and scientists, most of whom are still revered. At an academic level, the exact timing and precise details of this age are the subjects of much ongoing discussion, with the foremost topic being who started it. Although the precise details are not the subject of this chapter, we suggest that various discoveries and theories from the late 16th century probably had roles in initiating the Age of Enlightenment. The heliocentric model of the universe proposed by Nicolaus Copernicus (1473–1543) in his seminal book *De revolutionibus orbium coelstum*, published in 1543 (*1*), drew together his lifelong observations and the earlier theories proposed by astronomers as far

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back as Philolaus (c. 480–385 BC) and prominent Arabian scientists, such as Naṣīr al-Dīn al-Ṭūsī and Ibn al-Shāṭir. This book spurred many advances across all areas of science, triggering the scientific revolution, which merged with the Age of Enlightenment in terms of overall thinking and recognized protagonists.

Social Contract

It is important to look back at this period as we start to think about the central tenets of the role of science (and its communication) on the formulation of policy. Not only did much of modern science start to take shape at that time, but also the concepts of a society and, importantly, the responsibility of leaders. For example, Thomas Hobbes (1588–1679) published a ground-breaking treatise that established the concept of social contract. In *Leviathan or The Matter, Forme and Power of a Common Wealth Ecclesiasticall and Civil*, published in 1651 (*2*), Hobbes supported the idea of an absolute monarchy, but posited that the right for the monarch to govern was not ordained from God, but rather from the people. He proposed that this was the only true way that power could be legitimate. Importantly, the contractual nature of his treatise proposes that the population, in return for relinquishing some of their freedoms and submission to the authority of the ruler, should rightfully expect to receive protection of their remaining rights. The theory was further developed by a number of other great names of the time, including John Locke (1632–1704), who is commonly associated with proposing that individuals have a right to "life, liberty and property" (*3*).

The German philosopher, Immanuel Kant (1724–1804), described enlightenment as "man's emergence from his self-imposed immaturity," in his 1784 essay *Answer the Question: What is Enlightenment?* (*4*). Tellingly, he also said that the motto of enlightenment was "Have courage to use your own mind."

Of Coffee Houses and Learned Societies

In the United Kingdom, the sea-change in how society, the State, and the Church interacted as a result of enlightenment was far from as sweeping, or as bloody, as that of the French Revolution, but it did shape how the Government ruled. Nevertheless, the intertwining of advanced scientific theory and the preponderance of scientific studies into everything from anatomy and medicine to civilization and astronomy could also been seen as a double-edged sword, as it provided a broad justification for the civilized advanced western European countries to colonize far-away underdeveloped and "barbaric" countries. This pursuit had important consequences on global politics that last up to this very day.

It is also worth mentioning that none of these changes would have been possible if the growing numbers of polymaths, their acolytes, and those with a fervent interest, had not been able to meet, discuss, and publish their works. As a result, in addition to the hugely popular but informal coffee houses that sprang up in multiple centers around Europe, learned societies and periodical journals were established that thrived. In London, around 1660, the Royal Society was established and quickly received the Royal charter of King Charles II. Since that time, the ties between the Royal Society and the Government of the United

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Kingdom have been strong. The Royal Society not only funds research and supports the dissemination of science, but also provides scientific advice to the Government. Its stated mission is "To recognise, promote, and support excellence in science and to encourage the development and use of science for the benefit of humanity" (*5*). The motto, however, is slightly ironic, considering the advisory role has a clear foundation in the enlightenment tenet "*Nullius in verba*" (take no-one's word for it). However, since its early days, the Royal Society has been joined by a number of learned societies with advisory capacity to the United Kingdom Government, aided by the core focus on science outlined below.

Around the same time that the learned societies were becoming established, the first periodical journals for recording scientific and literary studies were started, some of which were born out of the societies (eg, *Philosophical Transactions of the Royal Society*) and some that were not. Thus, at this time, the concept of peer review came into force. This process has on the whole been a great asset to the advancement, and of course the rigor, of science, although it is coming under increasing scrutiny.

As discovery, knowledge sharing, and discussion grew, debating societies experienced a meteoric rise. These provided a forum for discussing anything, and attendance was generally open to anyone.

In summary, the intellectual evolution at all levels of the population during the Age of Enlightenment was phenomenal. Although those with the greatest minds of that time have long since died, their true legacy is in the acceptance of enlightened thought through all aspects of modern society and governance. Distributed throughout this legacy is the huge role of logical thinking and scientific discovery, which today is illustrated by the role that the communication of science has to play in modern governmental policy-making.

What Matters Is What Works

Since the transformative days of the enlightenment, the policies of the United Kingdom Government, and, for that matter, policies across other major European countries, have become increasingly based on evidence and critical thinking. This change has been seen especially in key areas of local and foreign policy, such as the economy.

From the 19th century onwards, the rational, objective shift in the thinking behind policies continued to develop, although always with the specter of inherently partisan, cultural, reactionary, or even populist ideas. For example, the separation of the Church and the State, an important result of the French Revolution, was a much longer, drawn-out process in the United Kingdom; some might say that it is still a work in progress.

From his first day as Secretary of State for Health in the first Government after World War II, Aneurin Bevan had transformation on his mind. His idea of accessible modern health care for all, paid for by taxes and free at the point of delivery was born out of a socialist belief (itself a dogma that captures the essence of Hobbes' social contract theory). He sought the advice and guidance of a broad range of experts and stakeholders, from medical leaders to funding experts,

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before presenting his plans to Parliament. With such a radical departure from the system that was then driven by the local councils, Bevan's National Health Service Bill received widespread opposition from some very influential people and organizations. Its chances of being passed sometimes seemed very slim, but the careful structure and logical detail of his proposals ultimately won through. He had used collection of extensive evidence and objective argumentation to implement a world-leading change in policy. This was a fantastic example of evidence-based policy-making.

Fast forward by 50 years, and Tony Blair's center-left Government, dubbed "New Labour," swept into power following nearly two decades of right-wing Conservative Government with Margaret Thatcher as Prime Minister for three terms. One of "New Labour's" aims for the Government was to focus on "what matters is what works". This manifesto principle indicated a clear intent to focus on designing policies around evidence and moving away from ideology. The search for sources of evidence and experts across all areas of policy leveraged existing associations and established new resources. As with many things related to governing a country, making structural changes can take time, especially when integrating or massively changing existing systems or procedures. Therefore, although it would be inappropriate to say that evidence, critical thinking, and, in essence, science only entered modern politics in the United Kingdom with "New Labour", there was certainly a sea-change in how important they became. In the rest of this chapter I look at some key examples of how the United Kingdom Government has been structured to achieve the "what matters is what works" principle. I also reflect on some of the areas where the empirical nature of evidence has clashed with the political aims of the party in power, for better or worse.

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Horizontal and Vertical Integration

The Government Office for Science was formally established in 2007, as a Cabinet office working closely with the Department for Business, Innovation and Skills. Its aims, summarized on its website, are "We ensure that government policies and decisions are informed by the best scientific evidence and strategic long-term thinking." The department is headed by the Government's Chief Scientific Advisor, currently Sir Mark Walport, who has held the position since 2013. Functionally, the Government Office for Science has two main sets of activities. The first is to conduct horizon-scanning or foresight studies to consider the latest scientific evidence and how it might help to guide policy development in the future and, in essence, keep the United Kingdom up with or ahead of the rest of the world. Second, the Chief Scientific Advisor chairs the Cross-Departmental Chief Scientific Advisors Committee (*6*). This committee is an essential link between the horizontal approach of the Governmental Office for Science and the vertical reach of each department, which, since 2010, have all had individual chief scientific advisors. These advisors are the border guards that determine how the Government departments use science properly to inform, develop, and measure policy. They maintain and develop links with individual scientists, experts, and,

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of course, the learned societies, keeping them at the very forefront of where science, technology, engineering, and medicine are heading.

I posit, however, that there is a slight chink in the armor here. In the process of ensuring that there is a focus on evidence-based policy-making, the impact of changes in policy is measured on the basis of pre-set end points. In turn, these are used to show the success, failure, or need for adjustment in the policy. These approaches all seem rather laudable and, indeed, sensible, but it is easy to end up forced into looking for, and finding, the exact change you were intending to see, while potentially missing something more substantial, or, worryingly, a significant long-term consequence imperceptible in the early days. In a slightly more pernicious manner, sources of evidence on some topics are very varied and one party could source and potentially find a wealth of evidence that supports an ideological aim. There is a risk here of seeing evidence-based policy built on policy-based evidence.

Sandra Nutley, Professor of Public Policy and Management at the University of St Andrews, United Kingdom, has published extensively on evidence-based policy-making. She is a firm supporter of the concept, but has a balanced view of the practical implications: "…research rarely provides definitive answers to policy questions and rational decision making rarely lies at the heart of policy processes". Professor Nutley also, rather sagely, suggests that evidence-informed or even evidence-aware policy would be a better description of the aspirations for the role of research in the policy making process (*7*).

There Is Nowhere More Critical for Science To Be Than in the Driving Seat

In modern medicine we see the cutting edge mingle with the tried and tested in order to provide the best possible outcomes for people, at an individual level when in need of medical care and at a societal level to promote health and wellness. Nowhere, therefore, is it more critical for science to be in the driving seat of policy-making, at all levels from central government to local care networks (or clinical care commissioning groups, as they are currently referred to in the United Kingdom). This focus on evidence also extends beyond the purely clinical sciences into economic modelling and other areas used to show the value of the United Kingdom National Health Service (NHS). The NHS is adored and derided, seemingly in equal measure and has been through numerous reviews and re-organizations, many of which have been driven by political will, and most of which have been focused on cost. One of the most significant revisions to the overall provision of care in the United Kingdom, was the establishment of the National Institute for Health and Care Excellence (NICE) in 1999 (https://www.nice.org.uk/), with the primary goal of developing clinical guidelines across most aspects of health-care provision. This work includes an important role in determining the cost-effectiveness of therapies. As such, this area of policy-setting was given partial autonomy from the Government. NICE was the successor of various bodies (eg, the National Screening Committee), but was given broader powers. It has continued to subsume other agencies, such as the

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as Health Development Agency in 2005. NICE has become a globally recognized and observed body (particularly within the health-care and pharmaceuticals fields), mostly because of its rational and transparent reliance on evidence from multiple sources. It does, however, have its detractors, especially when it comes to the decisions around the cost-efficiency of a new therapy: if NICE approves a particular therapy, it must be made available to any person meeting the criteria via the NHS, and if it does not approve a treatment, no-one may access it. The role of NICE should not be confused with that of the Medicines and Healthcare Products Regulatory Agency, which assesses the efficacy and safety of new therapies and decides whether they can be prescribed in the United Kingdom. It is possible, and increasingly common, therefore, for a new drug to be deemed safe for prescription by the Medicines and Healthcare Products Regulatory Agency, but to be unavailable via the NHS because of the cost-effectiveness analysis by NICE (such medicines may still be prescribed privately).

The model used by NICE for determining cost-effectiveness, is based around quality-adjusted life-years (QALYs), which are a measure of disease burden that includes both quality and quantity of life. In reality there are a range of complex considerations around QALYs, but, essentially, they provide a method by which the quality and quantity of life added back to a patient by a drug or treatment can be assessed. Decisions can then be achieved and benchmarked, since it is possible to assign a cost per QALY (ie, how much the NHS is willing to pay per QALY). The maximum threshold in April, 2015, was £30,000 per QALY (with a few exceptions). Herein lies the point of friction, and one that will lead us into a case study below. For a number of diseases, the prognosis is often not very good and no or few treatments are available. When a treatment is developed, it is often expensive because it has taken many years and cost many millions of pounds to research. Due to the very poor health of the patients, the drugs cannot always provide much additional life and might not improve the quality of life much either. For many patients and their families a small amount of additional time is often relished and fought for, but for NICE the high price and a small QALY advantage do not make for a cost-effective solution, and such drugs are rarely made available. As such, many negative NICE decisions can seem cold and are met with incredulity and anger. Pharmaceutical companies also battle with these decisions, since their new product has been proven effective for a particular disease but it will not be used in the United Kingdom via the NHS, which is a big blow for many reasons.

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Case Study 1: Cancer Drugs Fund

In 2011, the United Kingdom Government introduced a £200 million per year Cancer Drugs Fund (*8*) that was designed to provide access for cancer patients to drugs that were deemed not cost-effective by NICE. The fund increased to £280 million in 2014, and had been overspent in previous years. At the end of 2014, the drugs covered by the fund were re-assessed; 25 previously covered treatments were removed for new patients, although existing patients would still be covered.

On the face of it, this scheme seems reasonable and provides much needed drugs to patients who are desperate for more time. However, scratch the surface and there is much to be concerned about:

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- The fund directly undermines the authority of NICE, which was set up to deliver cost-efficient care for the United Kingdom on the basis of evidence and rigorous assessment – that is, they should be the arbiters for all treatments delivered via the NHS
- Many physicians and the general public do not support the prioritization of cancer care provision over other similarly impactful, life-changing diseases, as the NHS was designed to provide fair and equitable treatment for all patients that is free at the point of delivery

The Cancer Drugs Fund, therefore, is not a product of evidence-based policy-making, whereas the NICE system in general is a very good example of this.

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Case Study 2: Meningitis B Vaccine

For vaccinations delivered across the entire population, NICE does not provide advice or make decisions on cost-effectiveness. Instead, the long-standing Joint Committee on Vaccination and Immunisation (JCVI) is responsible for these tasks. In 2010, the JCVI started to look at the evidence supporting the potential introduction of a new childhood vaccine against meningococcal Group B diseases, one of the most deadly forms of meningitis. Thankfully rare, the disease had previously proved difficult to immunize against due to the nature of the bacteria that causes it, compared, for example, with *Haemophilus influenzae* type b, meningitis C, and pneumococcal infections, for which vaccines have proven very effective and have been used for many years.

Across a number of meetings where all the available data on the vaccine and on the epidemiology of the disease were analyzed and discussed, the JCVI concluded in July, 2013, that the general immunization of the population "…is highly unlikely to be cost effective at any vaccine price" (*9*). The JCVI had used the same basic approach as NICE to ensure consistency. However, there ensued a strong and consistent public and expert campaign to introduce the vaccine, which, along with additional evidence and some cost-modelling revisions (eg, including the cost of potential litigations) ensured that the JCVI re-evaluated their decision. In February, 2014, the JCVI published an advisory note to the Government that said that the proposed vaccine "… only demonstrated cost-effectiveness at a low price, [and, therefore,] plans should anticipate a sustainable and cost-effective programme" (*10*). In other words, they recommended that the Government should go ahead with a vaccination program if it could agree on a low price with the manufacturer.

This outcome was hailed as a great success for democracy and, in a way, it upheld the evidence-based decision-making process, albeit to highlight that evidence must be extensive and modelling must be extremely robust. The saga, however, did not end there and routine vaccination still had not started 1 year on from the decision due to protracted negotiations between the Government and the manufacturer of the vaccine. Deadlock was eventually broken in late March, 2015, when a different company assumed control of the vaccine.

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There are many more examples of where the policy direction taken on the provision of health-care and the route suggested by the science and other sources of evidence have separated. On the whole, however, the care provided to patients when they need it is world-class and sometimes world-leading.

Probably more contentious than health-care policy is how illegal drugs are handled. Here you not only have the ideology of the government of the day and the evidence generated by the experts, but the lawmakers and the tricky topic of policing must also be considered. All these factors coalesce with some highly polarized, and sometimes vocal, public opinion. Key amongst these is how the various illegal drugs are classified, which must take into account many factors, but most relate to risk to health (individual and societal). Dependent on classification, the legal system sets policing and sentencing structures. In the United Kingdom this classification system is split into three levels: A, B, and C, of which A is the highest and includes drugs such as heroin, cocaine, and MDMA (ecstasy).

The last major overhaul of policy in this area was in 1971, when the Misuse of Drugs Act was introduced. With that came the introduction of the Statutory Advisory Council on the Misuse of Drugs (ACMD), which states its remit to be "…mak[ing] recommendations to government on the control of dangerous or otherwise harmful drugs, including classification and scheduling under the Misuse of Drugs Act 1971 and its regulations" (*11*). On the whole, the Government follows the advice of the ACMD, although there have been notable occasions where the advice given was counter to the ideology of the Government of the day was not taken, showing that in some areas the Government chooses how much of the evidence-supported advice to actually follow. The friction this can create is highlighted in the following case study, which received a significant amount of media coverage at the time.

Case Study 3: Professor Nutt and Drug Policy

Professor David Nutt chaired the ACMD from January, 2008, and was never far from controversy, clashing with successive Home Secretaries. In January, 2009, he published a paper that drew comparisons of risk between illegal drug use and the harms associated with other legal activities – most notably, he highlighted that horse-riding was associated with around one serious adverse event for every 350 exposures, whereas taking ecstasy was associated with roughly one serious adverse event for every 10,000 exposures. On the basis of this and other evidence, the ACMD advised that ecstasy should be downgraded from a class A status to class B, but the Government refused to do so. At the same time, the Home Secretary reversed a decision by her predecessor to classify cannabis as a class C compound, returning it to class B. Furthermore, the Home Secretary made David Nutt apologize for his comments about ecstasy and horse riding.

Later in 2009, Professor Nutt gave a lecture and produced a leaflet that essentially brought into question the classifications of illegal drugs and showed that, on the basis of the harms scoring system used by ACMD, alcohol and tobacco would be classified as class B ahead of cannabis. He also questioned

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the rationale behind hunting down low-level cannabis users in order to protect them. He was promptly relieved of his position by the new Home Secretary, who stated "He was asked to go because he cannot be both a government adviser and a campaigner against government policy" (*12*) Professor Nutt went on to establish a completely independent advisory body on drug harm, which is consulted by many governments and the European Commission.

This sorry saga, shows that in this highly charged area, scientific advice can only go so far in shaping policy. The Home Secretary, on removing Professor Nutt from his post, made a very telling statement "As for his [Professor Nutt's] comments about horse riding being more dangerous than ecstasy, which you quote with such reverence, it is of course a political rather than a scientific point" (*13*).

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So Does Science Play an Appropriate Role in Policy-Making?

The case studies above are a few examples of where the evidence supporting a particular policy route is essentially ignored or questioned in order to suit a political decision. Such are the intricacies of setting policy. However, on the whole, I think it is fair to say that evidence does play a significant role in the formation of policy. Professor Nutley summarizes the situation rather adroitly "…research rarely provides definitive answers to policy questions and rational decision-making rarely lies at the heart of policy processes … [E]vidence-informed or even evidence-aware policy would be a better description of the aspirations for the role of research in the policy making process" (*7*).

Where Does This Leave Scientists?

One major aspect that is essentially missing from the above discussion is the role of an informed public. The Government is there to serve the people, making decisions for them in return for safety and security – the social contract referred to above. However, the Government has to make many decisions in areas where the people are not generally well informed, which not only increases the pressure on the Government to put the structures in place to ensure that evidence plays a key role, but it also enables them to weave their ideology into policy.

As such, the routes by which external scientists can interact with and provide guidance to the Government are very well developed. They afford the opportunity for any individual with a useable expertise to become part of a scientific advisory committee. The learned societies also have notable roles in ensuring that the voice of science is heard, since they work closely with individual departments and with the Government Office for Science.

One area where science needs to play a bigger part is in developing the narratives around complex scientific topics for the general public. This is, of course, easier said than done, but will eventually ensure that the public is more aware and more engaged in important topics, such as drug funding, vaccinations, and illegal drug policy. This in turn will ensure that the Government is truly making decisions that benefit the whole of society in all areas of policy, and, in a way, will help the public view policy commitments and pledges with a more

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critical eye – taking us back to mass movement of the early days of the age of enlightenment.

Summary

Since the days of Copernicus, Hobbes, and Locke, evidence in one form or another has played an increasingly important role in the formation and function of governmental policy in the United Kingdom. Arguably, though, the biggest and most recent step forward in this evolving relationship happened in the early 21st century, when the role of scientific advisors to all departments of the Government was formalized and mandated through the Government Office of Science. Nevertheless, what cannot be questioned is the ever-present role that scientific societies have played in, not only bringing the latest science to the attention of policy-makers, but also advocating for the importance of central funding for science of all genres. As such, the effective communication of science has a rich and proud history as well as a bright future in the policy setting environment – even if there are a number of noteworthy illustrations of conflict between the evidence and the ideological or populist aims of the Government.

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Chapter 3

Consumer Communication of Nutrition Science and Impact on Public Health

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This paper highlights the need for evidence-informed policies for health care and nutrition communication, including the use of nutrition and health claims on food and food supplements to raise awareness of the vital role of nutrition in health. Dietary interventions for vulnerable groups, such as the elderly, women of childbearing age, children, and adolescents, can contribute to reducing the risk of suboptimal intakes and deficiencies of micronutrients and of chronic, non-communicable diseases, to controlling costs of health care, and to promoting the health and quality of life of people globally. Examples of public health messages include the communication of the scientific evidence for (a) the use of folic acid/folate and iron to reduce, respectively, the risk of neural tube defects and prevalence of iron-deficiency anemia in pregnant women, (b) the relationship between calcium and vitamin D, bone health, and reduced risk of osteoporosis and falling, and (c) the cardiovascular benefits of long-chain omega-3 fatty acids from oily fish and fish oil supplements. Today, and in the future, the global, environmental, demographic and public health challenges relate to a double burden of undernutrition on the one hand and obesity, overweight, and non-communicable diseases, including diabetes, cardiovascular disease, and cancer, on the other. The need is not only to educate consumers but also to drive home the vital science-based food and health messages to those responsible for formulating public health policies.

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Introduction

The 21st century will be marked by unprecedented environmental, demographic, and public health challenges, particularly in the areas of food production, agricultural practices, and water and energy supplies, as well as their impact on food, nutrition, and public health policies (*1*, *2*). Achievements in food science and technology have resulted in a global food system of immense size and complexity, with the result that our food is largely safe, tasty, nutritious, abundant, diverse, and convenient, and less costly and more readily accessible than ever before (*1*). Today, the modern production-to-consumption food supply chain has made it possible to feed nearly 7 billion people.

The United Nations has projected that by 2050, the world population will reach 9.6 billion (*3*). Adults aged ≥60 years will constitute 19% (2 billion) and 27% (3 billion) of the world population by 2050 and 2100, respectively. There will also be proportionately more women than men aged 60–≥80 years by 2050. These changes in the age structure of the human population around the world are unprecedented and continuing, and the aging of societies will affect employment, taxation, pensions, education, and public health. The numbers of people with various chronic diseases and mental and physical disabilities will also increase dramatically, highlighting concerns over quality of life and provision of health care in later life. Nutritional status has a major impact on disease and disability, and current trends in most developing and developed countries indicate a double burden of undernutrition on the one hand and obesity, overweight, high blood pressure, and associated non-communicable diseases (NCDs) on the other. For the first time, the major cause of global deaths (63%) will be from NCDs rather than infections. Four categories of NCDs account for 80% of global mortality causes: cardiovascular disease, cancer, diabetes, and chronic respiratory diseases (*4*).

Innovative solutions are needed now and in the future to ensure global food sustainability and nutrition security, taking into account the whole food chain, food choices, and dietary patterns in order to make any improvements in the food supply, and nutrition and health status.

This chapter examines the growing concerns and challenges from the public health problems of obesity and overweight and suboptimal intakes of the essential micronutrients and other protective components in the diet, to the difficulties of making healthy food choices from such abundance, and to the need for science-based health policies, including effective nutrition and communication strategies.

Nutrition and Health Policy Implementation

International and national organizations have, over several decades, issued food, nutrition, and health guidelines, and countries have developed recommendations and guidelines to help address the emerging food and health issues. Thus far, obesity, hypertension, cardiovascular diseases, and diabetes have posed significant threats to health and well-being, to pandemic proportions. Of further concern is the growing number of children and adolescents who are overweight and at risk of obesity and early onset of type 2 diabetes. Taken

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together, obesity, sedentary behavior, diet-related diseases, chronic malnutrition, and maternal and infant health represent the greatest health-care policy and research challenges.

Unfortunately, in spite of all the efforts to communicate guidelines on nutrition and health, the goals remain largely unmet. After decades of dietary recommendations for greater consumption of vegetables, fruits, and whole grain cereals and reductions in saturated fats, free sugars, and sodium, the challenges to persuading consumers to change their food and dietary behaviors remain. These challenges can only be met by focusing on nutrition, health, and wellness in priority population groups and by harnessing the strengths of the various scientific and communication disciplines through active interactions, collaborations, and partnerships.

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World Health Organization (WHO) Policy Options To Achieve Better Nutrition for All

WHO has developed a Framework for Action for improving nutrition in mothers, infants, and young children, and for reduction of the risk of NCDs (*5*). The WHO nutrition-related policy and program options include:

- review of national policies and investments to integrate nutrition objectives into food and agriculture policy, program design, and implementation, to enhance nutrition-sensitive agriculture, ensure food security, and enable healthy diets
- development, adoption and adaption, where appropriate, of international guidelines on healthy diets
- encouragement of gradual reductions of saturated fat, sugars, salt/sodium, and trans-fat from foods and beverages to prevent excessive intake by consumers and improve nutrient content of foods, as needed
- explore regulatory and voluntary instruments, such as marketing, publicity, and labeling policies, and economic incentives or disincentives in accordance with Codex Alimentarius and WHO rules to promote healthy diets
- establishment of food-based or nutrient-based standards to make healthy diets and safe drinking water accessible in public facilities, such as hospitals, child-care facilities, workplaces, universities, schools, food and catering services, government offices, and prisons, and encouraging the establishment of facilities for breastfeeding
- and implement nutrition education and information interventions based on national dietary guidelines and coherent policies related to food and diets, through improved school curricula, nutrition education in the health, agriculture, and social protection services, community interventions, and point-of-sale information, including labeling

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These policy options are consistent with the WHO Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013–2020 (*6*) and provide the framework for communicating key facts about a healthy diet (*7*).

The WHO nutrition guidelines are based on the Cochrane Database of Systematic Reviews and the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the body of scientific evidence (*8*). The process involves the identification of priority questions and outcomes, retrieval of the evidence, assessment and synthesis of the evidence, formulation of recommendations, including research priorities, and planning for dissemination and implementation. There continues to be a debate on the sources and nature of the totality of the scientific evidence, particularly on the development of a scientific framework for weighing the strength, consistency and biological plausibility of the evidence as well as identification of the strengths and limitations of different sources of evidence (e.g. randomized controlled trials/human intervention studies, epidemiological prospective cohort studies, *in vitro* and animal studies, and history of use) (*9*, *10*). Although randomized controlled trials are considered to be at the top of the hierarchy of evidence, for some areas of nutrition science these human studies are sometimes poorly suited to the task. Nutritional effects tend to manifest themselves in small differences over long periods of time, there are few validated biomarkers for diseases, and even fewer for physiologically adaptive responses in healthy people, where homeostatic mechanisms keep physiology within an individual's normal range (*9*).

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Integrity of Scientific Reporting

Public health officials tend to view WHO guidelines and recommendations as authoritative, especially when they are graded by the expert guideline panelists as strong. However, a recent paper concluded that several of WHO's strong nutrition recommendations were based on low or very low confidence estimates (*8*). The authors concluded that the findings raised questions as to whether the GRADE system is being applied appropriately and the extent to which WHO panelists neglect uncertainties in the evidence when they consider the strength of recommendations. Clearly, further inquiry is required into why guideline panelists are making strong recommendations based on low or very low confidence estimates, in order to minimize any distortions or biases in reviews of the scientific literature to justify public health actions (*11*, *12*).

From a media point of view, the more outlandish the research or scientific finding, the more newsworthy a story becomes. It is more often the journalists who tend to be blamed for this, accused of willfully distorting and misrepresenting the science in order to generate headlines. However, a study in the *British Medical Journal* has reviewed press releases on health stories issued by 20 leading UK universities in 2011, and tracked the subsequent news stories (*13*). It found that many of the exaggerations and inaccuracies in the news reports originated in the press releases. Over one-third of the press releases made claims for the impact of the research on humans, when in fact the study was carried out in mice or rats. A third also made claims of causation when only an association had been identified.

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The reality is that journalists, like the public at large, tend to believe what the scientists tell them. The key issue is that interpreting results and conclusions in scientific papers relies on a degree of scientific literacy that most journalists do not possess. Clearly, understanding and interpreting a scientific paper should be a fundamental part of science education. Anti-industry sentiment, feelings of righteous indignation and intentional or unintentional bias can all influence the reporting of research results (*11*, *12*). Medical and health professionals, reporters, research institute press officers, government policy-makers, and the public should, therefore, be aware of such biases and view the scientific literature with a critical eye.

The public, and particularly socioeconomically and underprivileged groups, often lack crucial pieces of information and believe things that are not true (*14*). General exhortations about diet are less effective than using a simple piece of information that people do not already know about. The message must be said in an attractive and simple way, and it must be from a credible source (*15*).

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Consumer Understanding of Nutrition and Health Claims on Food Labels

Nutrition and health claims on food labels and in advertising and promotional activities, such as on leaflets or websites, are potentially powerful tools in consumer communication, as they convey information on food characteristics (e.g. high in protein, source of calcium) and health-related food benefits (e.g. vitamin D contributes to the maintenance of bones and teeth) (*15*). As such, nutrition and health claims can influence consumer preference and facilitate well-informed food choices. Applied correctly, these claims have the potential to enhance consumers' nutritional knowledge and healthy eating patterns, as well as to improve public health more generally.

For health claims on foods and dietary food supplements, national and international legislation requires substantiating evidence based on the totality of the available data and the weight of evidence, in terms of strength, consistency, specificity, and biological plausibility (*16*, *17*). The scientific assessments of the substantiating evidence for dietary recommendations are very similar. Evidence-based nutrition is, therefore, routinely used for three aspects of public health nutrition: the development and revision of dietary guidelines/recommendations; the establishment of daily nutrient reference values (NRVs) for macronutrients and micronutrients, such as vitamins, minerals and the marine omega-3 fatty acids, eicosapentanoic acid (EPA), and docasohexanoic acid (DHA); and the validation of health claims on foods and food constituents.

For example, in Europe, dietary guidelines advise people to reduce intake of saturated fat. Health claims declare a beneficial physiological effect, that lowering dietary saturated fat can lower the blood cholesterol level, a risk factor for cardiovascular disease. This health claim can in turn be connected to a nutrition content claim that the food is low in saturated fat, according to the criterion set in the Annex to Regulation (EC) No 1924/2006 (*18*).

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The beneficial outcomes for dietary goals and for substantiation of health claims are based on human intervention studies (randomized controlled trials where possible) and clinical, observational, and epidemiological, studies where some indicators of health, well-being, or reduction of risk of disease can be demonstrated (*19*). In Europe, however, for the inclusion of a health claim on the EU Register of Authorised Claims (*20*), the claims must not only be based on and substantiated by generally accepted scientific evidence, but also they are permitted only if the average consumer can be expected to understand the beneficial effects as expressed in the claim (*18*). As a result of this new feature of the European legislation, the role of the consumer has become much more prominent. The Annex to Regulation (EC) No 1924/2006 (*18*) takes as its benchmark the average consumer, defined as "the consumer who is reasonably well informed and reasonably observant and circumspect" (Recital 16 in the preamble to the Regulation). The type of data and information that could be needed to provide evidence that the average consumer adequately understands a particular claim includes methodologies to assess how consumers process information about a particular food and its claim, qualitative and quantitative marketing surveys and questionnaires, heuristic approaches to find out how individuals decide whether or not to purchase and consume a particular product, as well as purchase and consumption data for the monitoring of food uses (*15*). What is clear is that methods to generate evidence of attitudes, understanding, and purchasing behavior still need to be developed (*15*, *21*).

What little is known about consumers and health claims indicates that claims are seen as useful and helpful to make healthier choices, that it can take years of exposure for the claimed diet–health relationship to become familiar, that consumers are still skeptical about commercial health claims, and that they dislike long, complex, and scientifically worded claims.

Commercial Communications and Dietary Recommendations: Insights into the European Regulation

Dietary guidelines or advice issued by public health authorities and bodies and information in the press and in scientific publications are outside the scope of the EU regulations on nutrition and health claims (Recital 4, Regulation (EC) 1924/2006) (*18*). In contrast, claims made in commercial communications, whether in the labeling, presentation, or advertising of foods to be delivered as such to the final consumer, are within the scope of Article 1(2) of the regulation. In the European Union, every claim on a food or dietary food supplement must be on the authorized list (*20*) and otherwise comply with the regulation. Claims must not be false, misleading, or exaggerated, and unauthorized claims are prohibited and illegal. Commercial communications include: product labels and packaging and product advertisements in any form (e.g. print, broadcast, internet, mail, promotional features, catalogues, and product directories and leaflets). They may also include menus and diet codes if the communication is considered commercial and is used in a hospital or medical context to advertise or promote a product to the benefit of the manufacturer, retailer, or caterer.

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Regulation (EC) 1924/2006 (*18*) does not address the legal position of communications from food business operators to health-care professionals and does not address the status of other types of communications from health-care professionals to consumers. The whole area is open to debate among lawyers and enforcement authorities. However, the promotional purpose of the communication is the key determinant of what is commercial or not. Under food law in Europe, the Council Directive EC 2009/39 includes a useful statement which implies that the law should not prevent the dissemination of any useful information or recommendations exclusively intended for persons having qualifications in medicine, nutrition or pharmacy. The rationale underpinning this reasoning is that health-care professionals should be able to recognize the true nature of a food because of their specialized education or knowledge. Overall, a presumption exists in Regulation (EC) 1924/2006 that the provision of the information must not have any promotional interest, that the communications are not a disguised form of advertising, that the material is intended to provide specialist knowledge to qualified professionals, and that the communication is not intended for the final consumer.

Reference to five-a-day in relation to consumption of fruit and vegetables and the number of portions a product provides in a dietary recommendation are not considered to be within the scope of the Regulation (EC) 1924/2006. However, if there is an added reference such as "good for you because it contains one of your five-a-day", use of the term "good for you" would come within the scope of Article 10(3). General, non-specific claims for benefits such as "digestive comfort", "digestive health", "more vitality", "more healthy" and "superfood" would all require an authorized claim to back them up.

Wording of Health Claims in Europe

Regulation (EC) 1924/2006 (*18*) does not control the exact wording of a health claim, and there is a degree of flexibility in attempts to use more consumer-friendly words on packaging and in advertising to communicate the benefits of a product. Consumers prefer simple and trustworthy information over scientific details. However, currently there is a paucity of consumer research to determine what enables adequate understanding by the average consumer, and enforcement authorities have been very strict if marketers have strayed from using the prescribed wordings of claims on the EU Register.

The wording of health claims is determined by the totality of the available scientific data and by weighing of the evidence. Most of the authorized claims are based on the scientific opinions of the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies. Clearly, the health benefits described in commercial communication on labels and in advertising must not go beyond the scope of the evidence, or confuse or mislead the consumer. Nevertheless, for food marketers, wording of claims is a difficult balance between the "KISS" approaches—keeping it soft and sentimental versus keeping it serious and scientific.

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Examples of permitted nutrient function health claims in the European Union (*20*) are shown in Table I for selected nutrients, iron, folate, and vitamin D. Unfortunately, nutrition knowledge is often lacking and, although consumers seem to have a basic awareness of calories, for other nutrients their nutrition knowledge is much lower (*21*, *22*). Whereas enforcement authorities find the prescribed wording of the permitted claims a definite advantage, to ensure compliance with the law, it remains to be seen if such scientifically orientated wordings will help consumer understanding of nutrition and health. To date, flexibility in the use of words by marketers has been fraught with difficulties, and most products with health claims provide the more consumer-friendly wording along with the actual permitted claim.

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Table I. Examples of Permitted Nutrient Function Health Claims in the European Union. SOURCE: Reproduced with permission from Reference (*20*). Copyright 2015 European Commission.

Nutrient	*Health claim*
Iron	Contributes to the normal formation of red blood cells and hemoglobin
	Contributes to normal oxygen transport in the body
	Contributes to normal energy-yielding metabolism
	Contributes to normal function of the immune system
	Contributes to normal cognitive function
	Has a role in the process of cell division
	Contributes to the reduction of tiredness and fatigue
Folate	Contributes to normal blood formation
	Contributes to normal homocysteine metabolism
	Contributes to normal function of the immune system
	Has a role in the process of cell division
	Contributes to normal maternal tissue growth during pregnancy
	Contributes to normal psychological function
	Contributes to normal amino acid synthesis
	Contributes to the reduction of tiredness and fatigue
Vitamin D	Contributes to normal absorption/utilization of calcium and phosphorus
	Contributes to normal blood calcium levels
	Contributes to the maintenance of normal bones
	Contributes to the maintenance of normal muscle function

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Table I. (Continued). Examples of Permitted Nutrient Function Health Claims in the European Union.

Nutrient	*Health claim*
	Contributes to the maintenance of normal teeth
	Contributes to the normal function of the immune system
	Has a role in the process of cell division

Examples of Public Health Messages

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WHO developed a global guideline on daily iron and folic acid supplementation in pregnant women as a public health intervention for the purpose of improving pregnancy outcomes and reducing maternal anemia in pregnancy (*23*). The evidence-informed recommendations used the procedures previously mentioned, including an up-to-date systematic review of the scientific literature and application of the GRADE methodology to assess the strength and consistency of the evidence.

It is estimated that 41.8% of pregnant women worldwide are anemic. At least half of this anemia burden is assumed to be due to iron deficiency, and it is a public health problem in industrialized and non-industrialized countries. Dietary interventions aimed at preventing iron deficiency, iron-deficiency anemia, and suboptimal intakes of folate/folic acid in pregnancy include greater consumption of nutrient-dense foods, fortification of staple foods with iron and folic acid, iron and folic acid supplementation, and health and nutrition education. The strong recommendation of WHO is for daily oral iron and folic acid supplementation as part of antenatal care to reduce the risk of low birthweight, maternal anemia, and iron deficiency. The suggested scheme for daily iron and folic acid supplementation in pregnant women is 30–60 mg of elemental iron and 400 μg (0.4 mg) of folic acid per day throughout pregnancy, and the target group is all pregnant adolescents and adult women.

These WHO guidelines are consistent with the authorized well-established nutrient function health claims in the European Union for iron and folate, as shown in Table I. However, Regulation (EC) No 1924/2006 allows nutrient content claims for "source" and "high" on a food product on the basis of criteria to provide 15% and 30% of the recommended daily intake (more recently called the reference intake) in the Regulation on Food Information to Consumers (*24*) per 100 g or 100 mL in the case of products other than beverages, or 7.5% and 15% reference intake per 100 mL of beverages, or 15% per portion if the package contains only one portion. These content claims contain only fractions of reference intake (e.g. 200 μg/day for folic acid and 14 mg/day for iron) and not the levels of those nutrients required to achieve the beneficial effects for women of childbearing age, which could introduce an element of confusion. Typically, the only way to achieve the amounts of iron and folate/folic acid is not through consumption of conventional, nutrient-dense foods or even fortified foods, but with food supplement products targeted at this at-risk group of the population. Another example is that whereas

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the permitted health claim for folate/folic acid is "contributes to normal maternal tissues growth during pregnancy", the more recent Commission Regulation (EU) No 1135/2014 (*25*) will make it lawful to make a direct claim that folic acid supplementation helps to reduce the risk of neural tube defects, such as spina bifida and anencephaly. The new claim was authorized on October 24, 2014.

The claim is: "Supplemental folic acid intake increases maternal folate status. Low maternal folate status is a risk factor in the development of neural tube defects in the developing foetus." The conditions of use are: "The claim may be used only for food supplements which provide at least 400 µg of folic acid per daily portion", and "Information shall be provided to the consumer to the effect that the target population is women of childbearing age and the beneficial effect is obtained with a supplemental folic acid daily intake of 400 µg for at least one month before and up to three months after conception". This amount of folic acid is considerably more than that required for a "high" content of a product, which would be 30% of the reference intake (i.e. 30% of 200 µg/day=60 µg).

Neural tube defects occur in the very early stages of pregnancy, when a baby's brain and spine fail to form properly, leaving the spinal cord exposed. The most common neural tube defect is spina bifida, which is both the most common and most severe congenital abnormality compatible with life. Babies are born with a large proportion of the brain and skull missing and will usually either die at or shortly after birth. The neural tube is formed during the first 28 days of pregnancy, before many women are even aware that they are pregnant. Fortunately today, most neural tube defects are diagnosed at the week 20 ultrasound scan. Nevertheless, women and their partners have to make some very difficult decisions involving termination of pregnancy and other life-changing situations. The risk of neural tube defects is significantly reduced by up to 72% when supplementation with folic acid is consumed in addition to a healthy diet before conception and during the 12 weeks after conception.

The authorization of the folic acid neural tube defects health claim on food supplements will undoubtedly help support public health efforts to educate and inform women. In several countries, the public health authorities have considered the potential for mandatory folic acid fortification of bread flour, whereas other countries have focused on better targeted use of food supplements to children of childbearing age. The public health policy decision on mandatory fortification in the United Kingdom has been deferred for well over a decade (*26*, *27*). The key issues in the ongoing discussions relate to the technical challenges of implementation of a fortification policy, the overages of folic acid needed to counter the inevitable losses due to the baking processes, and subsequent shelf-lives of bread and other products, consideration of whether widespread fortification of all flour-containing products is appropriate (i.e. in products high in energy, salt, added sugars, and fat), and the extent of voluntary additions of folic acid to food products. In addition, from a scientific perspective, much more attention needs to be given to the intimate metabolic relationship between folic acid and vitamin B_{12} in relation to neuropsychiatric syndromes and neuropathology including depression, cognitive decline and Alzheimer's disease in older people. Higher intakes of folic acid in the presence of suboptimal intakes or deficiencies in vitamin B_{12} are known to aggravate these conditions (*28*, *29*).

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Attention also needs to be paid to the number of people who might not benefit from mandatory fortification of bread and flour because they avoid these products for reasons of food allergy or intolerances or because of food preferences.

There are, therefore, significant scientific, technical, legal, and consumer understanding issues that need to be addressed in the formulation of a public health policy, particularly as mandatory fortification of flour and bread would shift nutrient intakes for the whole population that consumes fortified foods, and not just for the target population.

Vitamin D and Public Health Outcomes

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Vitamin D deficiency is a major public health problem worldwide in all age-groups, even in those residing in countries with low latitudes, where it was generally assumed that ultraviolet radiation from sunlight was adequate enough to prevent this deficiency, and in industrialized countries, where vitamin D fortification has been implemented over the years (*30*). Although poor vitamin D status has been related to hypertension, diabetes, metabolic syndrome, cancer, autoimmune and infectious diseases, and other conditions, this essential fat-soluble vitamin is best known to consumers in connection with healthy bones and teeth. Assessment of the level of evidence for the various potential benefits have been undertaken recently (*31*, *32*) and the evidence for skeletal benefits is strong, especially for the reduction of risk of fractures and falls in older people. Vitamin D deficiency, which classically manifests itself as bone disease—rickets in children and osteomalacia in adults—is characterized by impaired bone mineralization. Vitamin D deficiency is common and insufficiency very common in non-pregnant women, children, and adolescents, as well as in the elderly (*33*). Lifestyle factors, such as daily exposure to sunlight, especially in winter months, levels of outdoor activities, the use of sunscreens and restrictions on dress, can all contribute to the high prevalence of subclinical deficiencies not only in children and adolescents but also in adults, particularly women, and older people.

There is a general consensus that the vitamin D metabolite 25-hydroxyvitamin D (25[OH]D) is the best biomarker of vitamin D status, but there is still some controversy about the serum concentration associated with optimal status (*34*). EFSA concluded in a scientific opinion (*35*) that reports from authoritative bodies and reviews show that there is a good consensus on the role of vitamin D in growth and development of bone, that human observational studies and intervention studies support an association between 25(OH)D as an indicator of vitamin D status and bone health outcomes (bone mineral density and bone mineral content) in children and adolescents, and that there is a dose-response relationship between vitamin D intake and serum 25(OH)D levels. In addition, the EFSA scientific opinion (*35*) stated that the scientific evidence demonstrated the occurrence of suboptimal vitamin D status in subgroups of children in a number of European countries, particularly in winter months. For children, the EFSA Panel on Dietetic Products, Nutrition and Allergies concluded that, on the basis of the available evidence, a cause and effect relationship had been established, and it recommended a health claim that reflected the scientific evidence: “Vitamin D

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is needed for normal growth and development of bone in children". In order to bear the claim, food should be at least a source of vitamin D as per the Annex to Regulation (EC) 1924/2006 (i.e. 15% of the reference intake per 100 g or 100 ml). Such amounts can easily be consumed as part of a balanced diet. The target population is children and adolescents up to 18 years of age (*35*). For the general healthy population, the permitted health claims for vitamin D in the EU are shown in Table I.

In November 2014, on the basis of EFSA scientific opinion (*36*), the European Commission authorized a new health claim for reduction of risk of disease (*37*) relating to the effects of vitamin D and the risk of falling for men and women 60 years of age and older. The authorized claim is: "Vitamin D helps to reduce the risk of falling associated with postural instability and muscle weakness. Falling is a risk factor for bone fractures among men and women 60 years of age and older. The claim may be used only for food supplements which provide at least 15 µg vitamin D per daily portion. Information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 20 µg vitamin D from all sources."

Currently in the United Kingdom, the National Institute for Health and Care Excellence and the Public Health Advisory Committees have been reviewing existing public health recommendations, how they are being implemented and what needs to be done to increase awareness of vitamin D for health and wellbeing (*38*). There is certainly an urgent need for raising public awareness of the importance of vitamin D for good health, with emphasis on the fact that it is contained in only a few foods, that safe exposure to sunlight is an important lifestyle measure, and that targeted use of food supplements is a safe and effective way to improve nutritional status (*38*).

Cardiovascular Benefits of Long Chain Omega-3 Fatty Acids from Oily Fish and Fish Oil Supplements

Considerable progress has been made over the past decade in improving understanding of the biological effects of dietary fatty acids. Omega-3 polyunsaturated fatty acids, specifically EPA and DHA, modulate metabolic and immune processes and confer benefits in areas of cardiovascular disease and neurodevelopment (*39*). The effects of EPA and DHA in healthy adults relate to primary prevention of cardiovascular disease and include helping to lower risk of blocked blood vessels and heart attacks and decreased risk of abnormal heart rate and sudden death. With respect to cardiovascular disease, prospective epidemiological and dietary intervention studies indicate that consumption of oily fish consumption or dietary supplements of omega-3 polyunsaturated fatty acids (equivalent to 250–500 mg of EPA and DHA daily) decrease the risk of mortality from coronary heart disease and sudden cardiac death (*39–41*). On the basis of available data, the EFSA concluded that an intake of 250 mg per day of EPA and DHA combined is sufficient for primary prevention in healthy individuals, and the EFSA Panel on Dietetic Products, Nutrition and Allergies proposed setting an adequate intake lower limit of 250 mg per day for adults,

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based on cardiovascular considerations (*42*). EFSA also stated that on the basis of the currently available evidence it is not possible to define an age-specific quantitative estimate of an adequate intake of EPA and DHA for children aged 2–18 years. It advised that dietary advice for children should be consistent with advice for the adult population, with one to two meals including fatty fish per week or about 250 mg EPA and DHA per day. It should be noted that, from the numerous epidemiological studies showing an inverse relationship between EPA and DHA intake and cardiovascular outcomes, a level of 250 mg per day was the lowest level that significantly reduced the risk of cardiovascular events (*43*). However, the greatest reduction in risk of coronary heart disease mortality (roughly 37%) was associated with intake of around 566 mg per day. Evidence from primary and secondary prevention studies of cardiovascular disease has also provided data suggesting that higher levels of combined EPA and DHA reduce mortality from coronary heart disease or sudden death in persons with and without cardiovascular disease (*39*). Authorized health claims for omega-3 fatty acids EPA and DHA in the European Union are: "Contributes to the normal function of the heart (250 mg/day)" and "Contributes to maintenance of normal blood pressure (3 g/day)" (*44*).

What is abundantly clear is that there is a total disconnect regarding the amounts of seafood and EPA and DHA that are needed in order to meet dietary recommendations and what is actually consumed (*45*). From a nutrition policy perspective, most populations are not meeting current recommendations for omega-3 fatty acid intake. Therefore, there is a need to establish an international nutrient reference value for EPA and DHA as part of an overall public health policy that with which intake levels can be compared to determine whether a given population is consuming the recommended intake. Having a nutrient reference value for EPA and DHA combined would help develop public health messages for which convincing evidence of the health-enhancing effects exists. Health professionals, such as physicians, dieticians, nutritionists, and nurses, who offer nutritional advice, as well as regulatory agencies and researchers, would then all know how strong the science is behind the recommendations, and that the evidence has been through a rigorous and transparent evaluation process. An internationally agreed nutrient reference values would provide the basis for commercial communications and for nutrient content claims and health claims on food and food supplement products (*46*, *47*).

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Conclusions

The development of evidence-informed dietary recommendations and guidelines as well as the scientific substantiation of health claims on foods and dietary food supplements depend on scientifically robust, transparent and independent assessments of the available evidence. The proper use of systematic reviews of the literature, such as the Cochrane Database of Systematic Reviews, and the use of GRADE methodology provide the frameworks to determine the extent to which cause and effect of a particular diet–health relationship can be demonstrated. Such a framework, when administered soundly, should provide a

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high level of consumer protection and legal certainty for companies and research organizations.

Following the WHO and Food and Agricultural Organization Second International Conference on Nutrition in November, 2014 (*5*), several policies and actions were recommended.

- implementation of nutrition education and information interventions based on national dietary guidelines and coherent policies related to food and diets, through improved school curricula, nutrition education in the health, agriculture, social protection services, community interventions, and point-of-sale information, including labeling
- building of nutrition skills and capacity to undertake nutrition education activities, particularly for front line workers, social workers, agricultural extension personnel, teachers and health professionals
- conducting of appropriate social marketing campaigns and lifestyle change communication program to promote physical activity, dietary diversification, consumption of micronutrient-rich foods such as fruit and vegetables, including traditional local foods and taking into consideration cultural aspects, better child and maternal nutrition, appropriate care practices and adequate breast feeding and complementary feeding, targeted and adapted for different audiences and stakeholders in the food system

Science-informed healthcare policies and communications to consumers to ensure good nutrition throughout the life cycle need to be targeted to specific population groups in such a way that the messages are attractive and simple. General exhortations, including dietary recommendation, appear to be less effective and, therefore, the message must say something that people do not already know and which motivates and stimulates interest. The communications must come from a credible source and draw on the scientific evidence to find proven solutions to address the major challenges in food and nutrition.

A key goal is to communicate and increase awareness of the benefits of good nutrition and particular foods and food components to women of childbearing age. Optimal development of infants depends on the diet of mothers, and pregnancy and lactation are periods when good nutrition is exceptionally important. Investment in the nourishing of pregnant and lactating women results in a significantly improved return in infant health outcomes (*48*). Likewise, the development of effective nutrition, health-care, and communication strategies for older people is necessary to modulate favorably the age-related decline in most organ functions and reduce the development and/or the progression of chronic disease.

Health-care costs are expected to rise dramatically in the next two decades, and much more attention needs to be focused on how they can be controlled. For chronic diseases, direct and indirect costs both contribute hugely to health-care expenditures, and the health spending in many countries is likely to outpace economic growth significantly. Obesity and overweight, leading to an impending epidemic of diabetes, will add to the severity of health-care costs in most countries of the world. Econometric and public health cost saving studies in well-researched

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areas, such as by the supplementary use of omega-3 fatty acids, vitamin D, and iron, could be used to demonstrate the benefits of these dietary components in lowering national health-care costs. The need is not only to educate consumers but also to drive home vital science-informed messages on food and health to policymakers that better nutrition is the key to reducing health-care costs. Such actions could help maximize the span of good health and quality of life for people at the different life stages.

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Chapter 4

The Role of Regulatory Science in Reducing the Public Health Impact of Tobacco Use

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The Family Smoking Prevention and Tobacco Control Act resulted in the United States Food and Drug Administration regulating tobacco products. The Food and Drug Administration set up the Center for Tobacco Products, which now funds a wide range of regulatory research projects. These include developing the science to assess whether regulatory actions should have a positive impact on public health. Regulatory science in the field of tobacco product regulation is relatively new, and methodologies to assess the risk of new tobacco and nicotine products, to individuals and to the population, require the integration of a wide range of scientific study.

Introduction

Tobacco use, and particularly cigarette smoking, is a major cause of premature mortality and morbidity. The impact of tobacco use on global health is so important that the World Health Organization (WHO) led the development of the first public health treaty, the Framework Convention on Tobacco Control (FCTC), to co-ordinate international approaches to the regulation of tobacco products. The treaty was first introduced in 2005, and by the beginning of 2015, 180 countries had become signatories to the treaty (*1*). The FCTC seeks to address tobacco control through a diverse set of approaches, including encouraging alternative crops for farmers, tax and international trade policies, health warnings, advertising, and product regulation (*2*).

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The United States is not a signatory to the FCTC, but has arguably set up the most sophisticated and best-resourced regulatory agency dealing with tobacco control. The introduction of the Family Smoking Prevention and Tobacco Control Act in 2009 gave the United States Food and Drug Administration (FDA) authority to regulate tobacco and funds to set up a regulatory infrastructure, including the formation and staffing of the Center for Tobacco Products (CTP) (*3*).

Numerous epidemiological studies have reported that cigarette smoking causes a range of serious diseases, including lung cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD). The relationship between smoking and disease is dose related. Risks increase strongly with increasing daily consumption and total duration of smoking, with duration being the dominant factor (*4*). Studies have also found that health risks diminish following the cessation of smoking at a rate dependent on the number of years of smoking and age at cessation. Risks either return to levels similar to those in never smokers, in the case of diseases such as cardiovascular disease and lung cancer, or slow in progression for diseases such as COPD (*5*, *6*).

This understanding led the United States Institute of Medicine (IoM), in a report on the scientific basis for tobacco harm reduction, to suggest that some of the harm caused by tobacco use might be lessened by the introduction of what it termed potential reduced-exposure products (PREPs). These were defined at the time as (a) resulting in the substantial reduction in exposure to one or more tobacco toxicants and (b) being reasonably expected to reduce the risk of one or more specific diseases or other adverse health effects (*6*). The IoM report was not specific about which toxicants should be reduced or the degrees of reduction, but rather expected that clinical and other studies would be used to determine whether toxicant reductions could reasonably be expected to result in reductions in health risks.

This harm reduction approach to reducing the public health impact of tobacco use has been included in the framework the FDA is considering. Under the governing Act, the FDA can set product standards as a means of reducing health risks across a product category, and has developed a mechanism for considering modified-risk tobacco products (MRTPs), an evolved term from PREPs (*3*). A further IoM report set out the scientific expectations to substantiate an application for an MRTP, which, importantly, included assessment of the likely change in risk to individuals currently using tobacco products who might switch use to a new product, and of the population as a whole, including ex-smokers and never smokers (*7*).

The FDA process for assessing an MRTP application involves a 1-year review process with redacted information made public. Mechanisms are in place for public comment and for scientific review by the CTP expert committee, the Tobacco Products Scientific Advisory Committee (*8*).

The first products to be accepted through the FDA MRTP approval process comprise a range of snus oral tobacco products (*9*). Over the past few decades, snus, defined by both its manufacture and toxicant content, has become especially popular among Swedish men as a replacement for cigarette smoking. It has been used for a sufficiently long period in enough of the population for there to be a large number of epidemiological studies quantifying the risk of use. An advisory

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committee of the United Kingdom Royal College of Physicians reviewed the epidemiological data and concluded that snus use was substantially less risky than cigarette smoking owing to no association between snus use and lung cancer or COPD (*10*). The key challenge for an MRTP application on snus, therefore, is probably not about proving that the products are lower in risk for people who switch completely from cigarettes to snus, but more about what risks are associated with dual use of snus and cigarettes and what would be the effect on ex-smokers and never smokers of starting to use snus with an MRTP indication (in the current application, with a change in health warning).

The challenge of achieving an MRTP indication is significantly greater for products that have no associated epidemiology because they have either not been used for sufficient time or have never been popular enough to allow population-level assessments. An example of this is tobacco-heating products, sometimes referred to as heat-not-burn products. Many of the toxicants found in cigarette smoke result from the pyrolysis of tobacco. The burning coal of a cigarette when puffed is around 900°C and much of the chemistry in the combustion zone occurs at 300–600°C (*11*). Nicotine, however, is released from tobacco at much lower temperatures (around 180°C) and, therefore, products that heat the tobacco to temperatures up to 200–250°C are likely to still contain nicotine in the aerosol, but tobacco toxicants will be far fewer or present at lower levels than found in traditional cigarette smoke.

Although the consequences of cigarette smoking on health are clear from epidemiological studies, cigarette smoke is a complex mixture of thousands of chemicals (at least 9,600 identified), more than 100 of which are thought to be toxicants (*12*, *13*). Individual dose responses for these toxicants are not known, nor are the effects of changing the composition of the complex mixture. As described later in this chapter, assessing the potential impact of new products such as these on population health related to tobacco use will require the integration of a range of scientific studies.

Moreover, there is an important element of communication by regulators regarding tobacco products deemed to be of lower risk than conventional cigarettes. This is an area where regulators are likely to be precautionary in their approaches. Regulatory science should give regulators more confidence that their approaches to both regulating tobacco products and to communicating to the public the differential in risk between different tobacco products are founded in sound science and are likely to be of public benefit.

Placing Products on a Risk Continuum

The risk continuum of tobacco and nicotine products, which we believe was conceived by Action on Smoking and Health in the United Kingdom and further developed by McNeill and Munafò (*14*), sets out the hypothesis that levels of exposure to toxicants and health risks differ between types of tobacco and nicotine products. Cigarettes and cigars are at the highest-risk end of the continuum and electronic cigarettes (e-cigarettes) and pharmaceutical nicotine-replacement therapy at the other. Thus, they order product categories on the risk continuum as:

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Cigarettes > cigars > pipes > chewing tobacco > tobacco gum > snus > e-cigarettes > nicotine-replacement therapy.

For some of these product categories, such as cigarettes, cigars, and snus, sufficient epidemiological data are available to allow assessment of the relative health risks. For others, such as nicotine-replacement therapy, which comprises products that are prescribed, generally for a short period, to aid quitting, evidence from groups that have used the products longer than indicated suggests a reasonably low risk profile. Others products, such as e-cigarettes, are emerging technologies for which some data related to toxicant exposure are available, but there are little or no epidemiological data to characterize the risk of long-term exposure. Others, such as tobacco-heating products (e.g. a battery-powered device used to heat tobacco), have been available for decades but have never had mass appeal and are not yet recognized on McNeill and Munafò's continuum.

In British American Tobacco's sustainability reporting, we have also presented a version of the product continuum (Figure 1) (*15*). Product categories are placed in order of toxicant exposure, noting that certain toxicant levels in snus might be relatively high but biologically relevant exposure (in terms of the key respiratory diseases associated with smoking) to these toxicants is low since the product is used orally rather than creating an inhaled aerosol (*16*).

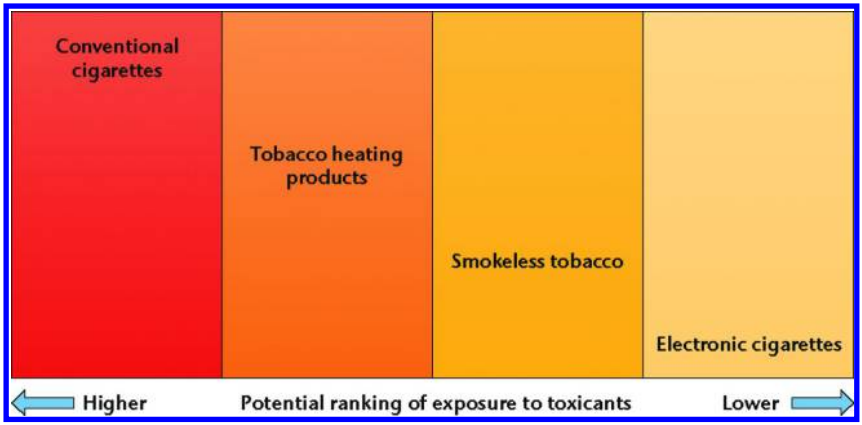

Figure 1. British American Tobacco continuum of toxicant exposure related to tobacco and nicotine products. Copyright 2014 British American Tobacco. (Figure has been altered slightly.)

It is not, in our view, yet possible to accurately position all four categories of product in terms of relative risk. The relative risks of using cigarettes and snus are known, and it might be assumed from current characterization (though uncertainties exist) that e-cigarettes should approach the risks of long-term nicotine-replacement therapy use, which is substantially lower than cigarette smoking. However, assigning relative risks is what is needed to allow regulators to assess whether differential approaches should be taken to the regulation of each category, and to determine what should be communicated to the public about the likely risks they will encounter if using one product or another.

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Identifying and Evaluating Toxicants in Tobacco and Tobacco Smoke

The FDA has involved its Tobacco Products Scientific Advisory Committee in the determination of which harmful or potentially harmful constituents (HPHCs) are present in tobacco and tobacco smoke. They have created a list of around 100 toxicants that were identified in the literature as being substances that individually had toxic properties, as assessed against a wide range of toxicological end points (*17*).

To define all toxicants in tobacco and tobacco smoke is difficult. The first major public health report on smoking and health issued in 1962 by the United Kingdom Royal College of Physicians (*18*) followed the early epidemiology of Doll and Hill (*19*). It estimated that tobacco smoke contains 300 chemicals, around 16 of which it designated as carcinogenic, and others, including ammonia, volatile acids, aldehydes, phenols and ketone, that were thought to play a role in smoking-related diseases by affecting the defense systems in the respiratory tract. In the 1980s, Dietrich Hoffmann and co-researchers at the American Health Foundation published a series of papers on toxicants in smoke and introduced a subset of 44 toxicants that represented the classes of toxicants in smoke and was subsequently known as the Hoffman list (*20*).

If assessing the potential risks of a new product includes measuring the reduction in exposure to toxicants, as originally set out by the IoM, then understanding the range of toxicants in historic and current cigarettes is important.

The measurement and reporting of these toxicants is very uncommon and, therefore, the range of toxicants present in cigarette smoke from products around the world is poorly described. For some years Health Canada and Brazil's Health Surveillance Agency ANVISA were the only regulators to require the measurement and disclosure of tobacco and smoke toxicants. In Canada, values for a subset of these were required to be printed on packs of cigarettes until Health Canada research found that smokers did not understand the information. Only a small number of other regulators, including regulators in Venezuela and Taiwan, have required reporting of tobacco and smoke toxicants. Most recently, the FDA has introduced required measurement and disclosure of values for 18 HPHCs, and is currently considering how to provide the public with this information in a way that will be clearly understood.

Rodgman and Perfetti (*21*) and Fowles and Dybing (*12*) identified around 150 toxicants with specific toxicological properties, and as the sensitivity of analytical instrumentation and understanding of compound and mixture toxicology continues to improve even more could be identified. Nevertheless, whether any subset of toxicants is more important than other toxicants to smoking-related disease formation remains challenging to determine.

Outside the United States, most countries have ratified the WHO FCTC to guide countries in setting tobacco control regulations. Two FCTC articles, Articles 9 and 10, relate to regulation of tobacco products, including the measurement and disclosure of tobacco and tobacco smoke constituents and emissions. WHO has formed the Tobacco Laboratory Network (TobLabNet) of independent international analytical laboratories, which is working to establish standardized

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methods for assessment of a selection of the toxicants, and includes some of the methods that were previously established by the International Organisation for Standardisation (ISO) and through Health Canada.

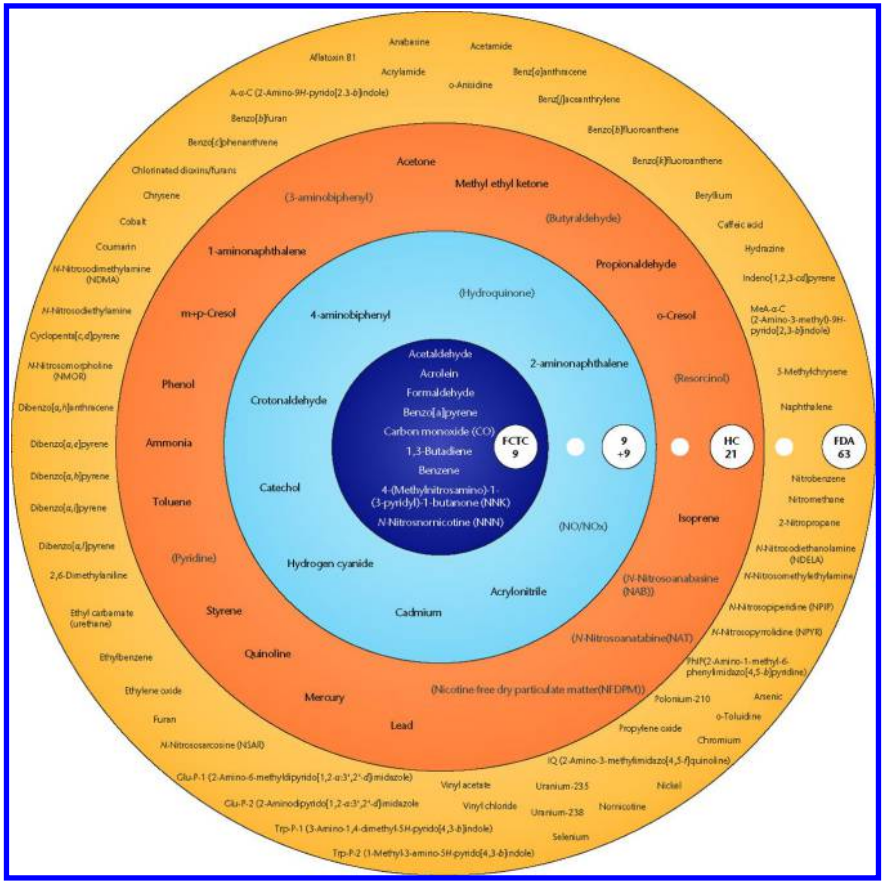

Figure 2. Harmful and potentially harmful constituents of tobacco and tobacco smoke identified by the United States Food and Drug Administration. Constituents highlighted in the inner circle are those suggested by the World Health Organization for mandated reductions. Reproduced with permission from reference (15). Copyright 2014 British American Tobacco.

WHO also has a scientific advisory panel, the Study Group on Tobacco Product Regulation (TobReg), which has issued various reports, including one recommending a possible approach to the mandated lowering of tobacco smoke toxicants (*22*). This group recommended focus on 18 toxicants in tobacco smoke (some differ from those currently being assessed by the FDA), nine potentially for mandated lowering and nine for monitoring. These toxicants were chosen because of their potential toxicity, for instance cancer potency factors, and because some, such as tobacco-specific nitrosamines (TSNAs), vary across products styles. Figure 2 presents HPHCs identified by the FDA.

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There are two key sources of toxicants in smoke – those that transfer directly from the tobacco to the smoke, such as heavy metals (e.g. cadmium), and those that are formed during combustion (e.g. carbon monoxide) either by pyrosynthesis or thermal breakdown (*23*). Some toxicants have more than one route of formation. For example, TSNAs can be transferred directly from the tobacco leaf and formed by pyrosynthesis during combustion. Toxicant precursor levels vary substantially in different tobacco blends, dependent upon the varieties of tobacco used, environmental conditions, agrochemical conditions during growing, and conditions during curing and storage (*11*). The combustion conditions within a cigarette, which vary dependent upon several factors, including the way in which the cigarette is smoked, can affect the total yield of an individual compound and the relative yields of constituents. Filter materials affect overall and individual smoke yields (*24*). In addition to reductions in yields of particulate-phase compounds through mechanical filtration by the cellulose acetate fibers, the plasticizer triacetin selectively reduces levels of phenols, and active carbon can selectively filter some vapor-phase toxicants, especially at ISO machine smoking flow rates (*25*).

The current ranges of commercial cigarettes manufactured and sold globally have a reasonably wide range of toxicant yields. We have developed a database of smoke yields obtained under Health Canada Intense smoking conditions from three sources (*26–28*), noting that such comparisons must be treated with caution due to the known difficulties related to limited standardization between laboratories for the analysis of smoke constituents (*27*, *29–31*).

We removed data for arsenic, methyl ethyl ketone, nickel, and selenium yields from the dataset as they were not provided by all three sources. Additionally, several brands were removed because of incomplete, duplicated, or erroneous data. Finally we removed data on reference products to ensure that only yields from commercial brands were included. The final dataset had information on 39 toxicants in 120 cigarette brands from 16 countries or regions.

We examined the data to see whether they were normally distributed. Several toxicants were normally distributed, but most (particularly nitrogenous toxicants, such as TSNAs and aromatic amines) were not. Consequently, the reference dataset was subject to an empirical cumulative distribution analysis that produced a percentile distribution within the toxicant yields. Although unlikely to be fully representative of the range of cigarette products on sale globally, with respect to either design features or brands, this database constitutes a reasonable comparator set for toxicant yields from novel products or conventional products from a different market.

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Table I. Summary of Toxicant Data Used To Create Cumulative Toxicant Load. SOURCE: Reproduced with permission from reference (*15*). Copyright 2014 British American Tobacco.

Smoke toxicant	*Units*	*Mean (range)*
Tar	mg/cig	29.4 (16.3–39.6)
Nicotine	mg/cig	2.11 (1.07–3.21)
Carbon monoxide	mg/cig	26.4 (16.4–40.7)
Nitrous oxide	µg/cig	232 (88–547)
NAB	ng/cig	20.4 (NQ–107)
NAT	ng/cig	121 (22–353)
NNK	ng/cig	112 (34–263)
NNN	ng/cig	136 (16–411)
1-aminonaphthalene	ng/cig	27.3 (11.7–54.8)
2-aminonaphthalene	ng/cig	17.6 (7.8–31.7)
3-aminobiphenyl	ng/cig	4.51 (2.10–9.15)
4-aminobiphenyl	ng/cig	3.58 (1.60–7.02)
Benzo(*a*)pyrene	ng/cig	17.8 (6.6–35.8)
Catechol	µg/cig	129 (44–307)
Resorcinol	µg/cig	2.28 (NQ–4.60)
Hydroquinone	µg/cig	127 (47–220)
Phenol	µg/cig	33.5 (8.1–175)
o-Cresol	µg/cig	7.99 (2.14–33.0)
m+p-Cresol	µg/cig	19.6 (6.1–76.2)
Formaldehyde	µg/cig	117 (29–229)
Acetaldehyde	µg/cig	1216 (752–1718)
Acetone	µg/cig	625 (385–851)
Acrolein	µg/cig	139 (79–209)
Propionaldehyde	µg/cig	105 (63–151)
Crotonaldehyde	µg/cig	57.2 (28.7–95.0)
Butyraldehyde	µg/cig	72.2 (48.7–99.5)
Hydrogen cyanide	µg/cig	319 (180–599)
Ammonia	µg/cig	31.4 (11.090.0)
1,3-Butadiene	µg/cig	93.8 (72.9–118)
Acrylonitrile	µg/cig	21.0 (12.1–34.3)

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Table I. (Continued). Summary of Toxicant Data Used To Create Cumulative Toxicant Load

Smoke toxicant	*Units*	*Mean (range)*
Isoprene	µg/cig	701 (395–1160)
Benzene	µg/cig	78 (50–102)
Toluene	µg/cig	136 (83–188)
Pyridine	µg/cig	36.8 (21.4–60.2)
Quinoline	µg/cig	0.69 (0.25–1.95)
Styrene	µg/cig	24.0 (15.1 33.3)
Cadmium	ng/cig	124 (44–225)
Lead	ng/cig	22.4 (NQ–70.9)
Mercury	ng/cig	6.20 (4.20–8.53)

NAB, N′-nitrosoanabasine; NAT, N′-nitrosoanatabine; NNK, 4-(methlynitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitrosonornicotine.

Two TSNAs are common to most lists of toxicants: 4-(methlynitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN). These have some of the largest ranges across cigarettes (Table I). Hecht (*32*) has proposed the introduction of very low limits on the levels of these two TSNAs. This proposal was made on the basis of a United States Surgeon General's Report (*5*), which concluded that levels of TSNAs might be responsible for the rising incidence of adenocarcinoma seen in some countries. Czoli and Hammond (*33*), however, found in Canadian smokers that the mean urinary levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of NNK, was approximately one-fourth that of their American counterparts. Canadian cigarettes are predominantly flue cured and have naturally lower TSNAs levels than the American-blended cigarettes smoked in the United States. The authors, noting that the rates of smoking-related diseases are similar in Canada and the United States, stated: "Even if it were possible to selectively reduce TSNAs without increasing exposure to other toxicants, the benefit may be negligible, given the levels of exposure associated with cigarette smoking; as some commentators have noted, the risk differential may be akin to jumping from a 19-storey rather than a 20-storey building, with the same outcome in either case".

The CTP is also concerned with tobacco product design features or ingredients that are believed to "raise different questions of public health". For example, a new tobacco product may not be legally marketed in the United States unless it is identical to one commercially marketed after February 15, 2007, but before March 22, 2011, or for which a substantial equivalence report was submitted by March 22, 2011, and, therefore, "does not raise different questions of public health." (*17*). On mentholated cigarettes, the CTP has made available a preliminary scientific evaluation of public health issues related to the use of menthol in cigarettes (*34*) and has invited public comments on the information that it will use to inform regulatory actions.

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So, although chemistry is a good starting point for the assessment of novel products designed to reduce risks, other sciences need to be brought to bear to assess the potential of reduced toxicant exposure to translate into reduced risk. In addition, new products might give rise to toxicants not found in the smoke of conventional cigarettes. The chemistries occurring in tobacco-heating products will differ from those in cigarettes given the very different temperature range and oxidative and reductive conditions, and the materials use in e-cigarettes, such as metals, could pose additional risks if transferred to the aerosol in sufficient quantities. Assessment of these products will require targeted analytical approaches to measure known tobacco toxicants and untargeted approaches to see what else might be present.

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Use of Computational Toxicology To Assess Priority Toxicants

Identification and characterization of the most important toxicants in cigarette smoke and other tobacco products, in terms of potential to cause disease, and the dose–response relationships of individual toxicants to various diseases would be of considerable value to manufactures seeking to reduce risks of their products and to regulators. Fowles and Dybing (*12*) described calculations conducted to prioritize the hazards for 158 chemical constituents in tobacco smoke. On the basis of published cancer potency factors and knowledge of typical yields in smoke, they proposed that 1,3-butadiene was the most influential of the volatile compounds in relation to cancer. They also suggested that four of the top five cancer-related toxicants were aldehydes or small organic compounds, contributing around 62.4% of the overall cancer risk, metals (e.g. arsenic and cadmium) a further 18.2%, and polyaromatic hydrocarbons (PAHs) only 0.8%. Notably, while PAHs would be found in the tar of cigarette smoke, many of the other toxicants would not. Acrolein and acetaldehyde were calculated to affect respiratory health, and hydrogen cyanide and arsenic were proposed to be associated with cardiovascular disease. Fowles and Dybing, however, noted limitations in their estimates (*12*). For example, they estimated the sum of the cancer risk indices that they had calculated and noted that the value seemed to be five times lower than would be expected from the cancer mortality attributed to smoking in the United States. Consequently, we investigated other possible paradigms that might be applicable to these and other tobacco smoke toxicants. Our current quantitative risk assessment paradigm is based on a combination of *in silico* and weight-of-evidence approaches: margin of exposure (MOE) calculations, mode of action (MOA) reviews, and physiologically based pharmacokinetic modeling, supplemented with *in vitro* pre-clinical tests. The data can be used to generate point-of-departure values for inclusion in MOE calculations and to provide support for the postulated MOA for specific toxicants. The results can be compared with predicted target-organ concentrations generated from physiologically based pharmacokinetic modelling as a first step in quantitative *in vitro–in vivo* extrapolation.

We have applied an MOE model, as described by the European Food Safety Authority guidelines (*35*), that permits the analysis of genotoxic and carcinogenic

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compounds. An MOE is the ratio of a benchmark dose (a reference point derived from either experimental or epidemiological dose–response data) to the specific human exposure. The European Food Safety Authority, when assessing food safety, deems MOEs greater than 10,000 to be low priority for risk management. We calculated MOE values from a wide range of different studies with various disease end points to produce a series of values representative of those in the literature. Review of the distribution of the MOE data enables assessment of the strength of the potential risk associated with specific compounds.

We applied the MOE calculation to some of the key toxicants present in tobacco smoke of a reference cigarettes (3R4F), a commercial control cigarette, and a reduced-toxicant prototype (RTP) cigarette (*36*), which was designed to reduce toxicant levels as much as possible while remaining possible to test in a clinical study. The MOE values enabled categorization of the toxicants into a series of priority bandings (*37*): top priority (MOE 1–10), very high priority (MOE >10–100), high priority (MOE >100–1,000), medium priority (MOE >1,000–10,000), low priority (MOE >10,000–100,000), very low priority (MOE >100,000; Table II).

The findings suggest that, toxicants, even those that are reduced substantially in the RTP prototype, need to be reduced substantially further, perhaps beyond the possibilities of what is achievable in a cigarette. To explore this further, we have estimated the yields for eleven toxicants that would be necessary for an assignment of low priority under the modes of exposure approach (Table III). For acrolein, for example, a yield of 4.6 ng/cig would need to be achieved. The RTP had a yield of 61 μg/cig as measured under Health Canada intense conditions, despite having been designed with a long filter containing adsorbent materials designed to reduced vapor-phase yields. The range of acrolein yields in the database presented in Table I is from 79 μg/cig to 209 μg/cig. Nanogram levels of acrolein in a cigarette are unlikely to be achievable.

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Table II. Margin of Exposure Priority Assignments for a Reference Cigarette, Commercial Control Cigarette, and a Reduced-Toxicant Prototype. SOURCE: Adapted with permission from reference (*15*). Copyright 2014 British American Tobacco.

Smoke constituent	*Priority*		
	3R4F	*Control cigarette*	*Reduced toxicant prototype*
Acrolein	Top	Top	Top
Acrylonitrile	Top	Very high	Very high
Formaldehyde	Top	Top	Top
Acetaldehyde	Very high	Very high	High
Isoprene	Very high	Very high	High
Styrene	Very high	Very high	High

Continued on next page.

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Table II. (Continued). Margin of Exposure Priority Assignments for a Reference Cigarette, Commercial Control Cigarette, and a Reduced-Toxicant Prototype

Smoke constituent	*Priority*		
	3R4F	*Control cigarette*	*Reduced toxicant prototype*
Benzene	High	High	Medium
1,3-Butadiene	High	High	High
m- + p-Cresols	High	High	Medium
NNK	High	High	Medium
Toluene	High	High	Medium
Naphthalene	Medium	Medium	Low
NNN	Medium	Medium	Low

NNK, 4-(methlynitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitrosonornicotine.

Table III. Estimates of Toxicant Yields Necessary To Achieve a Low-Priority Assignment in MOE Calculations. SOURCE: Reproduced with permission from reference (*15*). Copyright 2014 British American Tobacco.

Compound	*HCI 3R4F yield µg/cig*	*MOE from HCI 3R4F (assuming 20 cigs per day)*	*Target µg/cig for 10,000 MOE (assuming 20 cigs per day)*
Acrolein	155	0.3	0.0046
Formaldehyde	68.1	2	0.011
Cadmium	0.146	6	0.000086
Acetaldehyde	1534	45	6.9
Acrylamide	1.37 (ISO)	460	0.063
Benzene	104	252	2.6
1,3-Butadiene	76.5	220	1.7
Ethylene oxide	9.24 (ISO)	424	0.4
NNK	0.243	278	0.0067
NNN	0.276	2759	0.076
Benzo(*a*)pyrene	0.0162	16805	0.027

HCI, Health Canada intense smoking condition; MOE, margin of exposure; NNK, 4-(methlynitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitrosonornicotine.

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A criticism of tobacco toxicological risk assessments has been that studies have been applied to individual toxicants rather than the complex mixture of toxicants in tobacco smoke. Despite notable progress in risk assessment of simple mixtures of chemicals (*38*), analysis of complex mixtures remains challenging. We have investigated the utility of the MOE segregation tool in small-scale mixture assessment (*37*) through careful consideration of the MOAs of specific compounds. When MOA data are incorporated into this MOE model, they can also be used for quantitative risk assessment to prioritize tobacco smoke toxicants. With this approach two assumptions are made: 1) the compounds involved are similar in structure, and 2) they share similar toxicological properties. Although the MOE calculations suggest that reductions in yields, at least for some of the toxicants, are insufficient to significantly lessen the potential for biological effects, more sophisticated analyses combining MOEs and MOAs are yet to be completed.

Such approaches to computational risk assessment provide useful guidance on which toxicants might be most important and the extent to which levels might need to be lowered to potentially reduce risks. Findings suggest that to achieve substantial further risk reduction, new products with quite different toxicant profiles, such as tobacco-heating products and e-cigarettes, are likely to be necessary.

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In Vitro Toxicological Testing Strategies in the 21st Century

Standardized *in vitro* tests for genotoxicity have been available for many years (*39*). They are widely used in a range of different industrial sectors and have an important regulatory role in risk assessment, especially in detecting potential carcinogens.

Authoritative international guidelines have been developed for *in vitro* genotoxicity tests of chemicals and pharmaceuticals (*40*). These include the Ames test, the micronucleus test, and the mouse lymphoma assay. However, these tests have rarely been used by regulators to assess tobacco products. Health Canada does collect a limited amount of genotoxicity data on cigarettes sold in Canada, but these are obtained from total particulate matter trapped by drawing smoke through a Cambridge filter pad. This method misses the many toxicants found in the vapor-phase of cigarette smoke. Whole smoke, or in the case of some novel products whole aerosol, methods have been developed (*41*), but as yet have not been used by regulators.

In addition to what might be termed regulatory *in vitro* toxicology, there are considerable opportunities to develop and validate a range of specific *in vitro* models relevant to various tobacco-related diseases. The aim of these *in vitro* models is to develop physiologically relevant screening tools that can provide insights into the mechanisms of toxic effects related to cigarette smoke and to identify and assess disease-related biomarkers. In addition they can be used to compare the toxicological response of novel products compared with cigarettes. A similar approach is used by other industries that are interested in developing

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in vitro models in order to reduce animal experimentation, which is the standard approach for testing pharmaceuticals and cosmetics (*42*, *43*).

Many drivers are encouraging the development of alternative *in vitro* methods to animal testing (*44*), including the ethical issues surrounding animal testing and the improved appropriateness and meaningfulness of information on biological effects of tobacco-related products achievable from human *in vitro* models; *in vivo* animal models do not always accurately reflect human biology (*45*). Given that smoking causes a wide range of chronic diseases, including lung cancer, COPD, and CVD, we believe that a suite of *in vitro* models using human tissues and representing key events in disease development need to be established.

With use of the approach of adverse outcomes pathways as a framework, *in vitro* models to investigate the cellular and tissue responses of smoke during disease progression can be developed (*46*). Such *in vitro* models must be metabolically competent and able to assess appropriate disease end points. Biological processes related to inflammation and oxidative stress underpin more than one smoking-related disease (*47*, *48*) and, therefore, development of *in vitro* models to improve understanding of how these processes may initiate disease development is important. Although some of the *in vitro* models developed are relatively simple, it is also necessary to work on more-complex models that are more physiologically relevant to support biomarker discovery and development that can be translated into the clinic. For example with respect to the study of lung disease, whole aerosol exposure models are likely to better mimic the route of exposure and biology associated with product use, than submerged cell cultures, which use a sub-fraction of the total aerosol. Figure 3 demonstrates the application of a simple cytotoxicity endpoint in a whole aerosol model using NCI-H292 lung epithelial cells, as previously described (*49*).

Over the past few years, our in-house studies have focused on the development and application of a suite of *in vitro* models to assess tobacco and novel tobacco and nicotine products, including RTPs (*50*). In relation to CVD, we have demonstrated that endothelial repair following exposure to cigarette smoke is sensitive to different toxicant yields. This research also showed that osteopontin, an endothelial-specific protein, might contribute to inflammation and subsequent CVD in smokers (*51*, *52*).

A key event in the carcinogenic process is DNA damage. We have developed *in vitro* studies to assess DNA double-strand breaks in response to cigarette smoke. These studies use COMET (*53*) and a novel biomarker gamma-H2AX (*54*).

Goblet-cell hyperplasia and increased mucus production are common features of COPD and can be modelled *in vitro*. We have been working with a clinical research organization in the United Kingdom to develop an in-house *in vitro* model of goblet-cell hyperplasia to assess responses to cigarette smoke (*55*). The protein content in the mucus, or airway surface liquid, generated in this model can also be assessed following exposure to whole smoke, by use of proteomics. We have identified more than 350 proteins in this fluid, many of which are differentially expressed after exposure to smoke, and which comprise the largest set of proteins yet identified in this biomatrix (*56*). This approach, in addition to genomic and metabolomic studies, could help to identify new biomarkers of biological effect (BoBE) that could be used in future clinical studies.

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The challenges faced in the development and acceptance of *in vitro* models by the scientific and regulatory communities are best met through collaboration with academic partners, suppliers of testing equipment, contract research organizations, regulators, and others in the regulated industry. *In vitro* models need to be validated across a range of laboratories for robustness and reproducibility. Continued academic and industrial collaboration is essential to ensure we continue to actively participate in and understand the science that surrounds tobacco-related disease and the development of appropriate *in vitro* models. Much of the *in vitro* modelling work in the pharmaceutical and chemical industries overlaps with our research, and we think it is important to broaden collaboration across these groups to reduce and eventually replace animal experiments. Once fully characterized and validated, these tests may prove useful for comparing cigarette smoke with the aerosols generated by other products. Figure 3 illustrates the comparative cytotoxic response to smoke generated from a cigarette and aerosols emitted from a tobacco-heating product and an e-cigarette.

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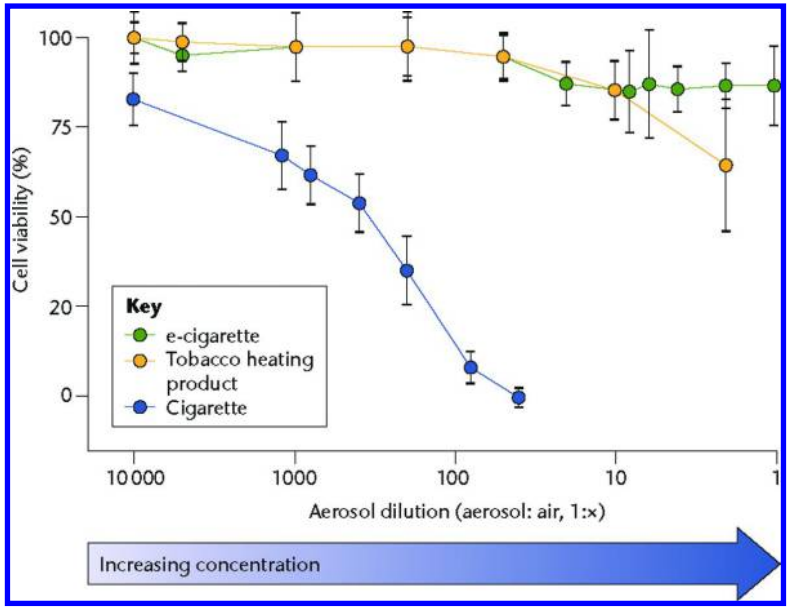

Figure 3. Cytotoxicity of cigarette smoke compared with aerosols formed from a tobacco-heating product and an e-cigarette. NCI-H292 lung epithelial cells were exposed for 30 mins to each product using the Health Canada Intense puffing regime. Aerosol dose is expressed as a dilution ratio with ambient air (i.e. 1 in x, where x is the air dilution factor). Data are plotted as mean +/– standard deviation. Copyright 2014 British American Tobacco. (Figure has been altered slightly.)

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Clinical Studies

Studies that characterize the interaction between products and people and measure biological end points that change following use are likely to be essential to the assessment of potentially reduced risk tobacco and nicotine products. Much of the chemical characterization of tobacco smoke discussed above involves smoking machines operating under specific conditions to generate the smoke that is then either collected on a Cambridge filter pad (for total particulate matter), via a liquid trap (for volatiles), or in an inert bag (for gases). Smoke constituent yields measured in machine smoking yields, however, cannot accurately reflect yields obtained by individual smokers. Human smokers exhibit a wide range of behaviors, which can notably influence toxicant exposures (*57*). Moreover, smoking patterns are not necessarily maintained when people switch to another product with different characteristics. For example, some e-cigarette users graze, taking many small puffs, perhaps partly because unlike a cigarette, which burns to extinction, there is no obvious signal that a session has finished, or perhaps because they are not obtaining the same amount of nicotine as they would with a cigarette.

Laboratory studies that measure pressure changes can assess the range of human smoking behaviors, which can be replicated on smoking machines to estimate likely exposures. These studies, however, tend to result in more-intensive use patterns than are seen outside the laboratory (*58*).

Unobtrusive techniques are available to estimate the levels of smoke particulate matter and nicotine obtained by smokers from cigarettes in everyday environments (*57*). The technique, called part-filter analysis, involves analysis of retained smoke particulates and nicotine in the mouth-end filter sections of smoked cigarettes. This technique has been used in a number of studies, including a clinical study of RTP cigarettes and a longitudinal study of smoking behavior (*59*). The advantage of such techniques is the ability to sample large numbers of subjects unobtrusively, as compared to clinically confined studies. This type of analysis might be possible to extend to tobacco-heating products if they contain filters, but extending it to e-cigarette use is likely to be more difficult.

Understanding exposure to toxicants is assisted by measurement of biomarkers of exposure (BoE). The IoM has defined a BoE as "a constituent or metabolite that is measured in a biological fluid or tissue that has the potential to interact with a biological macromolecule; sometimes considered a measure of internal dose", and, ideally, each would be specific to the source compound, correlated with exposure dose, easy to obtain, and able to be measured accurately (*6*).

Four basic biomarker groups are currently described in the literature: BoE, which include markers of external exposure and of internal dose; biomarkers of biologically effective dose; biomarkers of effect, which include markers of health impairment and early disease precursors; and susceptibility biomarkers, which include intrinsic genetic or other characteristics or pre-existing diseases that result in increases in internal dose, biologically effective dose, or target tissue response (*7*).

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BoE have been used to assess exposure to tobacco and tobacco smoke constituents in humans. They offer the potential to measure smoke constituent and toxicant exposure independent of subjects' smoking behavior by number of cigarettes smoked, puffing patterns, mouth spill, and inhalation patterns (*7*, *8*).

Various biomarkers have been assessed for their suitability in discriminating between toxicant exposures in smokers of different ISO tar yield cigarettes, and their applicability in evaluating other tobacco products. Data from clinical correlation studies, conducted with external contract laboratories, have demonstrated dose–response relationships between levels of specific urinary, plasma and salivary biomarkers and indicators for daily smoke exposure (*60*). Some of our recent research has involved evaluating the extent to which these BoE for crotonaldehyde, acrolein, NNK, pyrene, and 1,3-butadiene correlate with nicotine exposure (*61*).

Although some BoE, for example the measurement of NNAL as a metabolite of the TSNA NNK, are well established (*32*), many of the HPHCs identified by the FDA do not have established BoE. While helpful in assessing any changes in exposure to toxicants, considerable extrapolation is required to determine whether any reductions are biologically meaningful (*62*). Thus, there is a need to establish BoBE to indicate the body's response to exposure (*63*, *64*). These biomarkers should indicate early sub-clinical changes that, if sustained, could go on to have pathological consequences (*65*). In the context of tobacco studies, a BoBE would need to be a robust measure in response to cigarette smoking, to differentiate between smokers and never smokers, to be reversible on smoking cessation, and be minimally affected by inter-individual variability. Ideally, a candidate BoBE would be related to a disease-specific end point, but this requirement might not necessarily be achievable in the context of smoking-related diseases. In addition, it is helpful if the timeframe needed to see a change in the biomarker levels is reasonably short (weeks to months rather than years) to be useful in clinical studies predicting long-term risk (*7*).

A series of BoBE has been identified that ranges from biomolecules found in tissue or bodily fluids to physiological measurements, such as lung function tests and arterial imaging. None, however, has yet been validated for use in tobacco studies (*66*).

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Population Effects Modelling

The CTP has made it very clear that that it seeks to regulate tobacco to a population health standard. In the context of potentially reduced risk tobacco and nicotine products, therefore, they should not only lower risks in individual current tobacco users, but also have a positive public health benefit across the whole of society. Effects can be assessed through post-market surveillance studies that measure incidence of use in smokers, ex-smokers, and never smokers and, given sufficient long-term use of new products, could assess changes in health end points through quality of life surveys or biomarker studies (*8*). Regulators would prefer, however, that likely outcomes of a new product could be predicted before introduction to the market. No survey instrument has yet been able to predict

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population behavior. Prediction would also require evaluating the likely reactions of vulnerable groups, including those underage. The use of tobacco products is restricted to adults in all countries and, therefore, the surveying of vulnerable groups by tobacco manufacturers seems inappropriate.

A tobacco manufacturer wishing to market an MRTP would need to conduct all the relevant studies with little or no public guidance from the regulator. This seems an inefficient process. Arguably, if the regulator clearly set out that the conditions of testing and resources should apply to those underage, this change would encourage development of more products of potentially reduced risk.

Setting the Regulatory Science Research Agenda

The CTP notes that it has "moved science-based tobacco regulation forward and started a rigorous tobacco research program" (*9*). The program is focused on three strategic priorities of preventing initiation, particularly among young people, decreasing the harms of tobacco use, and encouraging cessation. The CTP is working with the Centers for Disease Control and Prevention to establish a world-class testing laboratory for tobacco products. It has also partnered with the National Institutes of Health to increase regulatory science capabilities. As part of this interagency partnership (the Tobacco Regulatory Science Program), it awarded $53 million in 2013 (to set up 14 Tobacco Centers of Regulatory Science, mainly in established academic centers). Representatives of the Tobacco Centers of Regulatory Science meet with the FDA to discuss the latest findings, although this meeting is not open to the public. The total value of the TCORS initiative is potentially $273m over 5 years (*67*).

As noted above, the IoM suggested that some of the harm caused by tobacco use could be reduced through the introduction, with regulatory oversight, of MRTPs (*6*). The governing Act provides avenues to introduce product standards for and approve MRTP applications as a means to achieve this. Yet the development of an assessment framework to prove a product standard applied to a category of tobacco products, or used in the evaluation of an MRTP remain scientifically challenging. A substantial amount of research is being funded to support these goals, by regulators and manufacturers, but there remain opportunities to accelerate progress with greater and more effective communication between these organizations. The result could be better products with clear information communicated to consumers in an accurate way, resulting in a reduction in the public health impact caused by tobacco and nicotine use.

Conclusions

A considerable amount of new science is needed to inform regulators seeking to reduce the public health burden of tobacco use through product regulation. The developing concept of a continuum of risk of tobacco and nicotine products brings the challenge of developing new methodologies to assess the likely risks to individuals and the population as a whole of new products.

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Chapter 5

FDA's Communication of Nicotine Science

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Changes in United States regulation of tobacco products and the growing popularity of electronic cigarettes (e-cigarettes) have substantially increased the importance of effective communication on the relative risks of a range of nicotine delivery products. The United States Food and Drug Administration Center for Tobacco Products (CTP) has demonstrated willingness to communicate nicotine science concepts, but in a manner that is perhaps more suited for a student of the federal regulatory science process than an average citizen. For example, the CTP has addressed the concept of a continuum of risk in formal documents and public speeches, but does not do so prominently on its website. There are several products that could potentially fit into the continuum between cigarettes and nicotine-replacement therapies, including e-cigarettes and smokeless products, but determining the relative risk of a specific product must be done through a scientific evidence-based process that takes time and judgment and follows statutory provisions. Meanwhile, the media are not restricted in the same way, and there have been abundant articles that address e-cigarettes and, to a much more limited extent, Swedish snus. The CTP has, however, used various forums – speeches, Federal Register announcements, and product applications – to overcome the statutory limits and become a leader in communicating the science of nicotine.

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Introduction

Communicating the science of nicotine has become an increasingly significant public health undertaking due to two fairly recent developments: enactment of the 2009 Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (*1*) and the growing popularity of electronic cigarettes (e-cigarettes). These legislative and market forces have dramatically changed the landscape and increased public awareness of nicotine delivery products. They have also reinvigorated the tobacco harm reduction debate and the question of whether governmental and public health authorities should be communicating about alternative products that potentially deliver nicotine in a substantially less risky manner to tobacco users, particularly smokers.

The United States Food and Drug Administration (FDA), the agency charged with implementing the Tobacco Control Act, is well aware of the need to communicate with consumers about the relative risk of a range of nicotine delivery products, but the agency must operate within a regulatory science structure. Although the FDA communicates clearly the dangers of cigarettes, the agency must be much more nuanced about communicating the relative risks of e-cigarettes and other nicotine delivery products with potentially reduced risks.

The FDA Center for Tobacco Products (CTP), which was established by the Tobacco Control Act, has demonstrated a willingness to address nicotine science, but in a manner that is more suited for a student of the federal regulatory science process than an average citizen. For example, CTP has addressed the concept of a continuum of risk in formal documents and public speeches, but does not do so prominently on its website. Continuum of risk is the notion that there is a risk range across nicotine delivery products, with cigarettes being associated with the highest risk and nicotine-replacement therapies (NRTs), such as gum and patches, with the least risk. There are several products that could potentially fit into the continuum between cigarettes and NRTs, including e-cigarettes and smokeless products, such as Swedish snus, but determining the relative risk of a specific product must be done through a scientific evidence-based process that takes time and judgment and follows statutory provisions.

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Modified Risk Tobacco Products

The Tobacco Control Act contains a provision for a company to submit an application to the CTP seeking an order that a product reduces harm or the risk of tobacco-related disease. The provision – Section 911 of the Tobacco Control Act on Modified Risk Tobacco Products (MRTPs) (*1*) – presents a process and standard that must be met before an order for a modified-risk tobacco product (MRTP) can be issued. The process is fully described in a 2012 *FDA Draft Guidance for Industry* document, and the standard, as cited in the Tobacco Control Act and the draft guidance, is twofold: an applicant must demonstrate that a product reduces harm and the risk of tobacco-related disease to individuals, and must show how a modified-risk order would benefit the health of the population as a whole (*2*). The MRTP process allows for determination of whether a product provides harm reduction and where it lies on the nicotine risk continuum.

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The CTP is currently assessing an MRTP application submitted by the company Swedish Match for its snus product line sold in the United States. Snus is a smokeless, spitless, traditional Swedish product widely used in Scandinavia. In August 2014, the CTP determined that the Swedish Match application was complete and a 6-month public review and comment period was initiated (*3*). As stated in Section 911 of the Tobacco Control Act, once an MRTP application has been determined to be complete, the CTP should seek to make a decision within 1 year (*1*). At the time of this writing, a CTP decision regarding the Swedish Match MRTP application was imminent.

The Tobacco Control Act provides the FDA with the authority to regulate cigarettes, smokeless tobacco, and roll your own products; but the Act does not reference e-cigarettes. A 2010 court case determined that all tobacco-derived products are subject to the Tobacco Control Act and, thus, e-cigarettes can be regulated by the CTP (*4*). In April 2014, the CTP issued draft regulations proposing an approach to regulating e-cigarettes (as well as electronic cigars and hookahs); there was a public comment period and now the CTP is developing final regulations (*5*).

The Swedish Match snus products and e-cigarettes are interesting to compare: for Swedish Match snus, there is an abundance of epidemiological evidence but limited sales in the United States, whereas for e-cigarettes there is very little human health information but the United States market has grown significantly in the past few years. Swedish Match has funded research but the vast majority of the evidence on the product comes from studies conducted in Sweden by governmental authorities. These long-term longitudinal studies form the basis of the so-called Swedish experience, which refers to the fact that Swedish men over the past three decades have switched from smoking to snus and have not suffered from tobacco-related diseases (*6*). This phenomenon has been documented in hundreds of scientific articles and has been cited globally in reports from governmental authorities. Conversely, e-cigarettes are a new product and, understandably, there is limited health evidence and certainly no epidemiological studies.

The tobacco regulatory science process is moving forward, but until the process is complete the CTP cannot fully comment on the degree to which products such as e-cigarettes and Swedish snus are less risky than smoking. The media, however, is not restrained by the regulatory process, and there has been abundance of articles that have addressed e-cigarettes, and to a much more limited extent, Swedish snus. Some of the articles are informative, and at least touch upon the concepts of risk continuum and harm reduction and present some information about nicotine. Many, however, are largely opinion pieces that cite sales and use numbers and draw conclusions based on very limited data.

Ideally, the public, particularly smokers, would turn to credible, knowledgeable organizations, such as the CTP, to obtain information. The CTP web site provides some useful information about e-cigarettes and Swedish snus, but, as previously stated, the regulatory science process limits what the CTP can communicate about the relative risk of these products. For example, the CTP web site does not address whether e-cigarettes or Swedish snus is less risky than smoking cigarettes. Nevertheless, a deeper examination of the information

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available via the CTP web site would uncover documents containing compelling information and formal statements about continuum of risk and harm reduction. Three information sources in particular contain intriguing evidence and statements that provide insight into the type of science and risk communication that is likely to be forthcoming from the CTP: transcripts of the public speeches of CTP Director Mitch Zeller, the draft regulations relating to e-cigarettes, and the Swedish Match MRTP application. The intention of these information sources is not to provide basic risk communication advice to smokers or to the general public, but they do contain very useful regulatory science policy statements and evidence.

In this chapter I examine these information sources and assess how they communicate the science of nicotine and the concepts of continuum of risk and tobacco harm reduction. I begin by defining these concepts.

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Key Terms and Concepts

Nicotine

Nicotine, or (S)-3-(1-methyl-2-pyrroli-dinyl) pyridine, is a colorless or pale yellow oily liquid. It belongs to a large family of amine-containing chemicals called alkaloids, which are mainly produced by plants. Although nicotine is particularly abundant in tobacco plants, detectable amounts are also found in related plants, such as potatoes and tomatoes. Nicotine in plants probably functions as an insecticide, and concentrated solutions of nicotine were once widely sold for this purpose.

What is often hard for the public to accept is that, although nicotine is addictive, it is not especially hazardous, as stated in the preface of the UK Royal College of Physicians (RCP) 2007 report *Harm Reduction in Nicotine Addiction: Helping People Who Can't Quit* (*6*). The RCP operates through committees which prepare reports on a variety of public health issues, including nicotine and tobacco use and harm reduction. These reports have significant impact in the United Kingdom and globally, and are comparable in stature to reports issued by the United States Surgeon General. The RCP first addressed tobacco policy in its 1962 report *Smoking and Health* (*7*), and has remained at the forefront of tobacco policy ever since.

Harm Reduction in Nicotine Addiction: Helping People Who Can't Quit makes the case for harm reduction strategies to protect smokers (*6*). The report was prepared by the RCP Tobacco Advisory Group, chaired by Dr. John Britton, who in the report preface states that "We demonstrate that smokers smoke predominantly for nicotine, that nicotine itself is not especially hazardous, and that if nicotine could be provided in a form that is acceptable and effective as a cigarette substitute, millions of lives would be saved" (*6*). The report is intended to contribute to the national and global policy debate, and Dr. Britton also recommends the following: "We also argue that the regulatory systems that currently govern nicotine products in most countries, including the UK, actively discourage the development, marketing and promotion of significantly safer nicotine products to smokers" (*6*).

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There are several similar statements made throughout the report, including the following: "Extensive experience with nicotine replacement therapy in clinical trial and observational study settings demonstrates that medicinal nicotine is a very safe drug" (*6*).

Harm Reduction

Harm reduction is a philosophy intended to be an alternative to prohibition of high-risk lifestyle choices. At the core of harm reduction philosophy is the acknowledgment that some people will always engage in behaviors that carry risks, such as intravenous drug use, unsafe sex, and smoking. A harm reduction approach attempts to lessen the consequences of such behavior when eliminating the behavior altogether is not realistic. This definition corresponds to the statutory language in Section 911 of the Tobacco Control Act (*1*), which defines an MRTP as "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products."

Tobacco harm reduction and the health impacts of nicotine are more likely to be addressed by the scientific community than by regulatory agencies. The roles of regulatory agencies and scientific institutions are quite different, and it is far easier to offer advice than it is to make regulatory decisions that will have profound societal impact. Thus, the examination of the science of nicotine and tobacco harm reduction and how it may inform governmental policy has been largely undertaken by scientific organizations. Two of the leaders in this area are the Institute of Medicine (IOM) in the United States and the RCP. Both these organizations are highly credible, have a close relationship with government agencies, and have a history of addressing nicotine and tobacco products.

Over the past couple of decades, the FDA has funded several of the IOM committees formed to address tobacco and nicotine science and policy issues. Two such committees directly addressed harm reduction: the Committee to Assess the Science Base for Tobacco Harm Reduction, which wrote the 2001 report *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction* (*8*); and the Committee on Scientific Standards for Studies on Modified Risk Tobacco Products which wrote the 2011 report *Scientific Standards for Studies on Modified Risk Tobacco Products* (*9*). Both of these reports have had a significant impact on nicotine and harm reduction science as well as on legislative and regulatory actions.

The 2011 IOM report *Scientific Standards for Studies on Modified Risk Tobacco Products* offers the following definition of harm reduction products: "The concept of harm reduction informs the public health rationale for permitting the development and potential marketing of modified risk tobacco products (MRTPs). The basic premise of harm reduction is the continuation of a potentially hazardous or dangerous behavior, with the aim of decreasing the potentially adverse consequences of these behaviors" (*9*). Additionally, the 2011 IOM report cites the 2001 IOM report: "…a product is harm reducing if it lowers total tobacco-related mortality and morbidity, even though use of that product may involve continued exposure to tobacco-related toxicants". The RCP 2007 report

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also devotes considerable attention to tobacco harm reduction, including an entire chapter on the ethics and human rights associated with the concept.

Risk Continuum

The concept of a nicotine and/or tobacco risk continuum is based on the premise that products vary considerably in their impact on human health, with cigarettes being the most risky, and NRT products posing the least risk.

Although it does not use the term risk continuum, the RCP report *Harm Reduction in Nicotine Addiction* does place products in context: "…products based on medicinal nicotine, which we will assume to be the least hazardous alternative, and smokeless tobacco products, which we will assume to be more hazardous that medicinal nicotine, but much less hazardous than smoked tobacco products" (*6*). The report uses the term risk profile when assessing the health impact of the two categories of products. The chapter on the risk profile of smokeless tobacco products differentiates between various products and concludes that "Smokeless tobacco products differ substantially in their risk profile in approximate relation to the content of toxins in the tobacco."

In 2009, a group of leading tobacco researchers and policy analysts issued an article in the journal *Tobacco Control* that presented the results of a process called the Strategic Dialogue on Harm Reduction. The dialogue and resulting article occurred well before passage of the Tobacco Control Act, but the authors were prescient in their view that "consideration should be given to looking at the nicotine market as a whole and developing a more coherent policy that explores the impact of promoting the use of the least toxic forms of nicotine delivery and discourage the most toxic forms." The article, *The strategic dialogue on tobacco harm reduction: A vision and blueprint for action in the United States*, also offers a definition of tobacco risk continuum, based in part of the 2007 RCP report: "There is a very pronounced continuum of risk depending upon how toxicants and nicotine, the major addictive substance in tobacco, are delivered. Cigarette smoking is undoubtedly a more hazardous nicotine delivery system than various forms on non-combustible tobacco products for those who continue to use tobacco, which in turn are more hazardous than pharmaceutical products. There is potential for an ever-wider range of consumer-acceptable alternatives to the cigarette for smokers who will not otherwise cease their dependence on nicotine" (*10*).

Public Statements by Mitch Zeller, Director of the CTP

As CTP director, Mitch Zeller routinely give speeches in public settings, such as at conferences hosted by a range of stakeholders, including industry, tobacco-control organizations, and academic institutions. His speeches are often very effective at communicating complex and controversial concepts, most notably continuum of risk and the true harm of nicotine.

The speeches typically focus on the priorities for the CTP, including the development of an FDA comprehensive regulatory policy. Two different FDA

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Centers regulate nicotine products: CTP and the Center for Drug Evaluation and Research, which regulates nicotine-replacement therapies.

When speaking about a nicotine policy Zeller often cites the concept of risk continuum, which is understandable given that the Center for Drug Evaluation and Research regulates products at one end of the spectrum, while CTP regulates all other nicotine products, including cigarettes, which are the most harmful of nicotine delivery products.

Zeller gave the keynote address at the October 29, 2013, FDA Regulation of Tobacco conference sponsored by the Food Drug Law Institute. He touched upon the CTP priorities, including product standards and a comprehensive nicotine policy, and he closed by asserting that everyone, including regulators, should recognize that there is a continuum of nicotine delivery products (*11*). He cited the example of a reduced risk for the hypothetical pack-a-day smoker who completely substitutes all cigarettes with a smokeless product. However, he cautioned that although some products may reduce risk, they might still serve as a source of tobacco initiation, could keep the smoker from stopping nicotine use completely, and could lead to dual use (smoking and using a risk-reduction product).

Zeller also addressed the science of nicotine when he cited the pioneering nicotine researcher Dr. Michael Russell's quote that people smoke for the nicotine but die from the tar. Zeller built on the Dr. Russell reference to state that the FDA is aware that nicotine is not killing smokers, but all stakeholders must work together and with the FDA to ask who is using nicotine delivering products and how are they using them, to take into account fully the individual-level and population-level considerations (*11*).

Director Zeller gave a similar speech in June, 2014, at an event sponsored by the Legacy for Health Foundation (*12*). He stated that "It's time that all of us, in and out of government […] start looking at nicotine differently. For FDA, that means there needs to be an integrated agency-wide policy on nicotine containing products that's based on the science…" He again elaborated on the comments of Dr. Russell quote by stating "It's not the nicotine that kills half of all long term smokers. It's not the drug, it's the delivery mechanism."

Zeller continued to give a very informative and compelling description of nicotine science: "When nicotine is delivered attached to smoke particles that get inhaled into the lungs, that will kill half of all long term uses. The very same compound has been approved by FDA as a safe and effective medication for over 30 years to help smokers quit. It's not the compound, it's the delivery mechanism. We have to recognize some of these realities and figure out how they can impact regulatory policy" (*12*).

Deeming Tobacco Products To Include E-Cigarettes

In the April 25, 2014, Federal Register Notice, the FDA proposed to deem that additional products, including e-cigarettes, meet the statutory definition of tobacco products, and, therefore, were subject to the Tobacco Control Act (*6*). The Federal Register Notice included a lengthy preamble that included compelling

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and insightful statements about continuum of risk, tobacco harm reduction, and the science of nicotine.

The opening paragraphs of the section "Continuum of Nicotine-Delivering Products" provide a very clear and thoughtful presentation on the science of nicotine and the relative risk of nicotine delivery products. The paragraphs offer sound, state of knowledge information in a manner that does not violate the regulatory science process: "There are public health questions and concerns about currently unregulated tobacco products. Nevertheless, there are distinctions in the hazards presented by various nicotine-delivering products. Some have advanced the views that certain new non-combustible tobacco products (such as e-cigarettes) may be less hazardous, at least in certain respects, than combustible products given the carcinogens in smoke and the dangers of secondhand smoke. To the extent that certain products are shown to be less harmful, they could help reduce the overall death and disease toll from tobacco product use at a population level in the United States. This is a function of the existence of a continuum of nicotine-delivering products that pose differing levels of risk to the individual" (*5*).

The above paragraph uses cautionary phrases such as "Some have advanced the views…" and "To the extent that …" yet effectively communicates the core message that some nicotine delivery products may be safer than others. The paragraph also alludes to the Section 911 of the Tobacco Control Act on MRTP standards for individual-level risk ("…differing levels of risk to the individual.") and public health ("…use at a population level…) (*1*).

The underlying message throughout the lengthy (over 100 pages) "Background for Deeming All Tobacco Products" section is that, although there may be safer ways of delivering nicotine, there is currently not enough evidence to make definitive statements. For example, the following statement effectively summarizes the potential benefits yet cautions about e-cigarettes: "Although e-cigarettes may have short-term smoking reduction benefits, FDA cautions that long-term studies are not available to conclude that e-cigarettes are a proven cessation product nor to establish what effects e-cigarettes have in users who might otherwise quit, but instead engage in dual use of e-cigarettes and another tobacco product" (*5*).

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Swedish Match MRTP Application

Another example of how the CTP provides useful nicotine science information for an informed audience is the public availability of the MRTP application submitted by the company Swedish Match. The application is huge (over 120,000 pages) and complex, and it is likely that only students of nicotine science and policy will read beyond the executive summary. But the fact it is publicly available is significant, as is the decision by the FDA to have a 6-month review and comment period.

As of January 2015, over 140 comments had been submitted to the federal docket (FDA-2014-N-1051). The more detailed comments are from tobacco researchers and organizations, but there are also many comments from the general

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public who either use or have heard of the product. Some are supportive (e.g. "snus helped me quit smoking") and others express concerns (e.g. "snus is addictive and harmful"), but the comments indicate that the CTP is reaching an interested audience.

Section 911 of the Tobacco Control Act states that an MRTP application must be reviewed by the FDA Tobacco Product Scientific Advisory Committee (TPSAC), which was established pursuant to the Tobacco Control Act. The TPSAC reviewed the Swedish Match MRTP application during an April 9-10, 2015 meeting. The meeting was open to the public and webcast around the world, providing an excellent communication opportunity.

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Conclusions

There is an increasing need for effective communication on the relative risks of the range of nicotine delivery products. The CTP is well positioned to provide the necessary risk communication messages and has demonstrated a willingness to address complex and somewhat controversial concepts, such as continuum of risk. The CTP, however, is limited by the regulatory science provisions of the Tobacco Control Act. Until there is sufficient scientific evidence, the CTP cannot communicate fundamental messages such as "this product is less risky than smoking." Yet, it has overcome the statutory limits to become a leader in communicating the science of nicotine, albeit in forums (e.g. speeches, Federal Register announcements, and product applications) that are probably more appropriate for an informed audience than the general public.

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Chapter 6

Communicating Controversial Science: The Case of Tobacco Harm Reduction and the Ethics of Blanket Censorship

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It has long been accepted that cigarette smoking causes serious disease and death, and public policy has focused on reducing tobacco use. In the United States, the Food and Drug Administration (FDA) has had regulatory jurisdiction over tobacco products since 2009, and is committed to an evidence-based approach for regulatory decision making, anchored by sound science. In an effort to generate much more data about tobacco science, the FDA has established an inter-agency partnership with the National Institutes of Health, which is making available billions of research dollars to study priority questions about tobacco science and inform FDA regulations. This new funding should attract many new researchers, creating a larger and more diverse, transparent and results-orientated tobacco science community. The FDA has set an example in acknowledging tobacco manufacturers as both important stakeholders and potential sources of valuable scientific expertise. As a result, there is a general increase in scientific publications resulting from research undertaken by tobacco industry scientists. Additionally, most tobacco

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manufacturers have committed to developing products aimed at being substantially less risky than cigarettes and developing the science to evaluate the potential of such products to reduce risk to individuals and the population. At the same time, there is an increase in the number of scientific journals introducing blanket bans on publishing science from tobacco manufacturers, with the *British Medical Journal* being a recent example. In this chapter we look at the ethical dilemmas surrounding scientific censorship and the role of peer review in protecting scientific integrity.

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Introduction

It has long been accepted that cigarette smoking causes serious diseases and contributes directly to mortality. Public health efforts to reduce death and disease from tobacco use have focused on two main pillars: education to reduce uptake and to encourage the cessation of smoking, and the raising of taxes to make the habit less affordable (*1*). As a result of these efforts smoking prevalence has reduced significantly in many countries.

Although it appears that smoking prevalence has reached a global plateau (around 20% of the global population continues to smoke), the World Health Organization estimates that there could be between 1.5 and 2.2 billion smokers by the year 2050, and 1 billion smoking-related deaths in the 21st century (*2*) due to population growth. Evidently, the approach currently taken by public health bodies is not appropriate for all smokers. Interestingly, the policy of tobacco harm reduction was not included in the original Framework Convention on Tobacco Control in 2003 (*3*), and has since become an area of increased interest and contention. The persistence of smoking worldwide and the desire to offer an alternative to smokers who are unable to quit have been critical to this debate. Given the number of early deaths being predicted in the 21st century, some believe that tobacco harm reduction represents one of the greatest public-health opportunities of today (*4*).

The environment around tobacco product regulation has been changing rapidly in the past 5 years, and this rate of change is likely to continue. In the United States, the Food and Drug Administration (FDA) was given regulatory jurisdiction over tobacco products through the signature of the Family Smoking Prevention and Tobacco Control Act in 2009, which also established the FDA's Center for Tobacco Products (CTP) (*5*). The FDA has made a commitment to adopting an evidence-based approach for regulatory decision-making, underpinned by sound science.

The environment has also changed significantly in that most tobacco manufacturers are now committed to developing products aimed at being substantially less risky than cigarettes and to making tobacco consumers aware of the differences between these products. In light of this commitment, the tobacco

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industry has begun sharing and publishing more scientific material than in the past. The industry is also committing to a more transparent approach regarding research, funding, and potential conflicts of interest. This means that there has been an increase in the number of manuscripts and reports that represent results from tobacco industry scientists, or those funded by the industry.

At the same time, though, there has been an increase in the number of scientific journals introducing blanket bans on publishing science sponsored and/or undertaken by tobacco manufacturers. In this chapter we look at the ethical dilemmas surrounding scientific censorship and the role of peer-review in protecting scientific integrity, particularly in the case of tobacco harm reduction.

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Potential of Tobacco Harm Reduction

The principle of harm reduction is to accept that humans are inclined to partake in risky behaviors, despite knowing they are risky. In order to reduce the risk of adverse outcomes, measures are taken (or modifications made) to decrease the risk without replacing the activity entirely. Examples are the use of seatbelts in vehicles, which have substantially reduced the risk of injury and death while allowing people to continue driving and the use of condoms to reduce the spread of sexually transmitted diseases.

Tobacco harm reduction is of interest because of the persistence of smoking worldwide and the moral obligation to offer smokers an alternative to the quit-or-die approach. The Royal College of Physicians (RCP) is a British professional body of doctors of general medicine and its sub-specialties (equivalent to the Royal College of Physicians and Surgeons of the United States). The Tobacco Advisory Group of the RCP has been at the forefront of policy development in the field of smoking for over 40 years. Under the chairmanship of Professor John Britton, the RCP published a landmark report entitled *Harm Reduction in Nicotine Addiction: Helping People who Can't Quit* in October 2007 (*6*). It was stated in this report: "Tobacco control policy needs to be radically extended to address the needs of smokers with implementation of effective harm reduction strategies. Harm reduction in smoking can be achieved by providing smokers with safer sources of nicotine that are acceptable and effective cigarette substitutes" (*6*).

The risks associated with using tobacco and nicotine products are suggested to be on a continuum. This concept was first conceived by the United Kingdom not-for-profit Action on Smoking and Health (or ASH, a charity funded by the UK Government that is active in advising the government on tobacco control issues), and was further developed by McNeil and Munafò (*7*). They set out the hypothesis that different tobacco and nicotine products are associated with varying levels of exposure to toxicants and, therefore, to risk. This nicotine harm continuum, from most to least dangerous, has cigarettes and cigars at one end and electronic cigarettes (e-cigarettes) and nicotine-replacement therapy at the other (ie, cigarettes > cigars > pipes > chewing tobacco > tobacco gum > snus > e-cigarettes > nicotine replacement therapy; Figure 1).

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The long-term effects on health of smoking cigarettes are clear from epidemiological studies. However, cigarette smoke itself is a highly complex aerosol, containing at least 9,600 identified components (*8*), and it is not clear which of these components are directly responsible for disease initiation and/or progression. It is generally thought that a small subset of these constituents (around 100) have toxic effects, although dose-response relationships for individual toxicants are not known. Various scientists and groups have previously identified and organized subsets of these toxicants into lists. The most comprehensive list of toxicants in tobacco and tobacco smoke so far is that of harmful and potentially harmful constituents published by the FDA (with assistance from its Tobacco Products Scientific Advisory Committee; Figure 2) (*9*, *10*).

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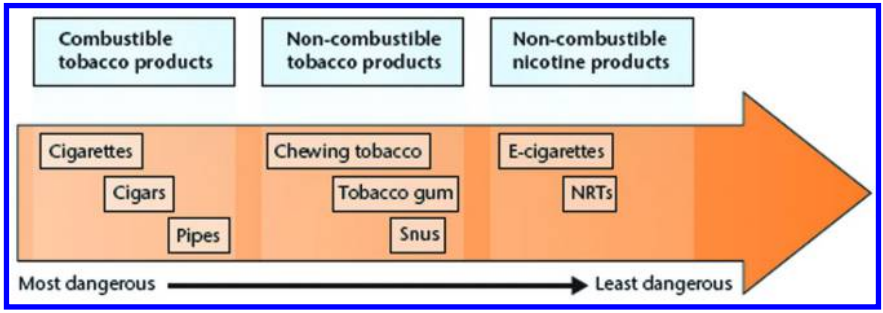

Figure 1. McNeil & Munafo's Nicotine harm continuum. Adapted with permission from reference (7). Copyright 2013 SAGE.

Philosophically, the ideas of consumers using products that contain fewer toxicants than conventional combustible cigarettes or do not involve inhalation are logical. Certainly, there is supporting epidemiological evidence available for some products, for example Swedish-style snus.

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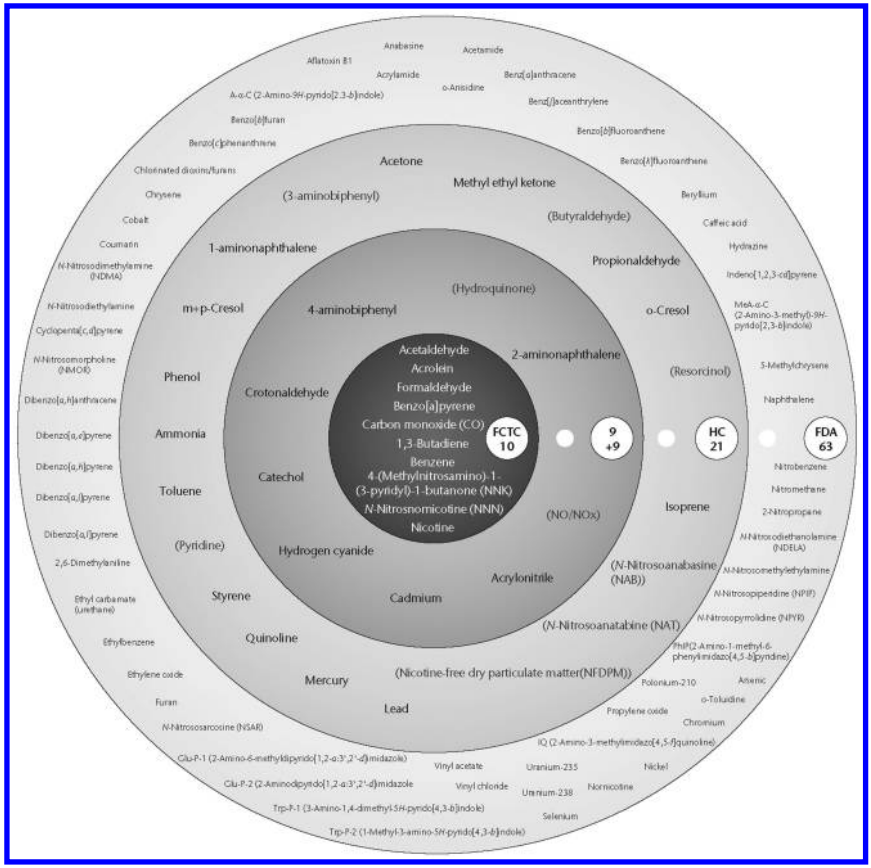

Figure 2. Harmful and potentially harmful constitutents of tobacco and tobacco smoke as identified by the United States Food and Drug Administration. Those in the inner circle are suggesed by the World Health Organization for mandated reduction. Adapted with permission from reference (10). Copyright 2013 British American Tobacco.

Dilemma for Public Health

Clearly, the introduction of a range of tobacco and nicotine products with a lower risk profile than cigarettes is potentially a great opportunity to improve public health outcomes. However, the concept is highly controversial for a number of reasons. It is easy to imagine that, on an individual level, switching to a less-risky product would bring benefits, but there could be unintended effects at the population level, which is just as important to public-health outcomes. There are also concerns about new products (e.g. e-cigarettes) acting as a gateway to conventional cigarettes and that use of such products could make smoking 'normal' again.

The biggest area of controversy, however, is neatly summarized by McNeil and Munafò as: "…the role of the tobacco industry in harm reduction. The

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tobacco industry has a long history of denying the health risks of smoking, and manipulation and deception around potential harm reducing products such as low tar cigarettes ... [Of course the] lack of interest from the pharmaceutical sector in producing 'recreational nicotine products' has left a gap which the tobacco industry has moved into, and several clean nicotine products have also now been patented by tobacco companies" (*7*).

So a key dilemma for public-health advocates is how to balance the tobacco industry's past with the public-health opportunity that exists today. Is it possible for this highly polarized group to find common ground?

Regulators clearly have a role to play here. For example, the concept of harm reduction is well-embedded in United States legislation, as manufacturers may submit applications for novel products to be evaluated as potential modified-risk tobacco products. In addition, the FDA recognizes that the regulated industry has a role to play and is a relevant stakeholder when considering how to regulate tobacco products. Therefore, the FDA has invited industry scientists to participate in its workshops. These actions have divided the tobacco control community. For example, in March, 2013, at a two-day FDA workshop entitled "Third-party Governance of Industry-Sponsored Tobacco Product Research: a Public Workshop" (*11*), Professor Ruth Malone of University of California, San Francisco (and Editor-in-Chief of *Tobacco Control*) declined to participate in the workshop because members of the tobacco industry were included as participants. In a letter to the FDA, she said: "Involving tobacco companies as 'stakeholders' on a panel with public health … suggests that all parties share … a congruent goal. This is a flawed assumption" (*12*). The FDA revised the schedule to put academia and public-health participants on the first day and industry representatives on the second day, but she again declined to participate (*13*).

Not surprisingly this created a stir in the blogosphere, with several leading figures in public health weighing in. Clive Bates (former Director of ASH) commented: "That attitude might have been credible 10 years ago … Harm reduction is one of the very few areas where tobacco-company and public-health interest may align. It may well be worth having industry-funded research on it – the idea of a facilitated discussion is to work out if there is a case. No credible scientist should approach that question with her or his mind made up" (*14*).

The lawyer, Scott Ballin, who is another long-standing member of the tobacco-control movement, has commented previously that traditional tobacco control advocates in the United States and elsewhere remain more focused on fighting the "tobacco wars" than in finding a path forward by which to advance public-health goals (*15*).

It is well accepted that there were three original aims for public health in the context of tobacco control: to reduce and then eliminate harms caused by tobacco use; to eradicate the tobacco industry; and, finally, to get rid of addiction (*16*). The public-health attitude to smoking, therefore, has been quit or die, with very little consideration given to smokers who are unable to quit.

Interestingly, at a press conference associated with a symposium entitled "E-cigarettes: Killing me Softly or the World's Greatest Public Health Opportunity?" at the EuroScience Open Forum in Copenhagen in 2014, a leading tobacco-control advocate commented: "Perhaps it is time just to focus on the first goal" (*17*).

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Critical Need for Good Science

This decade is likely to see the emergence, popularization, and characterization of tobacco and nicotine products with the potential to reduce individual health risks for tobacco users. These include oral tobacco products, such as snus, tobacco-heating products (also referred to as heat-not-burn), and electronic nicotine delivery systems, including improved medically regulated nicotine products.

For some of product categories, such as snus, there is good epidemiological evidence that allows an assessment of the relative risk. For newer products and emerging technologies, including e-cigarettes and tobacco-heating products, few data are available. Those that do exist mainly relate to toxicant exposure, with very little on epidemiological or chronic health end points. Media attention has been growing, but the studies available are of varying quality, and reporting can provide consumers with mixed, sometimes contradictory messages. For example, the following were among headlines in leading daily newspapers and journals: regarding potential risks, "Some e-cigarettes deliver a puff of carcinogens" in the *Daily Mail* on May 3, 2014, versus "E-cigarettes are 'less harmful than ordinary cigarettes': Healthcare professionals may recommend smokers use them instead of cigarettes" in the *New York Times* on July 31, 2014; and regarding the efficacy of e-cigarettes to aid smoking cessation, "E-cigarettes 'don't aid quitting' study says ", in *Nature* on March 24, 2014, and "E-cigarettes better than patches and gum as aid to kick the habit" in *The Independent* 2 months later (*18–21*).

Such confusion underscores the need for more, high-quality research. This must be consumer-focused and pragmatic, open-minded and driven by integrity, and conducted rigorously with high-quality study design. Data and comments must be available and relevant for policy-makers to access, which usually means publication in peer-reviewed journals. Additionally, experts should be confident and vocal in challenging bad science.

Although novel products are in their infancy in terms of research compared with conventional combustible cigarettes, the absence of burning and smoke suggest that they could make a positive contribution to reducing the public-health impact of tobacco use. The tobacco industry has expertise and facilities available to rapidly and substantially expand research into these products.

Changing Environment

The environment around tobacco product regulation has been changing rapidly in the past 5 years, and this rate of change will continue. The most significant change recently was the creation of a sixth FDA center, the CTP, in 2009, which supports the FDA's commitment to evidence-based regulatory decision-making (*5*).

Despite its commitment to a scientific, evidence-based approach to underpin regulatory decisions, the FDA (and other regulators) is still learning much about tobacco science. There are substantial gaps in the scientific record. For example, there is a critical need for standardized analytical methods to measure tobacco and smoke constituents and evaluate new products. In an effort to fill in some of

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these gaps, in early 2012, the CTP published a list of key research priorities, and in the summer of 2012, the FDA established an inter-agency partnership with the National Institutes of Health, which is now called the Tobacco Regulatory Science Program (TRSP) (*22*). This partnership is making available potentially billions of research dollars to study priority questions about tobacco regulatory science in order to inform FDA regulatory decision-making. The first major awards from the TRSP were made in September, 2013, when the CTP announced the creation of 14 Tobacco Centers of Regulatory Science (*23*). Each one was awarded US$4 million per year for 5 years, making the total value of this initiative US$280 million. Further significant awards in this field are expected, as the Family Smoking Prevention and Tobacco Control Act requires that a certain percentage of user fees, which are collected from tobacco manufacturers in the United States, is used to fund scientific research of interest to the CTP (*24*). Early calls in the TRSP encouraged transnational collaborations, and permitted commercial organizations to be involved. British American Tobacco (BAT) has acted as a supporting partner in 12 grant applications in the TRSP during 2013–2014, agreeing to provide, for example, expertise, products, or sample analysis.

This new funding source, focused on the emerging discipline of tobacco regulatory science, will naturally change the dynamics of the research landscape, particularly in the United States. An injection of funding of this scale and funding from a sustainable source always attract a new generation of research scientists. Ultimately, this should create a larger, more-diverse, more-results-orientated, and less-polarized community studying the challenges of tobacco science and tobacco regulatory science. The other natural consequence of this new funding will be a significant increase in the amount of tobacco regulatory science manuscripts and data being published in the literature. There will, however, likely be a shortage of suitable peer reviewers for this content, meaning that expertise held by scientists in the tobacco industry may become viewed as useful and valued.

Certain kinds of research will only be funded by tobacco companies themselves. National legislation across the world requires tobacco manufacturers to submit particular types of data, and the underpinning science will need to be carried out by the industry. Irrespective of who undertakes research, though, there is a clear need for standardized, validated analytical methods and publication of reference values. Even within-laboratory results can vary substantially (Figure 3). Clearly, this level of variability in measurements makes it difficult at present to accurately validate levels of key compounds in tobacco and smoke samples. Getting this right is critical to evidence-based regulation.

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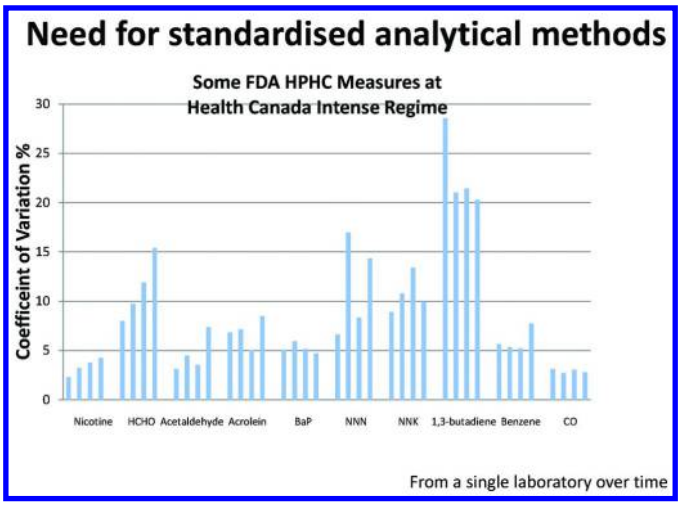

Figure 3. Need for standardized analytical methods. Copyright 2014 British American Tobacco.

A Changing Industry

Many tobacco companies are developing novel products that aim to be less risky than conventional cigarettes. The tobacco industry has expertise and facilities available to rapidly and substantially expand research into these products.

The BAT Group is researching products across the risk continuum, from tobacco-heating products, to oral products and e-cigarettes, to medically regulated nicotine-delivery systems. In our sustainability reporting, we have presented our version of the product risk continuum (Figure 4) (*25*).

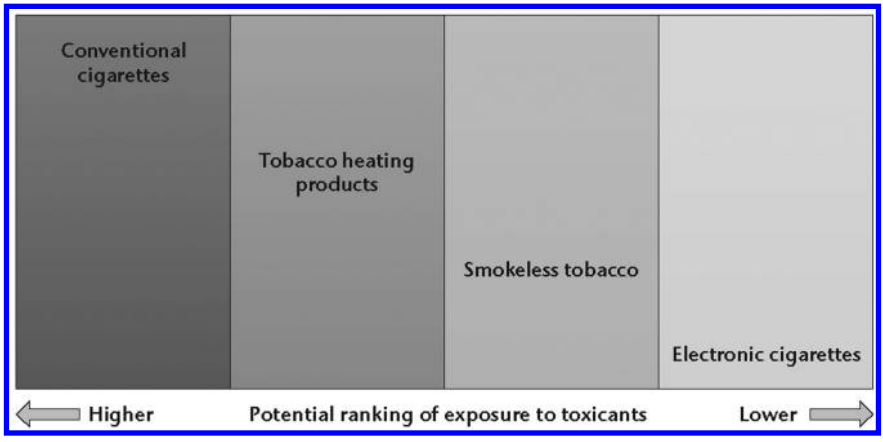

Figure 4. British American Tobacco's product risk continuum. Copyright 2014 British American Tobacco.

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Also, as part of our duty as a responsible tobacco company, BAT has made a public commitment to a much more open and transparent approach to sharing information about our research into harm reduction. We were the first tobacco company to initiate a stand-alone scientific website, bat-science.com; we were the first to allow external visitors to tour our R&D facilities in Southampton and Cambridge; and we were the first tobacco company to publish a dedicated Science & Technology Report in early 2014, which gave an overview of BAT's progress and aspirations in 10 different areas of tobacco science (*26*).

BAT's staff attends scientific conferences to present our work and engage in dialogue with other scientists in the field, including academics, regulators, and public-health stakeholders. We are publishing as much work as possible in peer-reviewed scientific journals. Over 150 BAT authored manuscripts have been published in more than 50 different journals since 2008 (see the library on bat-science.com). Our senior scientists also act as peer reviewers for more than 40 journals, which emphasizes the technical expertise held within the industry. It is heartening that the vast majority of journal editors and editorial boards continue to believe that good science speaks for itself, and should be judged objectively by the peer-review process. Although estimates vary as to the number of scientific, technical, and medical journals in operation today, well over 8,000 are being indexed for Impact Factors (a key quality metric). In practice, this means that there are many journals prepared to consider research funded by the tobacco industry, as long as potential conflicts of interest are clearly disclosed.

In terms of how we operate our research programs, we follow best practice as laid out in the pharmaceutical and food industries. In respect of clinical studies, we obtain ethics approval for all from the relevant committees.

Just as pharmaceutical companies do, we register all our clinical studies in advance of study initiation, on the ISRTCN or ClinicalTrials.gov databases. It is well accepted that the registration of a clinical trial forms a commitment to publication of the results from the study.

Also, every academic who receives funding for fundamental research from BAT today is encouraged to publish the results that arise from the project, irrespective of the findings, as well as to acknowledge the funding source.

Other companies are starting to follow this approach in increasing the level of openness and transparency, by launching other dedicated science websites, and opening up their R&D facilities to visitors.

Bans on Research Funded by the Tobacco Industry

Against a backdrop of a changing industry, which is increasingly opening up to share research materials and outputs, there is a move amongst some medical and public-health journals to prohibit publication of research that has been funded by the tobacco industry. In practice, this is still a very small number of journals.

Some of these titles are highly cited, respected journals that can influence practice and policy. This list includes the journals of the Public Library of Science (including *PLoS Medicine, PLoS Biology,* and *PLoS ONE*), the BMJ Group (including *Tobacco Control, The BMJ, BMJ Open, Thorax*, and *Heart*), the three

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journals of the American Thoracic Society, the *British Journal of Cancer* (owned by Cancer Research UK), the *European Journal of Public Health* (owned by the European Institutes of Public Health), and the journals of the American Cancer Society.

The issue has been debated in the past, most significantly around the time that the American Thoracic Society prohibited publication of articles with tobacco support in 1996 (*27*). Richard Smith, who was then the Editor of *The BMJ* co-wrote a piece strongly disagreeing with that decision. He said: "Indeed, the Society's directive that its members should not accept funding from the tobacco industry is a good step … But the extension of the rule into the pages of its scientific journals … is a threat to medical science, to journalism and ultimately to a free society" (*28*). *The BMJ* continued to encourage debate on the subject of industry-supported re/search in 2000, and later debated heatedly in 2003 (*29*, *30*).

The case of *The BMJ*, which introduced a new policy of refusing to consider tobacco-funded research in October, 2013 (*31*), is particularly interesting, as this is a reversal in policy. Historically, *The BMJ* had preferred to judge manuscripts individually on their merits, and had included reports of studies supported by the tobacco industry because, despite stating it was "passionately anti-tobacco", it was also "passionately pro-debate and pro-science". Richard Smith concluded that a ban would be "anti-science" (*30*). In early 2013, though, BMJ Group began to change its position. In a *Tobacco Control* editorial, published on Jan 1, 2013, the writing team (led by Ruth Malone, Editor-in-Chief) announced that the journal would no longer consider research funded by the tobacco industry. There were a number of reasons behind the decision, including the large number of "...publications based on tobacco company internal documents [which] show that the tobacco industry uses its funding of research and researchers to suppress, delay and thwart dissemination of knowledge and to create confusion" (*32*). The editors felt they could "not allow" their journal "to be put into the service of advancing tobacco industry goals" (*32*).

The issue of whether to publish research funded by the tobacco industry seems, therefore, to be based on a historical view of the industry hiding and manipulating research results. In the time frame of these bans (e.g. over the past 10–15 years), however, many leaders in the industry have made concerted efforts to improve reporting and increase transparency.

Ethical Considerations

There are many controversial areas in scientific research across industries – chemical, cosmetic, food, pharmaceuticals, and tobacco – but this does not mean that the science is not valid or that it has nothing to contribute to improved understanding of various issues.

The key argument is that suppression of ideas is a threat to science and the concept of free speech, and, therefore constitutes an unacceptable form of censorship. Michael Stein, a former Editor-in-Chief of *Clinical Pharmacology & Therapeutics*, was quite articulate on the practical issues with these types of bans, stating that it is difficult to define tobacco-industry support and that a definition is

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required to implement such a ban. How, then, do you treat different industries in the same way? Oil and gas companies are under fire about the environment, as are food companies about the rise of obesity. These questions lead into territory about the morality of who carried out the work, not just the science itself (*33*).

The issue of the potential censorship of work funded by the tobacco industry has been discussed in other forums too. The majority of publishers and journals appear to be willing to judge manuscripts on their merits with the help of expert peer reviewers.

Professor Anne Glover, former Chief Scientific Advisor to the European Commission, commented in 2013: "there is a fundamental mistrust of industry and industrial R&D by society, and this mistrust is increasingly hampering [Europe's] ability to innovate". She advocates that industry must "engage with its critics and examine its practices" (*34*).

Prohibiting publication of research funded by tobacco companies not only affects the reporting of tobacco science, but might hinder the publication of important information in other areas. For example, Reynolds American is associated with the production of a potential treatment for the Ebola virus via its subsidiary Kentucky Bioprocessing (*35*, *36*). Should this research not be published? If the tobacco industry were to develop products that could contribute to the reduction in cigarette smoking prevalence, how might public-health organizations and policy-makers learn of them without publication?

Who should make decisions about what should and should not be published is an important question, especially when the decision must take into account issues beyond the scope of sound science, such as morality and ethics. In general, peer-reviewed publications are seen as the gold standard for science publication, although who the peer reviewers are and to what degree their opinions are taken into account in editors' final decisions is not always clear. The Committee on Publication Ethics (publicationethics.org) provides useful guidelines for publishers, journals, editors, authors, and peer reviewers. The organization promotes integrity in research publication and, thereby, the scientific record. It supports the disclosure of conflicts of interest and discourages peer-reviewers from allowing their reviews to be influenced by the origins of a manuscript, nationality, religious or political beliefs, gender, or commercial considerations. That is, it asks them to consider only the science.

Another issue potentially skewing the scientific record is that sound science is being done by small start-up companies, for example in the field of e-cigarettes. These companies are characterized by innovation and sometimes collaborate with academics. Viewed as independent, there seems to be less hindrance to having this research published. If, however, a start-up company were acquired by 'big tobacco', the academics are frequently no longer able to collaborate and publication becomes less likely.

In an event on high-level science for policy consultation, "Evidence-based policy versus policy-biased evidence – the challenge of feeding scientific evidence into policy making (sci-com.eu/home/index.php/events/past-events?sytart=20)" held on June 29, 2012, a group of 27 global thought leaders came together to discuss the challenges of formulating policy in the emerging area of harm reduction science (*37*). A key theme of the event was "evidence-based policy

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versus policy-biased evidence". Participants agreed a set of 15 recommendations on the role and voice of industry. These included recommending that industry continues to have a role and a voice, not least because of the substantial investments it makes in science. As such, the integrity of the science must be positively asserted. The need for transparency is crucial on all sides. Whilst there might be actual or perceived conflicts of interest, there are clear ways of handling these through the declaration and peer-review processes.

Conclusions

Tobacco harm reduction has great potential to transform public-health outcomes, provided that is it supported by rigorous and high-quality research, driven by integrity and completed in a timely manner. Once available, data need to be published in the scientific literature. As the tobacco industry is actively involved in such research, and as there is a new commitment from the tobacco industry to openness and transparency, a blanket prohibition on publication of industry research is not the answer, especially when guidelines for disclosure of potential conflicts of interest are now well established. Research with the potential to contribute to public health should be published regardless of the source, and the peer-review process should be used to judge the science on its merits without having to take into account moral agendas.

The FDA's CTP relies on the most current science to make regulatory decisions on tobacco products, and "science is critical to [their] mission of reducing death and disease from tobacco use" (*38*). Clearly the CTP, and other regulators, can only benefit from a system which ensures that all scientific outputs in this new field of tobacco regulatory science are objectively evaluated by the peer-review process, and sound work is published (with any potential conflicts of interests clearly disclosed).

As we said in our letter to *The BMJ* in 2013 (*39*), it has been argued that tobacco harm reduction is potentially the world's greatest public health opportunity today. To have this kind of impact, those with an interest must find pragmatic ways to work together to find solutions based on sound science. For this research to be disseminated widely, it will be important for the science publishing industry to retain an independent, critical, yet open approach.

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Chapter 7

Science, Values, and the Political Framing of Indirect Land Use Change (ILUC)

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Indirect Land Use Change (ILUC) refers to deforestation and agricultural expansion due to increased crop prices. It is a controversial spillover effect of biofuels that is estimated by "shocking" agricultural market models with high biofuel scenarios. The validity of this modeling is highly contested in biofuel regulation. As a case study of ILUC discourse, this chapter analyzes how ILUC science was interpreted and strategically framed during rulemaking for the California Low Carbon Fuel Standard (LCFS) in 2007–2009. The analysis covers three stages of the initial rulemaking process: academic advisory reports, agency rulemaking documents, and public comments. It finds that at every stage, stakeholders blended values-based and science-based arguments. Even when stakeholders framed their stances as firmly based on science, their interpretation of "right" action in the face of uncertainty also depended on normative values. The takeaway for policy-makers is that ILUC is not an issue where policy answers can be straightforwardly derived from science.

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Introduction

In September, 2014, the California Air Resources Board (CARB) held a workshop on a major science policy controversy: carbon emissions from indirect land use change (ILUC). ILUC refers to deforestation and agricultural expansion driven by crop prices. It is a market-mediated spillover effect of biofuels, estimated by "shocking" agricultural market models with high biofuel scenarios and seeing how equilibrium levels of cropland, grassland, and forest acreage are affected. The policy debate about ILUC emissions began in early 2007, when it was raised during CARB's initial rulemaking for California's Low Carbon Fuel Standard (LCFS). Critics have argued ever since that the models overestimate ILUC and should be empirically validated. But, at the 2014 workshop, CARB staff bluntly told stakeholders that it was "not productive" to compare model results with real-world data (*1*).

Why would regulators rely on models and reject empirical data in determining compliance with environmental standards? The challenge is that ILUC represents a new paradigm of environmental impact assessment that considers not only the greenhouse gas (GHG) emissions produced within a product's supply chain ("direct emissions"), but also spillover effects throughout the global economy ("indirect emissions"). These price-mediated effects must be simulated with market models because, by definition, indirect causation cannot be directly observed or imputed from data (*2*).

Thus, policy-makers are in a quandary: although indirect emissions make for a more comprehensive emissions assessment, estimates are "highly uncertain, unobservable, unverifiable, and dependent on assumed policy, economic context, and inputs," according to the Intergovernmental Panel on Climate Change (*3*). This issue is not just a problem for biofuels. Fuels were the first battleground for indirect emissions accounting due to the uproar over ILUC, but the issue will likely be controversial for any climate policy going forward.

This chapter examines the ILUC debate for the California LCFS, which was the first regulation to consider ILUC accounting. As the crucible of ILUC policy discourse, the LCFS is a key case study for tracing the emergence and evolution of the ILUC debate. This analysis traces ILUC discourse across three stages of initial LCFS rulemaking: advisory reports from academic researchers in 2007, CARB's administrative proceedings in 2007–2009, and public comments submitted to CARB in 2009 prior to the final regulatory decision. For each stage, the chapter examines how policy actors interpreted and framed ILUC science and policy. Framing means "to select some aspects of perceived reality and make them more salient … in such a way as to promote a particular problem definition, causal interpretation, moral evaluation, and/or treatment recommendations" (*4*). It is a form of strategic communication, since constructing a frame around an issue means that certain aspects are emphasized and others are cut out of the picture.

The principal finding from the first two rulemaking stages (academic advisory reports and CARB proceedings) is that although academic and regulatory actors framed their stances as based on scientific findings, their interpretation of "right" action in the face of quantitative uncertainty relied on normative judgments and ontological assumptions. Their discourse thus blended science-based and values-

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based arguments. As for the third stage (public comments), many stakeholders rhetorically invoked "science" and "scientists," but only a minority cited specific reports, findings, or data. This pattern of science communication – strong on rhetoric, thin on details – was especially pronounced among ILUC supporters. This is arguably a surprising result, since non-governmental organizations (NGOs) in Europe used the seminal *Science* paper from Searchinger *et al.* (*5*) as a "battering ram" in their ILUC advocacy (*6*).

More broadly, the content analysis of public comments reveals the range of frames that stakeholders used in discussing ILUC science and policy. Stakeholders could emphasize different types of scientific knowledge (model results versus empirical data), different aspects of the emerging knowledge (certainties versus uncertainties), different normative principles (equal accounting for all fuels versus comprehensive accounting of all emissions), different ontological emphases (real data versus real GHG reductions), and different risks of making the wrong policy choice (stifling innovation versus increasing emissions), to name a few possibilities. All these frames involve selection and subjective judgment. The takeaway for policy-makers is that ILUC is not a policy issue where the answers can be straightforwardly derived from science. As Sarewitz observes: "when cause-and-effect relations are not simple or well-established, *all* uses of facts are selective" (*7*).

In exploring these issues, this chapter begins with a technical primer on ILUC modeling. Next, it reviews the rulemaking process and discusses how ILUC modeling was officially framed by academic advisors in 2007 and CARB staff over 2007–2009. Lastly, it presents the content analysis of public comments submitted to CARB in 2009 and closes with concluding thoughts.

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Technical Primer: The Development of ILUC Modeling

This section provides a layman's primer on ILUC science, emphasizing major conceptual developments rather than technical details. It focuses on basic questions: what is included in life-cycle assessment (LCA), what is the rationale for including land use change, how was ILUC modeling developed and with what uncertainties?

LCA

LCA quantifies the flow of energy and materials throughout the production, transport, and use of a product. For transportation fuels the life cycle is typically described as "well-to-wheels" to reflect that it starts with natural resource extraction ("well") and ends with consumption in a vehicle ("wheels"). This supply-chain orientation reflects LCA's origin as a tool for industrial process optimization and waste management.

Conventional LCA was designed to analyze impact of an average product from a static production process. This is useful for firms trying to optimize some aspect of this process or for consumers choosing between standard products (eg, paper versus plastic bags). However, as LCA began to be applied to policy

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and regulatory decisions, these constrained analytic boundaries started to pose problems (*8*). Policy decisions have the potential (and are, in fact, often intended to) drive large-scale technological changes or substitutions among competing products. In this case, what matters are arguably the marginal and dynamic impacts from increased usage of a product (*9*).

The LCA community began recognizing this challenge in the early 2000s (*10–12*). What emerged was eventually a division of LCA methods into Attributional LCA (ALCA), which accounts for direct effects within traditional lifecycle boundaries, and Consequential LCA (CLCA), which expands the system boundaries to the broader economy and considers how increased demand for one production affects markets for (and emissions from) related products. In addition to the input–output mass balance models used to estimate direct effects, CLCA adds economic models to estimate market-mediated indirect effects.

CLCA's strength is that that the information it generates is more aligned with the functional goals of environmental policy. Nevertheless, it introduces even more uncertainty. As summarized by Plevin *et al*. (*9*): "The more comprehensive the consideration of consequential effects, the more uncertain are the results." This trade-off is at the heart of ILUC policy debates.

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Accounting for Land Use Change Emissions

Land Use Change (LUC) refers to changes in land cover or management. LUC is relevant to GHG accounting because it can cause a flux between terrestrial and atmospheric carbon. For example, when degraded or agricultural land is converted to forest or grassland, carbon from the atmosphere is sequestered in vegetation, roots, and soil. Conversely, when forests and grassland are converted to agriculture, this stored terrestrial carbon is released to the atmosphere. The LUC debate within biofuel policies is therefore focused on how to quantify GHG emissions from the expansion of agriculture.

In attributing LUC to biofuels, analysts consider both direct and indirect causation. Direct land use change (DLUC) refers to expanded bioenergy cropland, such as cutting down Indonesian forests for oil palm plantations. But ILUC can involve the expansion of any agriculture anywhere in the world, so long as it is induced by higher commodity prices due to biofuel production. For example, if farmers in the United States respond to ethanol demand by growing more corn and less soy, this could raise global soy prices, which could drive Brazilian soy farmers to expand production into rangeland, which could in turn drive displaced ranchers to cut down forest for cattle grazing.

Both above examples involve tropical deforestation, but they have different causal mechanisms and system boundaries. DLUC can be estimated by quantifying total land use change and attributing a proportion to biofuels on the basis of crop usage. Basically, this is an accounting approach using time-series data on land cover, crop yield, and food and fuel production. It's not an easy computation, given the limitations of satellite land cover data and the complexity of co-product accounting, but the point is that DLUC is amenable to empirical estimation. Also, as a direct consequence of biofuels production, it fits into the "well-to-wheels" boundaries of conventional ALCA.

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In contrast, ILUC must be simulated with CLCA models. It involves a multi-stage causal chain: biofuel production > domestic prices for agricultural commodities > international prices for agricultural commodities > land-use decisions of local farmers and ranchers around the world. In reality, each node in this chain has multiple drivers: biofuels are only one minor factor in domestic crop prices; international crop prices are also determined by trade policy, agricultural policy, food demand, transportation costs, yields from related crops, and weather; and local land use patterns depend on many social, political, cultural, and legal factors. Put together, it is a complex socioecological–technical system with many data gaps and many institutional variables that are difficult to represent in econometric analyses. Accurately accounting for all dynamics in order to isolate the causal signal of biofuels is simply not possible. The empirical intractability can be illustrated by considering the relationship between rates of corn ethanol production in the United States and Brazilian deforestation over time (Figure 1).

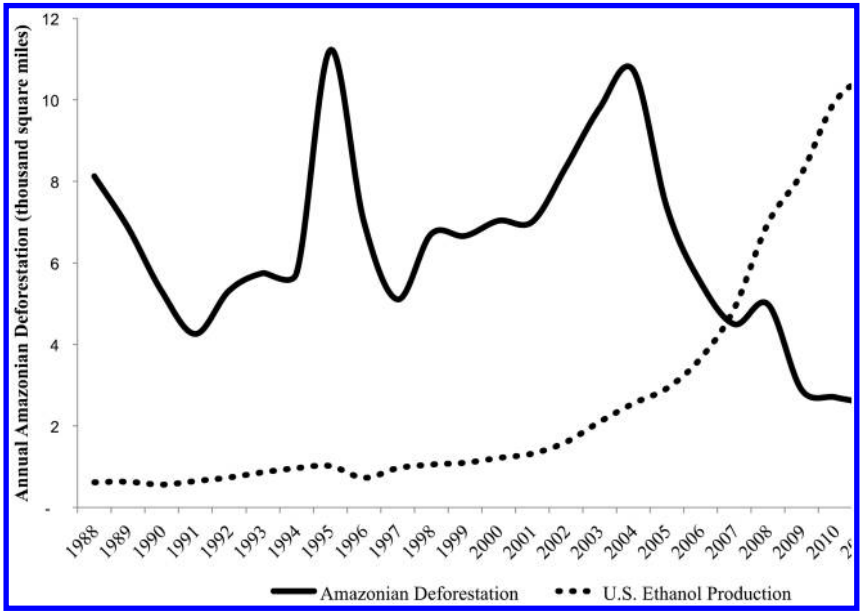

Figure 1. Rates of Amazon deforestation and United States ethanol production, 1988–2012. Based on data from the Brazil National Institute for Space Research and the United States Energy Information Administration. Adapted with permission from reference (13). Copyright 2013 Renewable Fuels Association.

Biofuel advocates use these data to argue that there was no ILUC, since deforestation plummeted when corn ethanol production climbed dramatically (*13*). Critics argue counterfactually that deforestation rates might have dropped even further were it not for ethanol. The point is that neither claim can be empirically validated. Data-based accounting does not work with indirect causal chains in complex systems. Without being able to reliably predict what commodity prices and, in turn, land use patterns would have been in the absence of biofuel demand, analysts cannot isolate (or even reliably estimate) the causal

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signal of biofuel-induced ILUC. Thus, the only way to estimate ILUC is with models that simulate the impact of biofuels on commodity prices and land use patterns. Having explained why such models are necessary, we now turn to their development.

The Development of ILUC Modeling

ILUC is a relatively new field of study. Mark Delucchi at University of California, Davis, produced rough estimates of DLUC in the 1990s (*14*, *15*) and pioneered the conceptual work on ILUC in the early 2000s (*16*, *17*). The latter papers provided a conceptual framework for ILUC, but they did not attempt formal models since "the interplay of economic, technological, political, regulatory, environmental, and historical forces is particularly difficult to model" (*16*). This thinking was the state-of-the-art on ILUC when the issue was raised in LCFS discussions in 2007.

The first quantitative estimates of ILUC were published in February, 2008, by Searchinger *et al*. (*5*). Rather than building the comprehensive models envisioned by Delucchi, the Searchinger *et al.* paper pragmatically stitched together the results of an agricultural market model with historical land use data. The model, run by the Center for Agricultural and Rural Development, included ethanol as one of many value-added agricultural products, which meant that model runs generated equilibrium volumes of ethanol (*18*). It also estimated global cropland acreage based on land-supply curves. Searchinger *et al.* took these two outputs (ethanol volumes and cropland acreage) as generated by two model runs (baseline and high oil price scenarios) and causally attributed the change in acreage to the change in ethanol production. Next, since the model only reported aggregate cropland by region, Searchinger *et al.* used historical data on land use and soil carbon emissions to make assumptions about the type of LUC and resultant emissions. It was a crude approach with questionable causal attributions, but it succeeded in producing a number. And an alarming number it was: the paper estimated LUC emissions from corn ethanol at 104 g CO_2e/MJ, which exceeds direct emissions from conventional gasoline (*5*). (Note that this approach estimates total LUC without differentiating between ILUC and DLUC.)

ILUC research took off in the following years, particularly from 2009 onwards. As this post-dates the LCFS rulemaking, it goes beyond the scope of this background review. However, noting this briefly is worthwhile because it illustrates what was missing from the science in 2007–2009 during LCFS rulemaking. Broadly speaking, the maturing technical literature comprises three projects:

- **Refining models**: The Searchinger *et al.* (*5*) approach of "shocking" agricultural market models to estimate total LUC was widely replicated with a variety of econometric models and land use datasets (*19–21*). Tremendous effort has been devoted to making the models more sophisticated: updating parameter values to reflect new data (e.g. price elasticity of yield, productivity of converted land, and co-products), adding features absent in early models (e.g. idle land), increasing spatial

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resolution, and developing new databases of agroecological zones and emissions factors. The result is that LUC estimates dropped by an order of magnitude. Instead of Searchinger *et al.*'s estimate of 104 g CO_2e/MJ (*5*), current estimates of LUC emissions are typically 8–12 g CO_2e/MJ (*22*).

- **Probing uncertainty**: Searchinger *et al.* (*5*) declared that their results were robust, but this conclusion was repudiated by numerous studies of uncertainty, including sensitivity analyses (*23*), Monte Carlo simulations (*24–26*), and qualitative discussions from economists and modelers (*2*, *9*, *27–29*). These studies provide a more nuanced perspective on ILUC estimation. They confirm that ILUC likely exists and could be much higher than mean estimates. Yet they also demonstrate that estimates are extremely sensitive to model structures, assumptions, and inputs, such that there is an inherent indeterminacy in the modeling.
- **Empirical investigations**: as discussed above, ILUC cannot be isolated from empirical data. Nevertheless, researchers seek to bring data to bear on the problem as far as possible. Some have searched for a signal of ILUC in real-world land-use data (*30*), although more are focused on using data to improve the econometric models (*31*).

Unfortunately, this range of literature did not exist in 2008–2009. The concept of CLCA was just being developed in the LCA community, and the econometric modeling on ILUC was rough and exploratory. The infancy of the topic meant that critical literature and sophisticated analyses of uncertainty had not emerged. ILUC was an immature field of science when it was written into the LCFS, such that its interpretation and policy implications were very much open to debate.

How Was ILUC Framed in Official Rulemaking?

Overview of the LCFS

The LCFS requires California fuel providers to reduce the lifecycle carbon intensity (CI) of fuels sold in California by 10% from 2010 to 2020. CI is measured in g CO_2e/MJ of fuel energy. CARB assigns a CI score to each specific fuel, including hundreds of pathways for gasoline, diesel, natural gas, electricity, hydrogen, and biofuels. Fuel providers can meet their CI reduction obligations either by selling lower-CI fuels or by purchasing credits from other providers. It is a performance-based, market-oriented standard predicated on LCA.

The CI score for biofuels includes indirect emissions from LUC. This was by far the most controversial aspect of the carbon accounting. One reason is that CLCA is a new analytical paradigm, with neither standardized models nor established best practices in policy usage. In addition, the controversy was inflamed by the fact that biofuels are assessed with CLCA while all other fuels are assessed with ALCA, such that the lifecycle boundaries are asymmetrical. Including indirect emissions for biofuels dramatically reduces their potential as an LCFS compliance option, both absolutely and relative to other alternative fuels (Figure 2). For example, under ALCA accounting, corn ethanol has a significant

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carbon reduction compared to gasoline (30–35%, depending on the pathway), but ILUC basically renders it ineligible for LCFS compliance. Similarly, sugarcane ethanol goes from one of the lowest CI scores under ALCA to being worse than conventional natural gas under CLCA. Put together, the high stakes, enormous uncertainty, and asymmetrical LCA boundaries made ILUC intensely politicized during rulemaking.

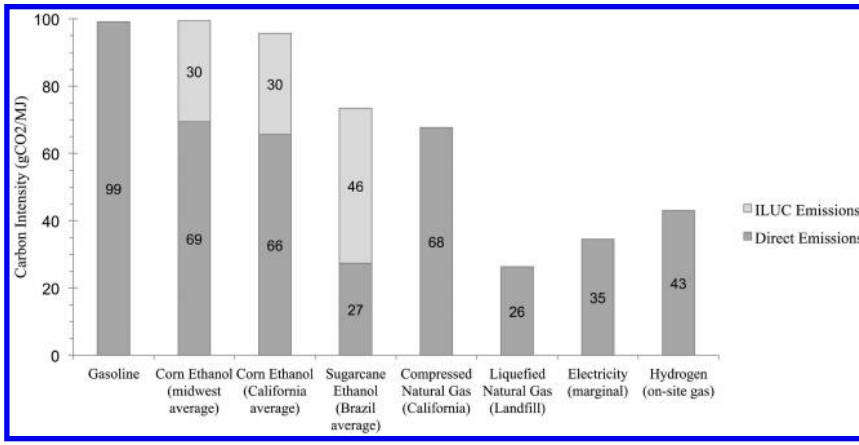

Figure 2. Current carbon intensity scores for selected fuels (32). Electricity and hydrogen are adjusted for energy efficiency ratio.

The Policy-Making Process

The LCFS was designed in three phases. First, Governor Schwarzenegger established the LCFS by executive order in January, 2007, following a few months of intensive formulation in his office. The Governor's order specified that CI would be based on "full fuel cycle accounting", but there was no indication that this was meant to go beyond conventional ALCA.

Second, academic researchers from the University of California were tasked with providing analytic input. They produced two reports: a technical report in May, 2007 (*33*), introducing the concept of indirect emissions, and a policy report in August, 2007 (*34*), recommending that ILUC be assessed for biofuels. These reports were the origin of the ILUC policy debate and are discussed at further length below.

Third, CARB proceeded with formal rulemaking. Whereas the executive order and academic reports were expeditiously produced in a matter of months, agency rulemaking stretched from 2007 through spring 2009. CARB held numerous public workshops, contracted with economic modelers from Purdue University, and released multiple policy drafts. On March 5, 2009, they released the final proposal, whose framing of ILUC is discussed more below. The proposal initiated a 45-day period for public comments, which are analyzed in the next section. Finally, on April 26, 2009, the LCFS with ILUC was approved in a hearing by the CARB Board.

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Framing of ILUC by University of California Researchers

The University of California (UC) reports took ILUC from academic obscurity to policy prime time. Appointing academic researchers with a formal advisory role provided an institutional mechanism for this unusually rapid policy application of emerging research.

The UC technical report, released in May, 2007, immediately signaled a departure from conventional ALCA by defining a life cycle as "all the physical and economic processes directly or indirectly in the 'life' of the product" (*33*). By including economic processes and indirect effects, this definition radically departed from International Organization for Standardization standards, which define a life cycle on the basis of physical flows in the product system. This redefinition truncated debate about whether indirect emissions should be included and leaped straight to the question of how to include them. Yet while the technical report raised the issue of ILUC, it also laid bare the analytical challenges, concluding: "Although there is wide consensus that these effects may be important, there is no well-accepted method for calculating the magnitude of these effects. Because land use change is a market-mediated effect, is [sic] not clear how to treat these effects in a fuel life cycle LCA." (*33*).

The UC policy report, released in August, 2007, pivoted to argue strongly in favor of ILUC accounting. Specifically, it recommended that CARB develop a "non-zero estimate" to use for the first few years of implementation while working to develop more-robust measurements in the longer term. The report summarized the core analytical and policy issues as follows:

> *Between enormous data gaps, uncertain soil science, economic modeling uncertainties, and uncertainties about future policies and prices, it is not possible at this time to accurately measure the impact of carbon releases from the soil due to increased biofuel production. On the other hand, not including these effects is problematic. If global land conversion were ignored, this effect would effectively be assigned a value of zero, which we know to be wrong. Instead, the LCFS could include a rough estimate of the portion of emissions from global land use conversion that is potentially attributable to crop-derived biofuels. While rough, such an estimate would send the correct signal about biofuels pathways that involve land use conversion.*
>
> —Alexander E. Farrell and Daniel Sperling (*34*)

Three dimensions of this strategic framing are important to highlight. First, the UC researchers privileged normativity over epistemology. They prioritized what should count over what they could count, "correct signals" over "accurate measures". For a performance-based regulation, this was a remarkable position.

Second, when characterizing the science, the UC researchers did not claim that initial ILUC estimates would be based on firm science – which is how CARB staff and many policy comments subsequently defended ILUC accounting. To the contrary, they bluntly stated that "there is little data about indirect land conversion effects" and that "[f]ew economists believe that an international computable

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general equilibrium model could predict such land use changes" (*34*). Yet, although they acknowledged that accurate estimates were not yet available, they suggested that further research could produce "accurate, robust, and transparent methods for measuring and accounting for indirect and land use emissions" (*34*). Accuracy was forthcoming. Measurement, as opposed to model estimation, was achievable. This is an interesting framing, on the one hand deeply engaged with current uncertainty, but on the other hand glibly overstating the certainty that could be delivered in the future.

Third, in framing their policy decision, the researchers did so narrowly, as a choice between zero and non-zero estimates. This is an example of a rhetorical strategy known as Hobson's choice, in which there is an illusion of choice but only one viable option, a take-it-or-leave-it choice with such tight constraints that the outcome is effectively forced. As explained by Stone (*35*): "Once the audience accepts the structure of a Hobson's choice – that the alternatives presented are the only one … and that [they] have the qualities imparted to them … then it is stuck with the offerer's preferred alternative." In this case, several other options might have been explored: delaying for further study, limiting credits from food-based biofuels, requiring biofuels to meet sustainable land-use criteria, accounting for DLUC and phasing in of ILUC as the modeling evolved, or developing polices for ILUC mitigation. As these options were not mentioned, however, the "non-zero" option – whatever that might mean in practice – appeared as the only reasonable choice.

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Framing of ILUC by Regulatory Staff

Rulemaking by CARB staff culminated in a final regulatory proposal, the Initial Statement of Reasons (ISOR), in March, 2009 (*36*). The analysis here focuses on ISOR, as it provides the clearest and most formal articulation of CARB's position on ILUC. However, it is important to recognize that CARB was committed to ILUC from the start of rulemaking. As early as November, 2007, staff presentations clearly included ILUC in biofuel LCA boundaries (*37*).

Yet, while CARB staff immediately adopted the functional recommendation from the UC report – that is, immediate ILUC accounting – they developed a different framing of both the policy decision and the underlying science. They framed the policy choice as a decision between excluding or including ILUC, with the significance of emissions as the sole deciding factor. The decision was summarized in ISOR as follows: "For some crop-based biofuels, the staff has identified land use changes as a significant source of additional GHG emissions. Therefore, the staff is proposing that emissions associated with land use changes be included in the carbon intensity values" (*36*).

Since CARB staff framed the policy choice as being based on quantitative significance, their characterization of ILUC science was pivotal. And here they departed significantly from the UC researchers: instead of engaging up front with the uncertainty and data gaps in ILUC modeling, CARB staff boasted that their estimates were "empirically based, defensible, and fully open to public scrutiny" (*36*). In making this claim, the ISOR executive summary repeatedly emphasized

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CARB's close collaboration with university researchers (i.e. science) and wrote off any critics as biofuel advocates (i.e. non-science):

> *[We worked] with modelers at the University of California and Purdue University to derive land use change estimates that are empirically based, defensible, and fully open to public scrutiny and comment … However, the magnitude of this impact has been questioned by renewable fuel advocates … Because the tools for estimating land use change are few and relatively new, biofuel producers argue that land use change impacts should be excluded from carbon intensity values pending the development of better estimation techniques. Based on its work with university land use change researchers, however, ARB staff has concluded that the land use impacts of crop-based biofuels are significant, and must be included in LCFS fuel carbon intensities.*
> —California Air Resources Board (*36*)

Indeed, CARB consulted with modelers running the Global Trade Analysis Project (GTAP) model at Purdue University to produce the most extensive ILUC analysis at the time. But as one peer reviewer noted, even though CARB's analysis was the "state-of-the-art" on ILUC, the field was still in its "infancy" (*38*). In quickly adapting GTAP to the purpose of ILUC modeling, there were still many structural limitations and 'guesstimates' about parameter values.

ISOR's technical sections and appendixes did discuss uncertainty in model inputs, including elasticity values, co-product credits, emissions factors, and time accounting. They presented sensitivity analyses, identified where more research was needed, and explained how staff and modelers used "best available science" when available and resorted to "best professional judgment of experts" when data were unavailable (*36*). However, these nuanced discussions of uncertainty and subjective judgment were buried, in contrast to the front-and-center summary statements of quantitative significance. Also, it is notable that these discussions focused on micro issues of parameter values rather than macro conceptual and epistemological issues. At no point was it mentioned, for example, that ILUC required new LCA system boundaries.

To summarize, academics wrestled with the dialectic of ILUC – concerning but uncertain – and sought to resolve it by recommending a non-zero estimate. Regulatory staff adopted their recommendation and pursued immediate ILUC accounting, but they framed their decision as firmly science-based. As the literature on science policy-making and regulatory science has long observed, "…the legitimacy of American regulatory decisions uniquely depends on rational justification" (*39*), such that regulators have a strong incentive to overstate the certainty and determinacy of science (*40*). Regulators are especially prone to be "under critical" of science when policy consensus precedes scientific consensus (*41*), as was the case of ILUC in the LCFS, and commonly use science for strategic policy legitimation rather than decision-making (*42*). While not a surprising result for science policy scholars, it is an important component of ILUC policy-making.

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How Was ILUC Framed in Public Comments?

Thus far, this chapter has reviewed the emergence of ILUC modeling and analyzed how it was framed by academic advisors and agency staff during policy formulation. How was ILUC science framed in broader public discourse? To answer this question, this section presents a content analysis of public comments from the 45-day public comment period during March and April, 2009.

Comments from this period, which are archived on CARB's website, include 230 comments submitted before the hearing and 44 comments presented during the hearing (*43*). Since this chapter's specific focus is ILUC discourse, content analysis was only conducted on the subset of comments that mentioned "indirect land use," "indirect land use change," "land use change," "land use impacts," or "indirect effects." Letters solicited by CARB as peer review were excluded from this sample, while multiple comments by one author were condensed into one comment for analysis. In total, 104 public comments on ILUC were included in this content analysis.

These comments varied greatly in depth, length, formality, technical sophistication, and authorship. They included everything from two-paragraph emails from concerned citizens to five-page group advocacy letters to 20-page (or even 120-page) critiques from academic or industry experts. The passages on ILUC ranged from single sentences to dozens of pages. The authors varied from single individuals to nearly 200 signatories representing a diverse set of affiliations. The heterogeneity of comments and small sample size (especially when divided into sub-categories based on policy position) posed a challenge for meaningful statistical analysis or quantitative coding (e.g. counting word frequency or length of text). Instead, the content was manually coded for qualitative attributes using a combination of closed (deductive) and open (inductive) codes. Since no previous studies have sought to identify the framing of ILUC, the inductive identification of frames from this analysis is a significant contribution to the literature on ILUC discourse and policy-making.

Coding proceeded in three rounds: first, the portion of text related to ILUC was identified; second, closed coding was used to categorize each comment's overall policy recommendation and use of scientific evidence; third, open coding was used to characterize the discursive arguments in the comments. The codes assigned during open coding typically use *en vivo* language, which means that they represent that actual words and terms used by the comment writers. This is why there are many similar codes (e.g. describing GHG reductions as "real," "actual," or "true") that need to be grouped together into thematic categories. It is also worth noting that open coding is a recursive process, with all comments read multiple times to ensure that the codes were consistently identified across all the comments (*44*).

The open codes were further analyzed using the constant comparative approach, in which they were inductively and iteratively organized into higher-order categories throughout the coding process (*45*). This means that the scientific, normative, and ontological frames discussed below were not pre-determined. They represent thematically related groups of codes that emerged from the inductive coding. For example, statements about "not picking winners"

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or maintaining a "level playing field" are variations on a theme about treating all fuels equally, which is also related to critiques that ILUC accounting is "unfair" or "biased" against biofuels. To capture the higher-order theme in these codes, they were grouped into a frame of "fair accounting." In the remainder of this section, the content analysis results are presented as follows: policy stance; use of scientific evidence; framing of ILUC knowledge; normative framing; ontological emphases; and conspicuously absent issues.

Overall Policy Stance

The policy decision for ILUC was framed by the UC researchers as a narrow choice: should ILUC be assigned a value of zero or non-zero? Although CARB staff did not frame it in quite the same way, they, too, presented it as a dichotomous choice – should ILUC be included or excluded? – with quantitative significance portrayed as the sole deciding factor. But many public comments rejected these narrow frames and raised a wider set of policy options, scientific interpretations, and decision factors. Overall, the comments were grouped into five categories of policy recommendations. They are as follows, accompanied with representative quotes from the comments:

Support ILUC Accounting: 35 comments (34%) supported CARB's decision to account for ILUC. As will be discussed at greater length in the frame discussion, most cited environmental concerns and normative principles of integrity and full accounting. The comments in this category overwhelmingly came from environmental and clean energy NGOs, along with several letters from major oil companies, other business interests, environmental regulators, unaffiliated individuals, and health NGOs. This category only included one letter from academic researchers, which was organized by the Union of Concerned Scientists. Here are examples of how these comments summarized their policy recommendations:

> *We … support CARB's decision to incorporate the indirect land use effects of fuel production, a key LCA component that will ensure we achieve true global GHG reductions*
> —Remy Garderet, Energy Independence Now (*46*)

> *We urge you to ensure that your policies are based on the best science, including consideration of emissions from indirect changes in land use.*
> —Patricia Monahan, Union of Concerned Scientists (*47*).

Exclude Agrofuels: five comments (5%) agreed that ILUC was significant but argued that the appropriate response was to exclude food-based biofuels from the LCFS. These comments were also distinguished by their use of the term "agrofuels," which is common in European biofuels discourse but unusual in the United States. These comments were submitted by one environmental NGO and four non-affiliated individuals, the latter of whom appeared to have incorporated form-letter text. A representative statement of this position is:

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We encourage CARB to adopt a precautionary approach and to exclude agrofuels from the LCFS … When considering the inclusion of agrofuels, it is important to recognize that emissions from indirect land use change (iLUC) are a major source of pollution
—Andrea Samulon, Rainforest Action Network (*48*)

Oppose ILUC Accounting: 25 comments (24%) opposed CARB's proposed ILUC accounting. Nearly all cited concerns about the unfairness towards biofuels as well as model uncertainty, with a few arguing that ILUC should be excluded because it was "just a theory." These comments were largely submitted by agriculture and bioenergy companies and trade organizations, along with a smattering of academic researchers, environmental NGOs, a national security think tank, and unaffiliated individuals.

[I]ncluding the indirect effect of land use in determining the carbon content of a fuel is … problematic. Not only is the scientific community not in agreement on how to measure and value such a figure, to apply the land use analysis to biofuels alone is intellectually inconsistent and unfair.
—Mark Cole, US Development Group LLC (*49*)

[A] prudent approach for the LCFS is to promulgate a robust regulation based on direct carbon effects, including direct land conversion for feedstock production
—Ashley Boren, Sustainable Conservation (*50*)

Delay for Study: 29 comments (28%) recommended that the decision on ILUC be delayed until more research and modeling could be conducted. Most emphasized that this should include indirect effects for all fuels, not just biofuels. A subset offered a specific proposal or timeline for research. These comments were predominantly submitted by companies and trade organizations with bioenergy interests, along with several academic and national laboratory researchers (including the widely cited letter from 111 bioenergy researchers), agribusiness interests, clean vehicle advocates, and unaffiliated individuals.

While I agree with the goal of including indirect land use changes in LCFS, we don't have the data or the current collection capacity required for an appropriate or accurate assessment.
—Kirk Leonard, no affiliation listed (*51*)

We are … requesting that CARB Board take the following actions: A. Submit an LCFS regulation based on direct carbon effects, including direct land use impacts. B. Commission the National Academy of Science to conduct an 18-month study on indirect effects of all transportation fuel candidates to develop and validate a robust science-based tool that can be used within the LCFS.

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—Blake Simmons, Sandia National Laboratory; Harvey Blanch, Lawrence Berkeley National Laboratory; Bruce Dale, Michigan State University (*52*)

Technical Input: 10 comments (10%) provided technical input but did not take an explicit position on whether or when to include ILUC in the LCFS. To some extent this could be interpreted as tacitly accepting ILUC accounting, though most were sharply critical of CARB's approach. These comments were submitted by a wide array of stakeholders (academic researchers, biofuel companies, environmental NGOs, an agricultural trade organization, a national security think tank, an oil company, and an economic consultant) with no type dominating.

[I] accept the CGE model and that of GTAP as being appropriate … however the complexities of the issue are great and the current assumptions used in this analysis cannot be supported.
—William Wilson, North Dakota State University (*53*)

I would present a word of caution when using remote sensing or any other geospatial dataset to assess land use change. The error associated with the dataset cannot be larger than the rate of change in order for it to be a useful tool.
—Kenneth Copenhaver, University of Illinois (*54*)

In total, a minority of comments supported CARB's approach to ILUC accounting (Support ILUC Accounting, 34%), while a majority disagreed in some way, whether by arguing against the inclusion of any food-based biofuels (Exclude Agrofuels, 5%), against ILUC accounting (Oppose ILUC Accounting, 24%), against immediate implementation of ILUC accounting (Delay for Study, 28%), or about some technical element of ILUC accounting (Technical Input, 10%). Many reframed the issue by broadening the range of policy choices, raising concerns about the modeling, or suggesting that additional factors should be considered. As one comment explained the reframing: "[T]his is a false choice for the Board at this time. The Board is not limited to the choice between finalizing ILUC impacts at zero or adopting as final the specific calculated ILUC values include in the Proposed Regulations" (Stephanie Batchelor, Biotechnology Industry Organization) (*55*).

Use of Scientific Evidence

How did public comments use science as validation? Given that CARB framed the policy decision as fundamentally science-based, I expected comments to draw on data and scientific literature for legitimation. To test this expectation, comments were coded for the type of scientific evidence they cited:

- **Nothing Cited**: assertions made without reference to scientific knowledge

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- **Personal Knowledge**: referred to personal experience, anecdotes, or prior meetings.
- **General Science**: referred to "science," "scientists," "scientific consensus," "the data," "the literature," or "recent studies" but did not provide specific names, data, or references
- **Other Comment**: cited another comment submitted to CARB. Most commonly, this was a letter submitted by 111 bioenergy scientists
- **Statistics**: cited statistics related to agricultural yields, cropland acreage, or land use change but did not provide references; if specific reports or papers were cited as the source for these numbers, the code was upgraded to "scientific literature"
- **Scientific Literature**: cited specific published reports, peer-reviewed articles, or the names of scientists who had published peer-reviewed articles; the bar was set very low; even mentioning the name "Searchinger" would earn this code

Broadly speaking, these codes can be grouped into low, medium, and high science. Low-science includes "nothing cited" and "personal knowledge." Medium-science includes "general science" and "other comment," which invoke the rhetorical power of science but not data or citations. High-science includes "statistics" or "scientific literature."

The unit of analysis for coding was an assertion or point of argumentation, which was typically a sentence but ranged from a phrase to a few sentences, depending on writing style. Essentially, this considers how commenters justified each substantive point that they made on ILUC. After coding was completed, I determined each comment's highest type of scientific information. The majority of all comments (63%) either never mentioned science or invoked it only rhetorically, while a much smaller proportion (23%) cited scientific literature (Table I).

Few studies have conducted similar science-focused content analyses of public regulatory comments, so it is somewhat difficult to contextualize these results. On the high end, Proctor (*56*) analyzed public comments on the Clinton Forest Plan and found that 30–32% cited science as their source of authority, although this did not distinguish between general invocations of science versus specific citations. On the low end, Roth *et al.* (*57*) analyzed public comments on United States tobacco regulation and found that a mere 6% invoked a scientific frame, even though the Food and Drug Administration adopted a predominantly scientific frame in justifying the regulations. We might also look to a study of Congressional hearings by Burstein and Hirsch (*58*), who found that 12–16% of witnesses cited "systematic research" in their testimonies. In comparison to these previous studies, the level of science communication in the LCFS comments seems substantial. Yet given that CARB framed the ILUC debate as fundamentally science-based, more comments citing scientific literature in supporting or contesting the policy decision might have been expected.

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Table I. Type of Scientific Information Cited in Public Comments

	Low Science		*Medium Science*		*High Science*		
Policy Stance	*Nothing Cited*	*Personal Knowledge*	*General Science*	*Other Comment*	*Statistics*	*Scientific Literature*	*Total*
Support ILUC	21 (*60%*)	0	10 (*29%*)	0	1 (*3%*)	3 (*9%*)	35
No Agrofuels	2 (*40%*)	0	0	0	0	3 (*60%*)	5
Oppose ILUC	0	2 (*8%*)	6 (*24%*)	6 (*24%*)	4 (*16%*)	7 (*28%*)	25
Delay for Study	6 (*21%*)	2 (*7%*)	5 (*17%*)	6 (*21%*)	3 (*10%*)	7 (*24%*)	29
Technical Input	1 (*10%*)	0	0	0	3 (*30%*)	6 (*60%*)	10

Numbers indicate a count of comments. Percentages are calculated within each row.

Perhaps the more interesting result comes from differential rates across the categories of comments. In the category of Support ILUC Accounting, only four comments (11%) scored as high science, compared to greater rates of high science in the Oppose ILUC Accounting (44%), Delay for Study (34%), and Technical Input (90%) categories. Although the small sample sizes mean that not too much should be read into specific percentages, the overall differential is noticeable. It is also interesting to compare this to Pilgrim and Harvey's (*6*) description of European ILUC debates during the same period: "major NGOs used the Searchinger science [paper] as a political battering ram." Surprisingly, ILUC supporters for the LCFS did not invoke the Searchinger *et al.* paper in making their case. Rather, the majority (60%) made assertions about ILUC without any reference to scientific research, while only one referenced the Searchinger *et al.* paper.

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Framing of ILUC Knowledge: Certainty versus Uncertainty

Another dimension of science communication relates to which attributes of scientific knowledge were emphasized. This was analyzed with open coding. In the discussion below, frames are denoted in bold italics and individual codes are in quotation marks.

What jumped out was that nearly all comments in Oppose ILUC Accounting (92%), Delay for Study (93%), and Technical Input (80%) emphasized the ***scientific uncertainty***, including model uncertainty as well as the lack of empirical data. Codes related to uncertainty included descriptions of the science as "uncertain," "new," "premature," "nascent," or in "infancy," emphasizing that it was "controversial," "unsettled," or "lacks scientific consensus," specifying that models "need peer-review" or "need sensitivity analyses," or arguing that the ILUC estimates "conflict with data" or "need empirical validation." For example:

> *[T]he outcomes are unusually sensitive to the assumptions made by the researchers conducting the model runs. In addition, this field of science is in its nascent stage [and] is controversial in much of the scientific community.*
> — Blake Simmons, Sandia National Laboratories, on behalf of 111 scientists (*59*).

> *Scientists are only beginning to explore the indirect relationships (if any) between biofuels production in the U.S. and land use changes around the world. To base such a critical policy decision upon such an uncertain and unsettled body of knowledge inserts a significant, unfounded bias.*
> —Carol Werner, Environmental and Energy Study Institute (*60*)

> *Ongoing scientific discourse and research clearly suggest we are not currently able to estimate indirect land use changes (particularly international land conversions) with an acceptable degree of certainty.*
> —Geoff Cooper, Renewable Fuels Association (*61*)

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In contrast, only a third of Support ILUC Accounting comments (31%) acknowledged ***scientific uncertainty***, usually using milder terms about how the science was still "evolving," would need "updating" or "refinement," and was "limited to magnitude":

> *Good science says that indirect land use change (ILUC) is a real, significant effect; only its magnitude is uncertain.*
> —Stephen Burns, Chevron (*62*)

> *There are uncertainties inherent in estimating the magnitude of indirect land use emissions from biofuels, but assigning a value of zero is clearly not supported by the science. ... Over time, greater accuracy and detail in a more refined analysis can be reflected in future LCFS rulemakings.*
> —Patricia Monahan, Union of Concerned Scientists, on behalf of 177 scientists and economists (*47*)

> *[T]he science and modeling around indirect land use emissions are new and evolving; but this does not provide justification, as critics contend, to wholly ignore this central issue. Instead, it provides a key reminder for ARB to continue to refine the numbers over time.*
> —Emily Bateson, Environment Northwest (*63*)

Instead of discussing uncertainty, a majority of Support ILUC Accounting comments (54%) framed the science in terms of ***scientific certainty***. Many characterized CARB's analysis as "good science," "sound science," "strong science," or "appropriate modeling," or they suggested that ILUC effects were "clear" or "self-evident." About a quarter (24%) argued that CARB's estimates were "conservative" or "should be higher." For example, here are several quotes evincing certainty, none of which provided data or citations:

> *The data on land use change indicate that the emissions related to biofuels are significant and can be quite large.*
> —Patricia Monahan, Union of Concerned Scientists, on behalf of 177 scientists and economists (*47*)

> *We believe CARB's conclusions on indirect land use change are supported by good science and the proposed numbers for indirect land use emissions is actually fairly conservative.*
> —Bonnie Holmes-Gen, American Lung Association in California (*64*)

> *The indirect land use change calculations clearly show corn ethanol to not be a net carbon reducer.*
> —Tom Frantz, Association of Irritated Residents (*65*)

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All the Exclude Agrofuels comments also claimed ***scientific certainty*** about the destructive land use impacts of biofuels. Some also addressed ***scientific uncertainty***, going so far as to characterize the modeling as "not credible," but they used uncertainty to argue that all agrofuels should be struck from the LCFS:

> *Increased land pressures from industrial agriculture necessary to produce corn ethanol clearly leads to numerous indirect land use changes elsewhere ... This self-evident fact clearly disqualifies corn ethanol biofuel from counting as emissions reduction.*
> — Gabrielle Shaw, no affiliation listed (*66*)

> *There is no one standard methodology that has been accepted as a legitimate way of measuring all indirect impacts associate with agrofuels production ... Yet, the risks of serious unintended consequences are real and well documented*
> —Andrea Samulon, Rainforest Action Network (*48*)

Normative Framing: "Full Accounting" versus "Fair Accounting"

The dominant normative frame for Support ILUC Accounting and Exclude Agrofuels was the primacy of ***environmental goals***. Comments in both of these categories emphasized that the LCFS was crucial for reducing greenhouse gas emissions and/or stimulating clean technologies. Both raised concerns about the environmental impact of biofuels. The Exclude Agrofuels comments argued that food-based biofuels should simply be excluded from LCFS compliance (using precautionary frames that will be discussed more below). The vast majority of Support ILUC Accounting comments (70%) argued that excluding or delaying ILUC factors would undermine the LCFS's environment goals or, even worse, could cause "perverse outcomes," such as increased emissions and deforestation.

In addition, most Support ILUC Accounting comments (57%) articulated that environmental goals required ***full accounting*** (ie, comprehensive assessment of all emissions sources). This frame of fullness included positive statements that CARB needed a "full" assessment of "all" emissions in the "entire" lifecycle, as well as negative descriptions of excluding ILUC as "omitting," "ignoring," "neglecting," or "failing to include" a significant emissions source. Furthermore, a sizable minority (23%) invoked moral values related to the frame of ***integrity***, such as "integrity," "credibility," and "responsibility." These three normative frames, often intertwined, are apparent in many Support ILUC Accounting comments:

> *California must include these [ILUC] emissions in order for the LCFS to be scientifically credible, ensure that the standard truly promotes fuels with lower carbon intensity ... [and] avoid the perverse outcome of having fuels increase rather than reduce global warming emissions.*
> —V. John White, Clean Power Campaign (*67*)

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A low-carbon fuel standard regulation without the inclusion of indirect land use changes would neglect the full lifecycle and include fuels with greater emissions than gasoline – thus undermining its purpose.
—Caitlin Toombs, Environment California (*68*)

We believe it is particularly important that the regulation account for all greenhouse gas emissions throughout the entire fuel cycle, including conversion of land to produce biofuels … Without these provisions, the LCFS would not be effective in reducing greenhouse gas emissions.
—Jenny Bard, American Lung Association in California, on behalf of fifteen medical and public health organizations (*69*)

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In contrast, nearly all comments criticizing ILUC accounting (88% of Oppose ILUC Accounting and 96% of Delay for Study comments) focused on the principle of ***fair accounting***. Comments employing this frame characterized ILUC as a "penalty," complained that it was "unfair," "inequitable," "biased" or "singled out biofuels," and advocated for a "level playing field" that is "technology neutral" and does not "pick winners" or "create winners and losers." Many pointed out that other fuels also had indirect effects and argued that if CARB was determined to assess ILUC for biofuels then it needed to assess these other indirect effects as well. For example:

CARB will penalize biofuels, particularly corn ethanol, for so-called indirect land use changes, while petroleum will be given a free pass, as CARB has chosen to largely ignore indirect emissions from these fuels.
—Brian Jennings, American Coalition for Ethanol (*70*)

By singling out biofuels for ILUC penalties, the ARB would be applying different standards to different types of transportation fuels and artificially creating winners and losers.
—Tom Buis, Growth Energy (*71*)

We are simply requesting the level playing field promised as part of the LCFS.
—Jeff Broin, POET (*72*)

Only a minority of Oppose ILUC Accounting (24%) and Delay for Study (17%) comments explicitly discussed the impacts of ILUC accounting. Although not the focus of these letters, these comments typically suggested that ILUC accounting would "stifle innovation," "not reduce emissions," or "adversely affect advanced fuels."

Comments from all categories used normative frames to discuss ILUC, but they emphasized different aspects. The key distinction is that supporters (Support ILUC Accounting) comments emphasized that achieving ***environmental goals*** required ***full accounting*** of all emissions, while critics (Oppose ILUC Accounting and Delay for Study) strongly emphasized the procedural principle of ***fair accounting*** across all fuels.

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Ontological Framing: "Real Reductions" versus "Real Data"

Many public comments contained ontological arguments, but different categories of comments emphasized different dimensions of truth and realness. Comments in the Exclude Agrofuels and Support ILUC Accounting categories, which were principally concerned with environmental impacts, emphasized ***real reductions*** in GHG emissions. This frame included ontologically-loaded language describing carbon reductions as "actual," "actually," "true," "truly," and "real." 100% of Exclude Agrofuels comments and 32% of Support ILUC Accounting comments used this language. For example:

> *Inclusion of indirect land use change is pivotal to ensure that the LCFS achieves real GHG reductions.*
> —Emily Bateson, Environment Northwest (*63*)

> *[T]he incorporation of both direct and indirect carbon emissions is important to ensure that the substitution of alternative fuels actually reduces carbon emissions.*
> —Richard Moskowitz, American Trucking Association (*73*)

> *CARB's decision to incorporate the indirect land use effects of fuel production [is] a key LCA component that will ensure we achieve true global GHG reductions.*
> —Remy Garderet, Energy Independence Now (*46*)

Critical letters instead emphasized the importance of ***real-world data*** about yield and acreage. Overall, 83% of Oppose ILUC Accounting, 73% of Delay for Study, and 80% of Technical Input comments made ontological arguments that invoked the importance of data. These comments highlighted the lack of empirical validation, utilized data on land use to discredit model estimates, or critiqued the accuracy and assumptions of ILUC models. For example:

> *Even at this late stage in the LCFS process, the … model runs still do not reflect basic on-the-ground realities, such as the use of marginal and idle lands.*
> —Blake Simmons, Sandia National Laboratories, on behalf of 111 scientists (*59*)

> *[I]n prior applications … the model predicted changes in land use between 2001 and 2006 that were actually the opposite of the real-world changes observed over time.*
> —Will Coleman, Mohr Davidow Ventures, on behalf of ten California clean energy investors (*74*)

> *[T]he assumptions behind ILUC models employed by CARB are contradicted by real world data.*
> —Tom Buis, Growth Energy (*71*)

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[T]he model is not well suited to make the precise measurements of ILUC impacts … Substantial additional empirical analysis is needed to justify the parameters and data used in making GTAP calculations.
—Mark Perlis, Counsel to Novozymes North America (*75*)

There's something ironic about this split in ontological emphases. ILUC supporters wanted ***real reductions*** but did not engage with the notion that these were determined by economic simulations, while critics emphasized the importance of ***real-world data*** but downplayed real-world policy impacts.

Absent Frames

Three issue frames turned out to be surprisingly uncommon. One was the ***Precautionary Principle*** (PP), which holds that preventive measures should be taken when an action poses potential risks to the environment, even if those risks are not fully established by scientific consensus (*76*). Given the infancy of ILUC science, one might have expected numerous comments to cite the PP in making the case for ILUC accounting. Indeed, the PP features prominently in European debates on ILUC (*6*, *77*). However, few comments on the LCFS invoked this frame, whether by citing the PP, urging "precaution," or suggesting a "precautionary" action. Aside from the Exclude Agrofuels comments (whose use of the word "agrofuels" already suggested a European discursive influence) only three comments mentioned the PP, and two of these used it to critique ILUC accounting. Supporters of ILUC accounting overwhelmingly framed it as sound science rather than a precautionary response.

A second notable absence in the comments was the ***zero/non-zero*** decision frame. Although the terms were mentioned by a handful of comments, none used it as a central organizing frame, and most only brought it up in order to argue that it was misdirected (for example: "instead of focusing on ILUC values and the zero/non-zero debate, ARB should focus on ways to encourage the biofuels industry to evolve toward what would be an industry-wide 'zero' value." (Michael McAdams, Advanced Biofuels Association) (*78*)). It may have been a powerful way to get the conversation moving on ILUC in 2007, but ILUC policy discourse shifted by 2009.

A third absence was a discussion of ILUC as a ***paradigm shift*** in carbon accounting. Only a few comments pointed out that indirect emissions represented a radical shift in LCA, such as: "The public policy decision to extend the scope of the LCFS from direct to indirect, market-mediated effects is a monumental one" (Brooke Coleman, New Fuels Alliance, on behalf of 25 advanced biofuel companies and interests) (*79*) and "the ARB is now proposing a significant shift in … internationally-recognized standards for lifecycle analysis by including emissions" (Tom Buis, Growth Energy) (*71*). The vast majority of comments discussed ILUC as just another LCA parameter. In most comments this was implicit, although some explicitly described ILUC as a "key LCA parameter" or part of the "well-to-wheel" lifecycle. Overall, the paradigm shift from ALCA to CLCA went largely under the radar.

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Conclusions

This analysis demonstrates the intertwining of value-based and science-based arguments in the LCFS debate on ILUC. Policy actors drew on both elements not only in framing the policy decision, but also in interpreting the data and economic models. Academic advisors prioritized "sending the right signals" regardless of uncertainty and assumed that further research could lead to "accurate" and "robust" estimate. Regulatory staff legitimated their proposal with claims of "empirically based" certainty, which the fine print revealed to be tied up with subjective judgment about what constituted "reasonable" and "appropriate" model inputs. In public comments, normative arguments about "full accounting" versus "fair accounting" dominated over technical arguments.

In highlighting these value-based assumptions and assertions, my intent is not to discredit LCFS rulemaking, but rather to provide a more nuanced look at a policy that is often portrayed as being science-based. A key theme in the literature on Science and Technology Studies (STS), science policy studies, and the politics of expertise is that policy is never straightforwardly derived from scientific evidence – and, in fact, scientific research itself involves values, norms, and beliefs (*80*). These themes are certainly evident in this case study.

Policy-makers considering indirect emissions, whether for biofuels or climate policies, cannot expect the answers to come solely from technical research. They must make a series of normative judgments, including issues such as: Should performance-based regulations account for market-mediated spillover effects? Are economic models appropriate for generating emission estimates? What is the acceptable threshold of certainty? What is the right balance between comprehensiveness and certainty in emissions accounting? In the case of the LCFS, academic experts and regulatory staff moved quickly through some of these questions, but public comments showed that they continued to be deliberated by stakeholders.

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Chapter 8

The Importance of Exposure Dose in Communicating the Ecotoxicology of Engineered Nanomaterials

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Future policy decisions related to the control of engineered nanomaterials during consumer use and disposal will be predicated in part on their toxicities to natural environmental systems. Using titanium dioxide nanoparticles ($nTiO_2$) as a model nanomaterial, this chapter critically evaluates the capacity of existing ecotoxicology literature to communicate the potential for harm to environmental systems by searching for confluence between the following: (a) $nTiO_2$ concentrations expected in surface waters; (b) $nTiO_2$ concentrations that result in specific toxicological responses to aquatic organisms; and (c) the availability of reliable methods or instrumentation that can quantitatively measure $nTiO_2$ concentrations in real aqueous solutions. This examination shows that direct measurements of $nTiO_2$ loading in aquatic ecosystems are limited by a dearth of analytical techniques that can simultaneously measure $nTiO_2$ size and concentration. Model predictions suggest that $nTiO_2$ concentrations concentrations in surface waters are likely to be significantly less than 100 μg L^{-1}, yet relatively few ecotoxicology studies use similarly low exposure doses. In fact, a survey of 30 well-cited $nTiO_2$ ecotoxicology papers found that only 22% of the associated experimental treatments used an environmentally relevant concentration of 100 μg L^{-1} or lower, despite reliable indications that these doses often result in toxic responses. The analysis presented in this chapter suggests that

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significant questions remain regarding the concentrations and toxicities of engineered nanomaterials in real aquatic systems, which will need to be addressed before the development of scientifically sound policies and regulations.

Introduction

In 1959, the headlines of mainstream engineering focused on big things. With Project Mercury, the newly created National Aeronautic and Space Administration (NASA) refined rocket and spacecraft technologies to carry astronauts into orbit, as an airline industry on ascent from infancy produced jetliners that transported people to destinations here on Earth. American automobile manufacturers churned out cars whose oversized dimensions evoked comparisons to whales, while state-of-the-art computers were, by comparison, even larger. Yet, it was against this big-world backdrop that visionary physicist Richard Feynman asked his peers to think about something considerably different–namely, the engineering of very small things. That year, in a speech to the annual meeting of the American Physical Society, Feynman posited the following simple question: "What would happen if we could arrange the atoms [in a material] one by one the way we want them…[rather than simply accepting] some atomic arrangement that nature gives us?" (*1*). He went on to describe a vast array of tiny innovations that could be attained using this as-yet undeveloped technological achievement, and in doing so, inspired an entirely new class of scientific endeavor based on nanoscale (10^{-9} m) materials.

Fifty-six years later, the field of nanotechnology is now the newest darling of mainstream engineering, with improvements in the synthesis and characterization of engineered nanomaterials moving us ever-closer to Feynman's vision. Deposition (*2–4*) and templating (*5–7*) techniques provide scientists and engineers with an unprecedented level of structural control at the nanoscale, while an extraordinary variety of controlled nanomaterial precipitation methods have resulted in a catalog of architectures that can be tailored to specific practical applications (*8–10*). In fact, engineered nanomaterials can now be found in nearly all classes of consumer and industrial products, with a striking diversity of uses ranging from electronics to textiles to toothpaste (*11*). The global market value for nanotechnology products was estimated at US$26 billion in 2014, with a projected compound growth rate of nearly 20% per year through the next 5 years (*12*).

Still, in the midst of this nanotechnology boom, concerns exist within the scientific and regulatory communities about the potential hazards of the materials being created (*13–16*). It certainly stands to reason that as nanomaterial manufacturing and utilization increase in the years to come, the potential for release to the environment and interactions with human and ecological systems will also increase, with mostly unknown consequences. The nascent field of nanoecotoxicology emerged approximately 10 years ago to begin addressing these concerns, and to date, scientists from around the world have published at least 200 peer-reviewed studies related to the specific environmental hazards

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of engineered nanomaterials (*17*, *18*). Many of these papers establish a link between nanomaterial exposure and negative consequences to target organisms from terrestrial or aquatic systems, which seemingly legitimates concerns over nanomaterial toxicity. However, it can be exceedingly difficult to determine whether the conclusions from these studies are environmentally relevant. For example, the influence that a nanomaterial exerts on a biological system depends on a vast array of physical and chemical factors, including composition, concentration, exposure time, size, shape, aggregation state, surface chemistry, and/or solubility (*19–21*), and there is often a significant mismatch between the conditions present in experimental systems with respect to these factors and the conditions expected in natural systems. The use of these unrealistic exposure scenarios was largely unavoidable, particularly during the earliest nanoecotoxicology studies, as nanomaterial quantification and characterization techniques, expected nanomaterial production estimates, and an understanding of the relevant environmental factors in need of consideration have evolved concurrently.

Nevertheless, findings from these primary research papers enter the classic cadence of scientific communication, where they are cited in other peer-reviewed articles and reviews, and possibly in mainstream scientific and periodical media, but generally in a much-condensed form that omits critical details of the experimental design for the sake of brevity. These conduits of information provide a scientific basis for early public opinions regarding engineered nanomaterial safety and the need for specific policies and regulations. However, without proper deference given to the extraordinary complexity of factors that influence nanoscale interactions and toxicity, the message communicated will be at best incomplete, if not entirely incorrect. Instead, a more thoughtful presentation of nanoecotoxicology research will attempt to prioritize the communication of ecological effects from engineered nanomaterial systems that exhibit the same physical and chemical properties that are most likely to be expressed in the actual environments in question. While this type of targeted assessment is certainly not easy to implement, there is significant value in at least attempting such a task, if for no other reason than to effectively characterize the environmental relevancy of existing research and to identify data gaps.

Hence, the objectives of this chapter are to critically evaluate whether contemporary ecotoxicology research is effectively communicating the real potential for environmental hazards posed by engineered nanomaterials and to identify some potential reasons that the field may be falling short in this effort. No single book chapter could comprehensively explore these topics for each of the vast abundance of nanomaterials being developed, the diversity of influential physical and chemical nanomaterial properties at play, and/or the varying dynamics present in all potential environmental systems. As a result, this analysis focuses its attention on how one relatively simple factor that influences the ecotoxicologic response (ie, concentration) is being considered in existing research for a single archetypal nanomaterial (ie, titanium dioxide nanoparticles [$nTiO_2$]). Within this context, the discussion that follows will examine the relationship between the following: (a) the anticipated concentrations of $nTiO_2$ in surface water environments; (b) the concentrations of $nTiO_2$ that result in

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specific environmental hazards; and (c) the availability of reliable methods or instrumentation that can quantitatively measure $nTiO_2$ concentrations in real aqueous matrices. Determining the extent to which these three factors converge is a necessary first step in communicating whether engineered nanomaterials are harmful to aquatic systems and in need of policy or regulatory development.

Background and Context

By definition, nanomaterials consist of base units that have at least one dimension smaller than 100 nm (*22*). Physical categorical systems for engineered nanomaterials generally focus on the number of dimensions exhibiting a nanoscale measurement with thin films or nanosheets, nanotubes, and nanoparticles exhibiting one, two, and three nanoscale dimensions, respectively (*23*). Chemically, engineered nanomaterials are even more diverse, but the most common are either carbon-based, such as carbon nanotubes, or metal-based, such as $nTiO_2$ or silver nanoparticles (*22–24*).

Among the myriad nanomaterial chemistries, $nTiO_2$ may be one of the most likely to accumulate to consequential concentrations in surface water environments (*25*). Due to its bright pigmentation, high refractive index, and resistance to discoloration, $nTiO_2$ is extensively utilized in a large variety of industrial and consumer products, including paints, sunscreens, cosmetics, and foods (Figure 1) (*26–28*). Delivery of $nTiO_2$ from these products to aquatic systems can occur directly during the release of particles from painted or coated surfaces (*29–31*) or the leaching of particles from a swimmer after sunscreen application (*32*, *33*). Because a considerable proportion of $nTiO_2$-containing products are disposed within municipal drains after human consumption or household use, effluents from wastewater treatment facilities are also expected to be a major route of delivery to natural waters. While $nTiO_2$ is largely captured within wastewater treatment systems, it has also been observed in the discharges released from these facilities to adjacent receiving waters (*34*, *35*). As a result of its prevalence in a vast array of common items, its presence in surface waters, and the relatively high degree of research effort given to it, $nTiO_2$ serves as the representative nanomaterial for this analysis.

Upon entry into the aquatic environment, several factors are likely to influence the concentration of $nTiO_2$ over time and its consequent impact on biological systems. First, TiO_2 exhibits an extremely low solubility under nearly all natural conditions (e.g. rutile TiO_2 has a solubility of 7.9×10^{-12} mol L^{-1} at around pH 7 (*36*)), meaning that any initial load delivered to an aquatic environment will persist as solid particles and not simply attenuate via particle dissolution. Instead, aggregation is likely to be the primary factor controlling the concentration of $nTiO_2$ suspended in surface waters, with $nTiO_2$ aggregates of sufficient size being lost from the water column and deposited to benthic sediments. Conversely, unaggregated $nTiO_2$ and those contained in smaller aggregates generally remain suspended and this fraction represents the effective environmental concentration exposed to planktonic organisms and fishes in the water column. The extent to which $nTiO_2$ aggregates is largely dependent on the

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pH, ionic strength, and natural organic matter concentration within the suspending solution, which control the relative influences of attractive (van der Waals) and repulsive (electrostatic and steric) forces near the particle surface (*37–40*). Finally, upon exposure to ultraviolet light, TiO_2 forms reactive oxygen species (*41*), which are an important mechanism of toxicity to aquatic organisms (*42*), suggesting that the amount of sunlight that reaches an aquatic system will also influence the ecotoxicity of $nTiO_2$. While these factors are not the primary focus of this chapter, it is important to understand that they can dramatically influence the extent to which a given concentration of $nTiO_2$ impacts aquatic ecosystems.

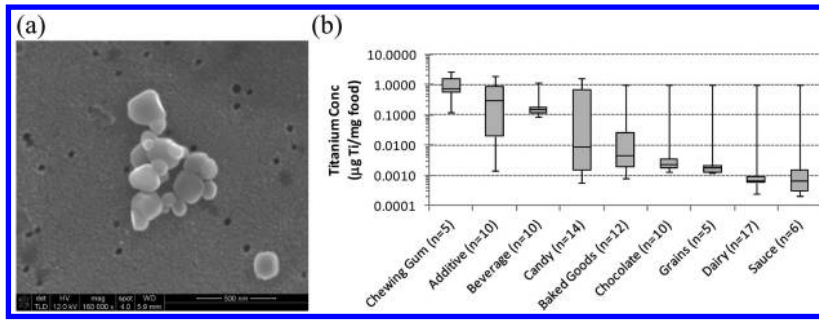

Figure 1. (a) Scanning electron microscope image of $nTiO_2$ from the dissolved hard coating of a chewing gum sample. (b) A bar-and-whisker plot showing total Ti concentrations for 89 different food products. Bars represent the lower quartile, median, and upper quartile for the designated categories and whiskers represent the corresponding ranges. Reproduced with permission from reference (28). Copyright 2012 American Chemical Society.

Environmental Concentrations

In order to determine whether the exposure doses used in the $nTiO_2$ ecotoxicology literature are environmentally relevant, we must first establish a realistic environmental concentration of $nTiO_2$ to serve as the basis for comparison. The definition of an environmental $nTiO_2$ concentration for this analysis is limited to surface water systems, but includes effluents from wastewater treatment plants as a point source of loading. As described later in this section, estimated concentrations of $nTiO_2$ in wastewater effluents are expected to be extremely concentrated relative to those in natural waters (*43*, *44*), but at the point of discharge an undiluted $nTiO_2$ concentration could be encountered and may persist for some distance downstream depending on local hydrologic and geomorphic considerations. In addition, for a variety of site-specific reasons (e.g. seasonal weather or local water operations), wastewater effluents can make up a significant proportion of the flow in some watercourses (*45*, *46*). Hence, estimated $nTiO_2$ concentrations in wastewater effluents are considered as an upper bound for the definition of environmental relevancy, despite the recognition that these effluents will generally be diluted via mixing with water from the receiving stream.

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Estimates of surface water concentrations for $nTiO_2$ found in the literature are typically based on either direct analytical measurement or predictive modeling (Table I, Table II). For the purposes of this investigation, the direct measurement of $nTiO_2$ concentrations in aquatic systems would be a much-preferred quantification approach because predictive models rely on assumptions whose inputs are currently not well constrained. Unfortunately, very few studies have attempted to measure $nTiO_2$ concentrations directly in real environmental matrices, as reliable methods for the determination of such concentrations have yet to be developed. The direct measurement studies that do exist generally use particle separation methods (e.g. filtration or centrifugation) that fail to isolate only the $nTiO_2$ size fraction from the remaining bulk solution, and consequently, measurement outputs are total Ti concentrations that include larger particles and/or dissolved Ti ions. These studies are often supported by microscopy approaches that illustrate a presence or absence of $nTiO_2$ in water samples, but cannot efficiently quantitate $nTiO_2$ concentrations.

Still, existing direct measurement investigations do provide some insights related to the concentrations of $nTiO_2$ expected in surface water environments. For example, by using a distinctive centrifugation method for size fractionation, Kaegi et al. (*30*) determined that water samples from an urban catchment in Switzerland contained approximately 8 μg L^{-1} Ti, represented by both dissolved ions and particles up to 300 nm. While this catchment was adjacent to a recently painted building facade, electron microscopy indicated that a significant proportion of the $nTiO_2$ present in the catchment samples exhibited strikingly different morphologies than those found in the captured facade leachate, leading the researchers to speculate that an additional source of $nTiO_2$ (e.g. road paints) exists in the catchment area. Neal et al. (*47*) measured Ti concentrations of 0.55–6.48 μg L^{-1} for the dissolved and particulate fraction (<450 nm) in filtered samples from various river systems in the United Kingdom. An additional ultrafiltration step established that 28–79% of the total Ti present in the rivers tested was not dissolved and was instead colloidal particles sized between 1 nm and 450 nm. Finally, three separate studies provide direct measurements of Ti for various size fractions released from wastewater treatment plant effluents. Kiser et al. (*34*) reported a total Ti concentration of <36 μg L^{-1} in the effluent from various wastewater treatment facilities across the United States, with nearly all Ti present as either the dissolved ion or a particulate fraction <700 nm. Similarly, Westerhoff et al. (*35*) evaluated the effluent from 10 different treatment plants throughout Arizona and determined a maximum total Ti concentration of 18 μg L^{-1}, and Johnson et al. (*48*) found an average Ti concentration of 3.2 μg L^{-1} for the dissolved and particulate fractions (<450 nm) in the effluents from one wastewater treatment plant in the United Kingdom. As apparent from this discussion, direct measurements of Ti concentrations specific to the $nTiO_2$ size fraction in real environmental samples remain elusive.

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Table I. Measured $nTiO_2$ Concentrations for Aquatic Systems

Authors	*Location*[a]	*Region*	*Concentration (μg Ti L^{-1})*	*Uncertainty*[b] *(μg Ti L^{-1})*	*Fraction*	*Notes*
Kaegi et al., 2008 (*30*)	Urban catchment (1)	Switzerland	~8	-	<300 nm (cent)	Includes both dissolved and colloidal
Neal at al., 2011 (*47*)	River catchments (4)	United Kingdom	2.1 (mean)	0.55–6.48 (range)	<450 nm (filtr)	28–79% estimated to be >1–2 nm (ie, not dissolved)
Kiser at al., 2009 (*34*)	WWTP (9)	Various States (USA)	<36 (range of mean values)	-	Total Ti	"Nearly all" Ti <700 nm; includes both dissolved and colloidal
Westerhoff et al., 2011 (*35*)	WWTP (10)	Arizona (USA)	<2–18 (range of mean values)	-	Total Ti	Includes all Ti fractions
Johnson et al., 2011 (*48*)	WWTP (1)	United Kingdom	3.2 (mean)	0.4 (std)	<450 nm (filtr)	Includes both dissolved and colloidal

[a] Values in parentheses are the number of locations sampled. [b] Uncertainty values/ranges/intervals are those provided in the original article. cent, centrifugation; filtr, filtration; WWTP, wastewater treatment plant effluents; std, standard deviation.

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Table II. Predicted $nTiO_2$ Concentrations for Aquatic Systems

Authors	*Location*	*Region*	*Concentration[a] ($\mu g\ nTiO_2\ L^{-1}$)*	*Uncertainty[b] ($\mu g\ nTiO_2\ L^{-1}$)*	*Fraction*	*Notes*
Mueller & Nowack, 2008 (*25*)	Surface waters	Switzerland	0.7–16 (range)		$nTiO_2$	Range min/max represents realistic and worst-case treatment scenarios, respectively; aggr not considered
O'Brien & Cummins, 2010 (*49*)	Surface waters	Ireland	~1.4 (mean)	0.22–2.70 (90% CI)	$nTiO_2$	Only considers $nTiO_2$ from exterior paints; cumulative statistics from two different treatment scenarios; aggr not considered
Gottschalk et al., 2009 (*43*)	Surface waters	Europe	0.015 (mode)	0.012–0.057 (Q15–Q85)	$nTiO_2$	Aggr and sedimentation from water column considered for surface waters
		Switzerland	0.021 (mode)	0.016–0.085 (Q15–Q85)	$nTiO_2$	
		USA	0.002 (mode)	0.002–0.010 (Q15–Q85)	$nTiO_2$	
	WWTP effluent	Europe	3.47 (mode)	2.5–10.8 (Q15–Q85)	$nTiO_2$	
		Switzerland	4.28 (mode)	3.5–16.3 (Q15–Q85)	$nTiO_2$	
		USA	1.75 (mode)	1.37–6.70 (Q15–Q85)	$nTiO_2$	

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Authors	*Location*	*Region*	*Concentration*[a] *(μg $nTiO_2$ L^{-1})*	*Uncertainty*[b] *(μg $nTiO_2$ L^{-1})*	*Fraction*	*Notes*
Gottschalk et al., 2011 (*50*)	Surface waters (various rivers)	Switzerland (various regions)	0.002–1.62 (range)	-	$nTiO_2$	Range for river-specific median values; considers conservative (no aggr) and optimistic (aggr) transport scenarios across geographic and temporal scales
Johnson et al., 2011 (*48*)	Surface waters (Anglian/ Thames rivers)	United Kingdom	0.25–8.8 (range of median values)	-	$nTiO_2$	Range for river-specific median values; considers various weather and regional use patterns; only considers $nTiO_2$ from sunscreens; aggr not considered
Musee, 2011 (*51*)	Surface waters	Johannesburg (South Africa)	0.003–0.27 (range)	-	$nTiO_2$	Assumes high WWTP treatment efficiency; only considers $nTiO_2$ from cosmetics; aggr not considered
Praetorius et al., 2012 (*52*)	Surface water (Rhine River)	Switzerland / Netherlands	<0.006 (range)	-	$nTiO_2$	Value within range depends on aggregation extent and distance from source.
Keller et al., 2013 (*26*)	WWTP effluent	San Francisco Bay (USA)	~3–35 (range)	-	$nTiO_2$	Life cycle approach using production and application data
Sun et al., 2014 (*44*)	Surface waters	European Union	0.53 (mode)	0.4–1.4 (Q15–Q85)	$nTiO_2$	Assumes no aggr or sedimentation from water column for surface waters
		Switzerland	0.67 (mode)	0.54–3.0 (Q15–Q85)	$nTiO_2$	

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Table II. (Continued). Predicted $nTiO_2$ Concentrations for Aquatic Systems

Authors	*Location*	*Region*	*Concentration[a] ($\mu g\ nTiO_2\ L^{-1}$)*	*Uncertainty[b] ($\mu g\ nTiO_2\ L^{-1}$)*	*Fraction*	*Notes*
	WWTP effluent	European Union	16 (mode)	13–110 (Q15–Q85)	$nTiO_2$	
		Switzerland	32 (mode)	26–220 (Q15–Q85)	$nTiO_2$	
Lazareva & Keller, 2014 (*53*)	WWTP effluent	London (United Kingdom)	1.28 – 29.18 (range of mean values)	-	$nTiO_2$	Life cycle approach that accounts for local differences in production, consumption, treatment, and waste management
		New York City (USA)	1.33 – 43.88 (range of mean values)	-	$nTiO_2$	
		Shanghi (China)	3.13 – 30.73 (range of mean values)	-	$nTiO_2$	

[a] Unless otherwise noted, concentrations refer to region-wide averages; [b] Uncertainty values/ranges/intervals are those provided in the corresponding paper. Q15–Q85, 15th through 85th percentiles.WWTP, wastewater treatment plant effluents; CI, confidence interval; aggr., aggregation.

Investigations that predictively model $nTiO_2$ concentrations in aquatic systems attempt to fill the void formed by the lack of direct measurements. In its most comprehensive form, the predictive modeling of environmental concentrations will consider all flows of a substance from various sources to their ultimate sink, while recognizing that this flow will be influenced by both physical and chemical transformations within treatment systems and the natural environment. However, in practice, the tremendous complexity of the nanomaterial economy, consumer use patterns, and environmental processes contribute to a lack of accurate model inputs, meaning that predictive modeling cannot realistically capture the intricacies of all potential flows of $nTiO_2$ to various environmental compartments. Still, over the past decade, these models have become increasingly detailed, and for the time being, are perhaps the best sources of information available to define the bounds for environmentally realistic $nTiO_2$ concentrations.

Many early predictive modeling investigations assumed that $nTiO_2$ enters the environment from only a single source, such as exterior coatings (*49*), sunscreens (*48*), or cosmetics (*51*) (Table II). Mueller and Nowack (*25*) were among the first to predict $nTiO_2$ release into the environment with a broader life-cycle approach, wherein assumptions regarding production volumes and product-specific treatment or release probabilities served to track the flow of $nTiO_2$ from a multitude of consumer products, through distinct waste treatment streams, and into relatively simple environmental compartments, such as air, soil, and surface water. Depending on two sets of assumptions related to waste capture efficiencies, Mueller and Nowack predicted environmental $nTiO_2$ concentrations of 0.7 μg L^{-1} (realistic scenario) or 16 μg L^{-1} (worst-case scenario) for Swiss surface waters. The authors noted that because these concentrations were the results of modeling assumptions informed by specific practices in Switzerland, they should not be universally applied to other countries. Gottschalk et al. (*43*, *54*) added surface water sediments to the list of environmental compartments used by Mueller and Nowack by accounting for $nTiO_2$ aggregation and its consequent settling from the water column. This approach resulted in predicted $nTiO_2$ concentrations for Swiss surface waters approximately two orders of magnitude lower than those provided by Mueller and Nowack. Praetorius et al. (*52*) and Meesters et al. (*55*) also demonstrated the potential importance of aggregation and sedimentation in their predictive modeling of the aquatic concentrations of $nTiO_2$. Country-specific and/or region-specific patterns in the handling of waste streams might also influence the environmental concentration of $nTiO_2$ (*43*, *44*), as might the baseflow of local river courses and the timing and distribution of wastewater treatment plant effluents delivered to them (*50*). Considering this broad review of the available literature, the preponderance of predictive modeling suggests that while $nTiO_2$ concentrations in surface waters could reach several μg L^{-1}, significantly less (<0.1 μg L^{-1}) is expected when accounting for the settling of $nTiO_2$ aggregates from the water column to aquatic sediments (Table II).

A consistent trend observed in the predictive modeling described above is the importance of wastewater treatment plant effluents in the delivery of $nTiO_2$ to surface waters. In fact, the two studies (*43*, *44*) that specifically provide predicted $nTiO_2$ concentrations for both surface water and wastewater effluents (using

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internally consistent assumptions for a valid comparison) suggest that $nTiO_2$ concentrations in effluents might be between one and three orders of magnitude higher than those found in surface waters, with mode $nTiO_2$ concentrations ranging from 1.75 μg L^{-1} to 32 μg L^{-1}. Two additional studies by Keller et al. (*26*) and Lazareva and Keller (*53*) are in general agreement with this range. However, it is important to note that the results of predictive models for surface waters and wastewater effluents are heavily dependent on estimates of global $nTiO_2$ production, which are not well characterized and vary widely in the literature (*25*, *56*, *57*).

The inherent challenges associated with directly measuring $nTiO_2$ concentrations in aqueous systems and broad uncertainties on the assumptions associated with predictive $nTiO_2$ concentration modeling make it exceedingly difficult to precisely define an environmentally relevant $nTiO_2$ concentration for the analysis that follows. Until more exacting measurement technologies and/or better constraints on global production estimates and fate/transport behaviors are available for $nTiO_2$, any definition of an environmentally relevant concentration is at best preliminary. However, this initial definition can certainly be informed by a thorough review of the available data. After the review completed above, an $nTiO_2$ concentration of 100 μg L^{-1} is deemed an appropriate and even conservative definition for environmental relevancy, as all mode/average $nTiO_2$ concentration estimates (both measured and model predicted) for surface waters and wastewater treatment plant effluents fall under this value, as do the vast majority of uncertainty ranges (Table I, Table II).

Ecotoxicology Studies

Over the past decade, the literature has been populated by an abundance of research related to the ecotoxicology of $nTiO_2$ in aquatic ecosystems. The general scientific approach adopted by these investigations includes exposing an aquatic organism to a particular $nTiO_2$ concentration range and measuring various biological response metrics. Several reviews of this body of literature are available elsewhere (*20*, *58*, *59*) and provide an initial summary of the potential risks posed by the environmental release of $nTiO_2$. However, in contrast to the more general reviews, the specific intent of this section is to critically scrutinize the environmental relevancy of the $nTiO_2$ concentrations employed in this research by comparing their experimental doses to the relatively low concentrations currently present in natural systems. As illustrated in the previous section, $nTiO_2$ concentrations ≤100 μg L^{-1} are currently expected in surface water environments even when including those systems that contain abnormally high loads, such as stream reaches located immediately downstream of wastewater treatment plant outfalls. Hence, within this analysis, 100 μg L^{-1} serves as the threshold definition for environmental relevancy, although many other concentration ranges will also be considered to thoroughly characterize the continuum of experimental conditions present in the literature.

Papers were identified for inclusion in this assessment via a systematic search of the ecotoxicology literature from 2006 to 2014, which generally resulted in

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the selection and assessment of three or four investigations from each calendar year and 30 papers in total (Table III). Selected articles through 2011 were among the 10 most highly cited $nTiO_2$ ecotoxicology papers from the corresponding years, whereas the selection of papers from subsequent years was slightly more random because insufficient time had passed to evaluate article impact. Great emphasis was placed on citation count during the paper selection procedure to focus on the research that is most commonly used to characterize the influence of $nTiO_2$ in aquatic environments. Still, in order to be used in this assessment, a paper had to clearly discuss the magnitude of a biological response that results from a designated $nTiO_2$ concentration, relative to an $nTiO_2$ free control. Those investigations that were structured in a different manner were excluded. All papers were selected either blindly or in a randomized fashion. The 30 selected papers were equally divided into three time ranges (2006–2008, 2009–2011, and 2012–2014) to evaluate whether the experimental conditions employed in these investigations changed as a function of the publication period.

The minimum $nTiO_2$ concentration considered in each selected paper was extracted and the collective analysis of these values serves as one metric by which to evaluate the environmental relevancy of concentrations used in existing ecotoxicology research. Figure 2 illustrates a cumulative frequency distribution of these values and indicates that nearly all selected papers (28 of 30) contained at least one treatment that utilized an $nTiO_2$ concentration of $\leq$10 mg L^{-1}. However, only 12 considered a more environmentally relevant $nTiO_2$ concentration of $\leq$100 μg L^{-1}. The number of selected papers that fall within this concentration category slightly increases with each subsequent publication period. These data suggest that ecotoxicology investigators might be responding to research that attempts to measure or predict environmental concentrations of $nTiO_2$ by adjusting their experimental dose ranges accordingly. Still, even in the most-recent publication period, only half of the selected papers considered an environmentally relevant $nTiO_2$ concentration.

On its own, an analysis of minimum $nTiO_2$ doses utilized by the selected papers does not adequately illustrate the level of effort devoted to each concentration. In fact, each paper should actually be considered a collection of many smaller studies with distinct experimental conditions. Hence, in order to more thoroughly understand how the selected papers prioritize the study of different $nTiO_2$ concentrations, the details from each individual experiment were also extracted and recorded. Distinct experimental details of interest included, but were not limited to, the concentration, size, crystal structure, and aggregation state of $nTiO_2$ particles, as well as the target organism, test matrix, lighting conditions, and toxicity metrics involved. Herein, the term treatment refers to a specific combination of these factors that make up an individual experiment within a selected paper. The 30 papers under consideration resulted in 701 distinct experimental treatments.

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Table III. Summary of Environmentally Relevant $nTiO_2$ Ecotoxicology Results from 30 Highly Cited Papers

Authors	*Number of citations*[a]	*Species*	*$nTiO_2$ Concentration (mg L^{-1})*	*Treatments ≤0.1 mg L^{-1}*[b]	*Effect Summary ≤0.1 mg L^{-1}*	*No-Effect Summary ≤0.1 mg L^{-1}*
Lovern & Klaper, 2006 (*60*)	290	*D. magna*	0.2–500	0	-	-
Adams et al., 2006 (*61*)	536	*E. coli*, *B. subtilus*	10–5,000	0	-	-
Hund-Rinke & Simon, 2006 (*62*)	213	*D. subspicatus*, *D. magna*	1–12.5	0	-	-
Zhang et al., 2007 (*63*)	130	*C. carpio*	10	0	-	-
Lovern et al., 2007 (*64*)	178	*D. magna*	2	0	-	-
Federici et al., 2007 (*65*)	266	*O. mykiss*	0.1–1	6E/5NE	Abnormal gill anatomy; tissue trace metals conc.; ATPase activity; TBARS activity; total glutathione; organ histology	Mortality; total tissue Ti conc.; hematological issues; plasma ion conc.; tissue electrolyte conc.
Sun et al., 2007 (*66*)	58	*C. carpio*	10	0	-	-
Reeves et al., 2008 (*67*)	193	*C. auratus* (cell line)	0.1–1,000	0E/3NE	-	Cell viability

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Authors	*Number of citations*[a]	*Species*	*$nTiO_2$ Concentration (mg L^{-1})*	*Treatments ≤0.1 mg L^{-1}*[b]	*Effect Summary ≤0.1 mg L^{-1}*	*No-Effect Summary ≤0.1 mg L^{-1}*
Zhu et al., 2008 (*68*)	195	*D. rerio*	1–500	0	-	-
Wang et al., 2008 (*69*)	80	*C. reinhardtii*	0.001–100	0E/3NE	-	Growth
Aruoja et al., 2009 (*70*)	336	*P. subcapitata*	15–236	0	-	-
Simon-Decker et al., 2009 (*71*)	144	*E. coli, C. metallidurans*	10–500	0	-	-
Wang et al., 2009 (*72*)	194	*C. elegans*	24–400	0	-	-
Miller et al., 2010 (*73*)	89	*T. pseudonana*, *S. marinoi*, *D. tertiolecta*, *I. galbana*	0.01–1	0E/8NE	-	Growth rate
Johnston et al., 2010 (*74*)	102	*D. rerio, O. mykiss*	0.05–5	0E/2NE	-	Total tissue Ti conc.
Canesi et al., 2010 (*75*)	63	*M. galloprovincialis*	1–10	0	-	-
Zhu et al., 2010 (*76*)	147	*D. magna*	0.1–100	2E/7NE	Immobilization; total living offspring	Mortality; length; days to first brood; average offspring; ingestion rate; filtration rate

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Table III. (Continued). Summary of Environmentally Relevant $nTiO_2$ Ecotoxicology Results from 30 Highly Cited Papers

Authors	*Number of citations*[a]	*Species*	*$nTiO_2$ Concentration (mg L^{-1})*	*Treatments ≤0.1 mg L^{-1}*[b]	*Effect Summary ≤0.1 mg L^{-1}*	*No-Effect Summary ≤0.1 mg L^{-1}*
Dabrunz et al., 2011 (*77*)	47	*D. magna*	0.5–8	0	-	-
Kumar et al., 2011 (*78*)	68	*S. typhimurium*, *Salmonella* spp., *E. coli*	0.008–8	8E/4NE	Cellular $nTiO_2$ uptake; mutagenic effects	Mutagenic effects
Xiong et al., 2011 (*79*)	111	*D. rerio*	10–300	0	-	-
Dalai et al., 2012 (*80*)	38	*B. licheniformis*	0.05–1	0E/10NE	-	Cell viability; live/dead count; intracellular ROS; superoxide dismutase production; GSH production; LDH release
Bar-Ilan et al., 2012 (*81*)	35	*D. rerio*	1–1000	0	-	-
Miller et al., 2012 (*82*)	52	*T. pseudonana*, *S. marinoi*, *D. tertiolecta*, *I. galbana*	1–7	0	-	-
Lin et al., 2012 (*83*)	31	*Chlorella* spp.	1–1000	0	-	-

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Authors	*Number of citations*[a]	*Species*	*$nTiO_2$ Concentration (mg L^{-1})*	*Treatments ≤0.1 mg L^{-1}*[b]	*Effect Summary ≤0.1 mg L^{-1}*	*No-Effect Summary ≤0.1 mg L^{-1}*
Bar-Ilan et al., 2013 (*84*)	20	*D. rerio*	0.001–10	19E/5NE	Embryo survival; metamorphosis timing; cellular $nTiO_2$ uptake; DNA adducts	Metamorphosis timing; cellular $nTiO_2$ uptake; DNA adducts
Ramsden et al., 2013 (*85*)	18	*D. rerio*	0.1–1	2E/7NE	Total tissue Ti conc.; white blood cell count	Erythrocyte count; total tissue trace metals conc.; ATPase activity; total glutathione activity; tissue histology; eggs produced; viable embryos
Maurer-Jones et al., 2013 (*86*)	10	*S. oneidensis*	1–100	0	-	-
Wu et al., 2013 (*87*)	26	*C. elegans*	5×10^{-7}–0.05	21E/21NE	Survival; body length; brood size; locomotion; ROS production	Survival; body length; brood size; locomotion; ROS production

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Table III. (Continued). Summary of Environmentally Relevant $nTiO_2$ Ecotoxicology Results from 30 Highly Cited Papers

Authors	*Number of citations*[a]	*Species*	*$nTiO_2$ Concentration (mg L^{-1})*	*Treatments ≤0.1 mg L^{-1}*[b]	*Effect Summary ≤0.1 mg L^{-1}*	*No-Effect Summary ≤0.1 mg L^{-1}*
Clement et al., 2013 (*88*)	42	*C. vulgaris, D. magna, P. tricornutum*	0.005–100	3E/10NE	Toxicity	Toxicity; growth rate
D'Agata et al., 2014 (*89*)	14	*M. galloprovincialis*	10	0	-	-

[a] Obtained from Web of Science (*90*) times cited metrics, updated on Sept 24, 2015. [b] Total number of experimental treatments within a given paper coded based on the observation of an effect or no effect, relative to a control treatment. E, effect; NE, no effect; conc., concentration; ROS, reactive oxygen species. GSH, glutathione; LDH, lactate dehydrogenase.

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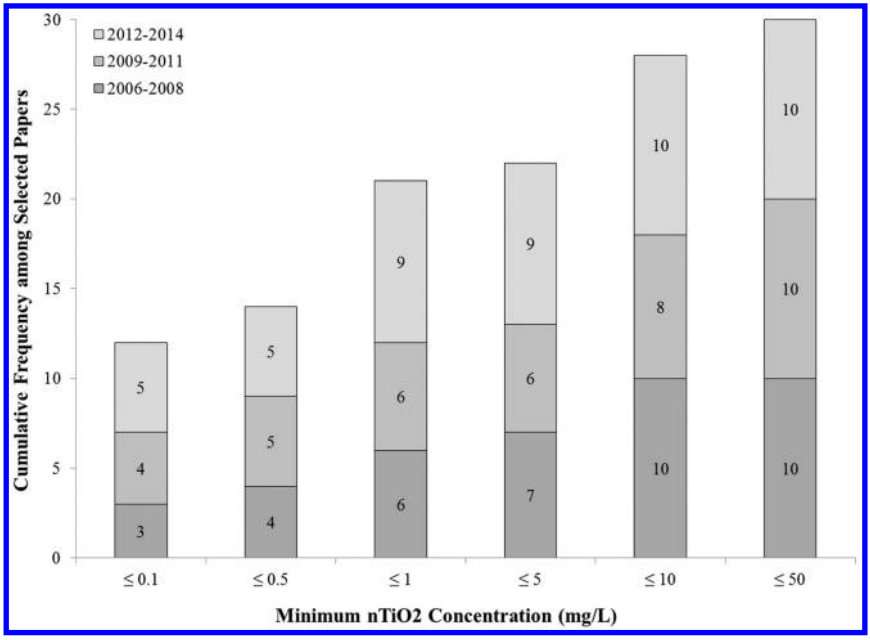

Figure 2. Cumulative frequency of minimum $nTiO_2$ concentrations used by 30 highy cited ecotoxicology papers from 2006 to 2014.

For each publication period, Figure 3 illustrates the cumulative percentages of experimental treatments that employ a designated $nTiO_2$ concentration. Considering all publication periods, approximately 72% of treatments from the selected papers utilized an $nTiO_2$ concentration of ≤10 mg L^{-1}, while only 22% used a more environmentally relevant concentration of ≤100 μg L^{-1}. As observed in the analysis of minimum $nTiO_2$ concentrations, there is a positive trend in the proportion of experimental treatments that consider relatively low $nTiO_2$ concentrations as the publication period increases. For example, the proportions of experimental treatments using an $nTiO_2$ concentration of ≤100 μg L^{-1} increases from approximately 10% in 2006–2008 to approximately 31% in 2012–2014. While these statistics indicate that assessing the potential impacts of low $nTiO_2$ concentrations has received greater priority in recent years, they also illustrate that the vast majority of experimental treatments still utilize high $nTiO_2$ concentrations, relative to those expected in real environmental systems.

One cannot dismiss, however, that the selected papers do contain 156 different treatments with $nTiO_2$ concentrations ≤100 μg L^{-1}, and these experiments are a valuable resource in a scientific realm that so often uses much higher $nTiO_2$ doses. Hence, to evaluate the findings from these treatments and establish which $nTiO_2$ concentrations result in biological responses, the toxicity metrics from each of the 701 experimental treatments were coded with an effect or a no-effect designation. For the vast majority of experiments, the determination of a biological effect relied upon the statistical measurement of significance for an $nTiO_2$-bearing treatment, relative to the $nTiO_2$-free control, with the significance level established by the

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authors of a given paper. In instances where statistical analyses were not provided, some expert judgment of the data presented in the paper was necessary; however, effect designations deferred to the authors' discussion within the article when possible. Many of the toxicity metrics considered by the selected papers were tracked over time, and a treatment was typically coded as an effect if a significant biological response occurred during any of the time periods considered. An exception to this rule existed in the coding of transient biological effects, which are those effects that were evident at a single time period or concentration but not at later time periods or subsequently higher concentrations. The occurrence of transitory responses was extremely rare, but when present, they were generally not considered effects unless the author provided an explicit discussion related to why a transitory effect was expected.

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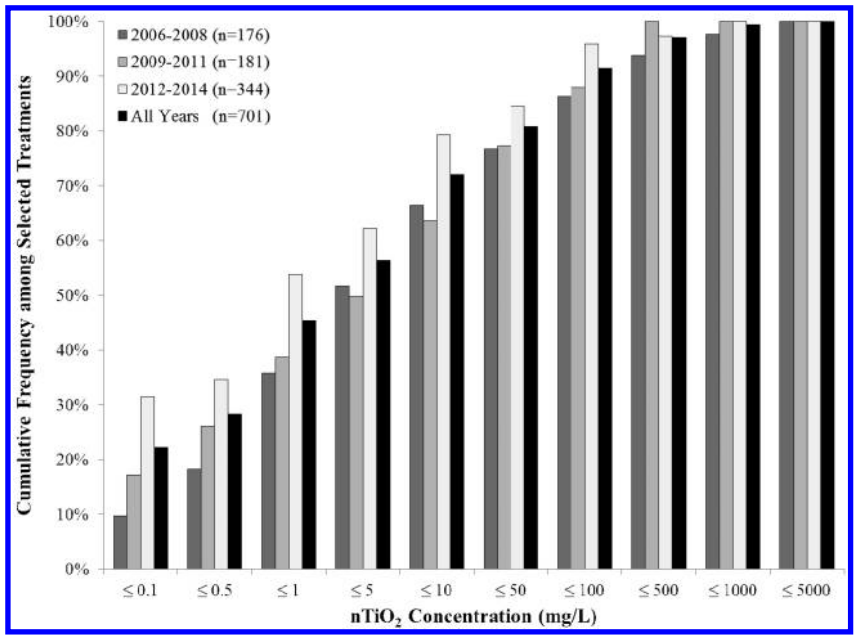

Figure 3. Cumulative frequency of $nTiO_2$ concentrations employed in the experimental treatments from 30 highly cited ecotoxicology papers from 2006 to 2014.

Of the 12 papers that contained at least one treatment exhibiting an $nTiO_2$ concentration of ≤100 μg L^{-1}, five discerned no biological effects to the target species for these concentrations (Table III). For example, Reeves et al. (*67*) and Dalai et al. (*80*) observed no impact to the cell viabilities of goldfish skin cells exposed to 100 μg L^{-1} $nTiO_2$ and a freshwater bacterium exposed to 50 μg L^{-1} $nTiO_2$, respectively. In addition, Wang et al. (*69*) and Miller et al. (*73*) established that the growth rates of five different species of marine phytoplankton were not influenced by environmentally relevant $nTiO_2$ concentrations of between 1 μg L^{-1} and 100 μg L^{-1}. Finally, at an $nTiO_2$ concentration of 50 μg L^{-1}, Johnston et al. (*74*)

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found no enhanced accumulation of Ti in the total tissue digests of either rainbow trout or zebrafish. The results from these five papers represent around 17% of the total environmentally relevant treatments from this analysis.

The remaining seven papers often illustrate measureable responses in organisms exposed to $nTiO_2$, even with concentrations as low as 50 ng L^{-1}. In fact, of those treatments using an $nTiO_2$ concentration ≤100 μg L^{-1}, 39% were coded as having an effect to a biological system (Table III). This proportion is slightly less than the approximately even split between effect (51%) and no-effect (49%) designations across all $nTiO_2$ concentrations (≤5,000 mg L^{-1}; data not shown), but nevertheless, indicates that there is strong evidence in the literature for potentially negative consequences in aquatic systems exposed to environmentally relevant $nTiO_2$ concentrations. The observed effects vary widely and are found in multiple organisms across many different toxicity metrics (Table III), with a few notable examples illustrated in Figure 4. For example, as early as 2007, Federici et al. (*65*) documented changes in juvenile rainbow trout exposed to 100 μg L^{-1} $nTiO_2$ that ranged from alterations in gill and organ morphologies to elevated indicators of oxidative stress. A similar study from the same research group (*85*) found a much-reduced list of impacts to adult zebrafish exposed to 100 μg L^{-1}, which included significant increases in the Ti concentrations found in total tissue digests. In addition, Kumar et al. (*78*) detected cellular uptake of $nTiO_2$ and mutagenic responses by bacterial strains in the presence of $nTiO_2$ concentrations as low as 8 μg L^{-1}. While studying the lowest $nTiO_2$ concentration range for any of the selected papers, Wu et al. (*87*) observed impacts to nematodes after long-term (larva to adult) exposure to $nTiO_2$ that included decreases in survival and growth at 50 μg L^{-1}, decreases in brood size at 500 ng L^{-1}, and changes in locomotion and increases in oxidative stress indicators at 50 ng L^{-1}.

The results from several of these seven papers also effectively illustrate a continuing advancement of $nTiO_2$ ecotoxicology research toward more environmentally realistic conditions related to both concentration and exposure duration. For instance, two early reports in the literature (*60*, *62*) showed that low mg L^{-1} concentrations of $nTiO_2$ result in no toxic responses to the water flea *Daphnia* spp. over a 48 h period, whereas later tests by Zhu et al. (*76*) and Clement et al. (*88*) extended the exposure time to 72 h and measured significant increases in toxicity metrics in some $nTiO_2$ suspensions with concentrations as low as 100 μg L^{-1}. In 2012, Bar-Ilan et al. (*81*) used a concentration range of 1 mg L^{-1} to 1,000 mg L^{-1} to study the impacts of $nTiO_2$ on zebrafish embryos, and followed up this study with one in 2013 that utilized an extended time period and more environmentally relevant $nTiO_2$ concentrations. In the later study, Bar-Ilan et al. (*84*) found that zebrafish survival from the embryo stage through juvenile metamorphosis was negatively impacted by $nTiO_2$ concentrations as low as 1 μg L^{-1}, while cellular uptake of $nTiO_2$ and DNA alterations were observed at 10 μg L^{-1} and 100 μg L^{-1}, respectively. With the exception of cellular uptake, all of the $nTiO_2$-associated impacts in this study were light dependent. Assuming this trend continues into the future, one can expect that the research published in upcoming years will answer many of the outstanding questions related to how environmentally relevant $nTiO_2$ concentrations influence its overall ecotoxicity.

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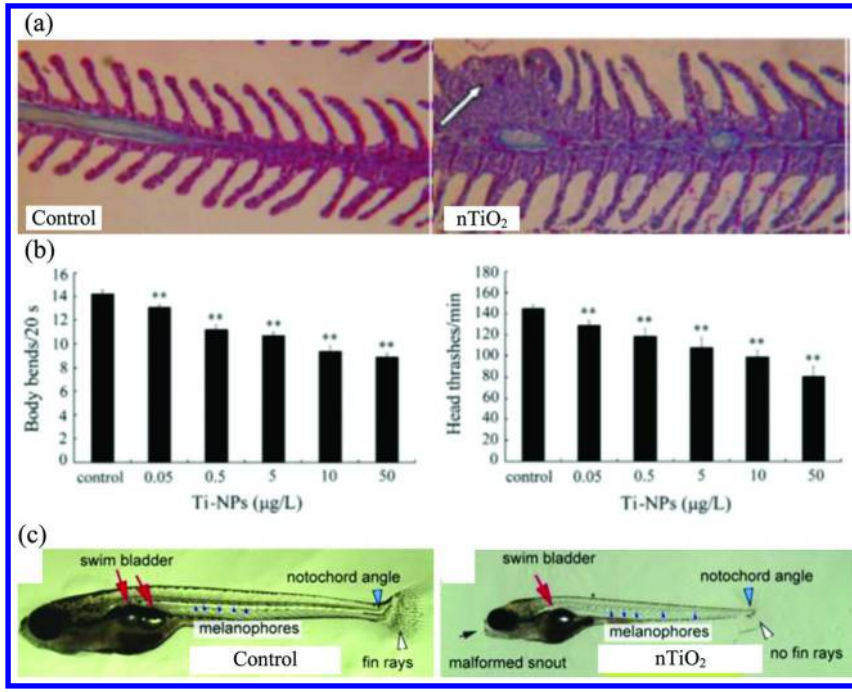

*Figure 4. Examples of biological responses coded as effects from environmentally relevant $nTiO_2$ concentrations. (a) Gill morphology of juvenile rainbow trout (O. mykiss) exposed to 100 μg L^{-1} $nTiO_2$ for 14 days that indicate a thickening of the primary lamellae and an increase in oedema (osmotic swelling) of secondary lamellae (white arrow), relative to control samples. Reproduced with permission from reference (65). Copyright 2007 Elsevier. (b) Alterations in the locomotion behavior of nematodes (C. elegans) exposed to low concentrations of $nTiO_2$ from the L1-larval stage to adulthood. **Significant ($P<0.01$) effects. Reproduced with permission from reference (87). Copyright 2013 Elsevier. (c) Delays in development, decreased growth, and tissue malformations at 23 days after fertilization in zebrafish (D. rerio) exposed to 1 μg L^{-1} $nTiO_2$ from embryogenesis through metamorphosis. Reproduced with permission from reference (84). Copyright 2013 American Chemical Society.*

While the hopeful trends toward more realistic and comprehensive study of $nTiO_2$ ecotoxicology noted above are somewhat anecdotal, they are supported by evidence in the quantitative portion of this analysis. For example, while each publication period in Figure 3 is represented by an identical number of papers (10), the number of treatments in the 2012–2014 publication period (344) is approximately double that of the more stable treatment counts exhibited by the 2006–2008 (176) and 2009–2011 (181) publication periods. The significant increase in treatment count for the 2012–2014 publication period is likely a consequence of the increasing complexity of the experimental designs from individual papers within this period, as well as the recent transition toward

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focusing on a single nanomaterial within each published paper. For example, only one (*87*) of the 10 selected papers from the 2012–2014 publication period included an ecotoxicology evaluation for nanomaterials other than $nTiO_2$, whereas the influence of nanomaterial composition was often an integral part of the experimental design of selected papers from earlier publication periods (which drops the number of $nTiO_2$-specific treatments per paper). This observation suggests that the nanoecotoxicology literature began with a broad survey of the potential impacts associated with nanomaterials (or nanomaterial classes) in general, and has recently transitioned toward using the results of these earlier efforts to refine methodologies that target more specific questions about the exact environmental conditions (e.g. concentrations, lighting, aggregation state) where biological impacts are possible. As a result, there are many reasons to believe that future ecotoxicology studies will be able to more effectively communicate the actual ecological hazards of $nTiO_2$ in real environments.

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Measurement Technologies

If future ecotoxicology studies do establish a firm causal link between environmentally relevant $nTiO_2$ doses and deleterious impacts to ecological systems, any ensuing monitoring or regulatory structure would require efficient and reliable techniques for determining $nTiO_2$ concentrations in complex environmental samples. However, such quantitative $nTiO_2$ measurement technologies, which may include both standardized analytical methods and/or novel instrument adaptations, have yet to be realized. $nTiO_2$, as well as other nanomaterials, are perhaps unique among the list of other environmental contaminants as they are defined by both chemical identity and solid particle size. As such, a successful analytical method for determining $nTiO_2$ concentrations must result in the elemental identification and quantification of only a narrowly defined size fraction (ionic<$nTiO_2$<100 nm) within a sample matrix that could contain myriad other dissolved and particulate constituents. By contrast, established methods for quantifying toxic metals (e.g. Pb) in surface waters generally focus only on the traditionally defined dissolved fraction, which is delineated as that which will elute through a filter whose pore size is 450 nm. It is immediately apparent from this discussion that, if using a similar method, all unaggregated $nTiO_2$ would be quantitated in the so-called dissolved fraction, but so would other Ti fractions, such as that which is truly dissolved (ie, ionic or not solid) and any TiO_2 particles that are greater than 100 nm but less than 450 nm.

These analytical complications are clearly illustrated by the past attempts to directly measure $nTiO_2$ concentrations in real aqueous samples, as discussed earlier in this chapter (Table I). In these papers, Ti-bearing constituents in water samples from either natural systems or wastewater treatment effluents are only partially fractionated using centrifugation or filtration to attain size clusters that contain not only $nTiO_2$, but also ionic Ti and/or Ti-bearing particles larger than 100 nm. It should be noted that Neal et al. (*47*) did achieved a modicum of success in further fractionating surface water samples by employing an additional 1 kDa (roughly 1–2 nm) filter, which served to partially separate TiO_2 particles

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from dissolved Ti. This method appears worthy of additional development. To partially compensate for the lack of a nano-specific fractionation method, electron microscopy coupled to an energy-dispersive electron spectrometer is often used for simultaneous sizing and elemental identification, respectively. This method, however, is not practical for quantifying $nTiO_2$ concentrations in a bulk sample because it would require the tedious task of counting particles one by one, as well as extensive sample preparation.

Bulk elemental identification and quantification of the filtered samples from these papers was completed using inductively coupled plasma (ICP) mass spectrometry (MS) and/or ICP optical emission spectrometry. Because ICP-based instrumentation has traditionally been used to quantify the concentrations of metal ions in solutions, samples are generally subjected to one of several acid digestion procedures in an attempt to dissolve any $nTiO_2$ particles before injection on the instrument. Raw instrument signals are considered against a series of dissolved Ti calibration standards of known concentration for quantification. In order for this measurement to be valid, the digestion procedure must have succeeded in completely digesting the solid $nTiO_2$ present the sample, as the atomization of any remaining solid particles in the plasma would presumably be different from that of the dissolved species found in the concentration standards. However, the efficacy of each digestion procedure in dissolving $nTiO_2$ receives very little (if any) attention in these papers. Hence, existing methods for $nTiO_2$ quantification in real aqueous matrices suffer from not only issues associated with size-specific fractionation, but also a need for the development of standardized digestion methods using $nTiO_2$ reference materials with known concentrations.

On the analytical horizon are next-generation $nTiO_2$ quantification methods that are grounded on traditional ICP-MS principles, but with several notable improvements for the characterization of nanomaterials. For example, simultaneous nanoparticle size fractionation and elemental analysis can be achieved using field flow fractionation (FFF) coupled to a traditional ICP-MS (*91–93*). While several FFF techniques are currently under development (*91*), in general, this collection of methods accomplishes the separation of nanoparticle sizes by applying an electric field across the flow of the mobile phase entering an ICP-MS. The result is a relatively rapid determination of concentrations for various particle factions. However the use of FFF-ICP-MS in environmental monitoring of complex solutions is hindered by the need for extensive method development to optimize a number of solution-specific parameters, including flow rates, injection timing, and sample pH (*91*, *92*). FFF-ICP-MS can also be complicated by relatively high detection limits and issues with sample aggregation during analysis, which limits the detection of primary nanoparticle sizes (*92*).

In addition, single-particle ICP-MS is also a promising technique which utilizes an ICP-MS for elemental analysis, but sample delivery operates in so-called single-particle mode, where $nTiO_2$ particles from very dilute solutions are injected into the instrument individually for analysis. Single particles are generally encapsulated by water droplets, meaning that the elements of interest (e.g. Ti) are spatially concentrated, which results in transient spikes in the instrument signal as the particles ionize and these elements pass through the detector (*91*). Assuming that all droplets contain single particles (as opposed

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to aggregates, for example) the signal intensity is proportional to the size of the spherical particle. This method requires the ICP-MS in use to be capable of very fast data collection, but otherwise requires relatively low instrumental effort or method development. However, a recent study by Lee et al. (*94*) showed that the minimum size detection limit for $nTiO_2$ is around 90 nm in deionized water, and likely higher in real environmental matrices. In fact, interferences from other elements commonly present in surface waters (e.g. Ca (*32*)) may push the size detection limit well above the demarcation point for nanomaterials, currently rendering this analytical technique impractical for the targeted quantification of nanoparticle concentrations. Hence, the development of methods for the quantification of $nTiO_2$ concentrations in complex matrices represents an enormous hurdle facing those concerned about the release of $nTiO_2$ to natural aquatic systems. Further development of these techniques, or others that are not covered here, will be required before any significant $nTiO_2$ monitoring or regulatory structure is developed.

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Conclusions

Perhaps the most valuable quality of the science and engineering community is our willingness to dive headlong into new problems without the luxury of a textbook full of knowledge for the systems in question. From inaugural studies that test the most basic hypotheses, scientific understanding of most emerging issues evolves over time, hopefully building into a fundamental comprehension that can be employed to answer the specific questions of modern society. It is clear from the preceding discussion that our understanding of the environmental hazards posed by nanomaterials like $nTiO_2$ is certainly still evolving and few definitive statements of toxicity are possible at this time. For example, little is known about the actual concentrations of $nTiO_2$ in real environmental systems, primarily because few (if any) analytical techniques are successful in reliably, efficiently, and selectively quantifying the elements that comprise nanoscale materials. In addition, a considerable percentage of available $nTiO_2$ ecotoxicology studies utilize an unrealistically high $nTiO_2$ concentration range, thereby limiting the knowledge gained from their results. Those studies that have used more environmentally relevant $nTiO_2$ concentrations regularly measure negative biological responses from test organisms, which only serves to further reinforce the need for such studies. Fortunately, this analysis also found evidence to suggest that improved study designs and measurement technologies are on the horizon, meaning that the knowledge of nanomaterial-bearing systems may yet advance to a point where, if needed, a monitoring or regulatory structure will be possible.

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Chapter 9

Risk Analysis Approaches for Establishing Maximum Levels of Essential Nutrients in Fortified Foods and Food (Dietary) Supplements

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Nutritional risk analysis addresses the essential nutrients and other substances with nutritional and physiological effects and the risk to health from their inadequate and/or excessive intake. In this chapter I review the principles of risk management in order to underpin regulatory developments around the world to establish maximum amounts of vitamins and minerals and other substances in fortified foods and food supplements. The proposed science-based risk management models for public health decision-making take into account international risk assessments and (a) the tolerable upper intake levels for vitamins and minerals, (b) the highest observed intakes for bioactive substances for which no adverse effects have been identified, and (c) the contributions to total intake from conventional foods, fortified foods and food supplements. The models propose the allocation of nutrient substances into three categories of risk and maximum levels in order to protect adult and child consumers from excessive intakes.

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Introduction

Nutritional risk analysis addresses the essential nutrients and related bioactive substances (other than a nutrient) in the diet and the risk to health from their inadequate and/or excessive intake. Nutritional risk analysis applies the same general approach as traditional food safety risk analysis to the consideration of excessive intakes of many constituents of food, such as food additives, chemical (pesticide and veterinary drug) residues, microbiological pathogens, contaminants and allergens. However, unlike these constituents, nutrients and related substances are biologically essential to life (in the case of the essential nutrients) or in other ways potentially favorable to health (*1*). Nutritional risk analysis, therefore, adds a new dimension to traditional risk analysis because there are two types of risk: that of suboptimal intake or deficiency and risk of adverse effects associated with excessive intake, as shown in Table I.

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Table I. Risk of Adverse Effects of Certain Essential Nutrients

	Too little	*Too much*
Calcium	Osteoporosis	Hypercalcemia, kidney stones
Iron	Anemia, impaired performance	Gastrointestinal side effects
Zinc	Growth failure	Affects copper status
Vitamin A	Growth abnormalities	Liver damage, teratogenic, brittle bones
Vitamin C	Scurvy, fatigue	Gastrointestinal side effects
Vitamin D	Skeletal deformities	Hypercalcemia
Folic acid	Megaloblastic anemia, neural tube defects	Masking of vitamin B12 deficiency

There are three major and complementary ways of delivering the essential nutrients and bioactive substances required for human health and well-being:

- promoting the consumption of nutrient-dense foods, such as fruits and vegetables, wholegrain cereals, dairy, and meat products
- increasing the availability and intake of foods with added nutrients (fortified foods)
- the appropriate use of food supplements

Each of these three approaches has been demonstrated to provide a safe way of ensuring the adequate intakes and nutritional status of populations and individuals at certain times in their lives (*2–4*). However, it is necessary for the scientific community, regulatory authorities, and industry to work together to ensure that the sum of intakes from all the sources does not lead to excessive intakes and any adverse effects.

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Nutritional risk analysis in food regulation provides a systematic and structured approach to assess public health and safety risks from foods and dietary food supplements, and to manage any characterized risk. The approaches address the nature and magnitude of the health risks, and how they should be managed and communicated to those affected. This chapter mirrors the Food and Agriculture Organization (FAO)/World Health Organization (WHO) (*5*) and the Codex Alimentarius Commission (*1*) principles and guidelines for nutritional risk analysis for the establishment of upper levels of nutrients and related substances in food products and the characterization of such risk. Some countries around the world have proposed that the maximum amounts of nutrients in fortified foods and food supplements should be based on, and limited to, fractions or small multiples of the recommended daily amount (RDA). Codex Alimentarius, FAO/WHO, and most national and regional approaches to setting of maximum levels, however, have developed methods and regulations that use nutritional risk analysis and not RDA-based maximum levels, as the latter approach is considered arbitrary and unscientific (*1*, *5*).

The increasing use of fortified foods, food supplements, specially formulated foods, and so-called functional foods have the potential to increase the intake of nutrient substances for population groups all around the world. The overall objectives of nutritional risk analysis, therefore, is to protect the consumer, ensure a safe food supply, harmonize an international basis for determining safe levels of intake, and to facilitate international trade.

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Principles of Nutritional Risk Analysis

Nutritional risk analysis comprises three distinct but closely linked components: science-based nutritional risk assessment; policy-based nutritional risk management; and nutritional risk communication (provision of information and judgement about risks). Particular emphasis is given to an initial step of problem formulation as a key preliminary risk management activity. The objective is to foster interactions between risk managers and assessors to help ensure a common understanding of the problems and the purpose of the risk assessment (*1*, *5*). The Codex Alimentarius principles and guidelines set out the considerations to be included in the formulation of the nutritional problem, including the priority it should be accorded, who should conduct the work, whether data are available to embark on the evaluation of nutritional risks, the relevant sources of intake, the identification of the (sub)population to be the focus of the risk assessment, and the health outcomes to be considered, as well as the resources available and timelines for completion of the assessment.

Nutritional Risk Assessment

The principles for scientific nutritional risk assessment are shown in Table II. In steps 1 and 2, nutrient-related hazard identification and nutrient hazard characterization/quantitative evaluation of critical effects, the process begins with the identification of adverse health effects associated with the nutrient

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substance, and makes use of human, animal, and *in vitro* data. Each data source has advantages and disadvantages. For example, animal data have the advantage of quite extensive and robust datasets and the disadvantage of uncertain and problematic extrapolation for application to humans. On the other hand, human data are sparse for many nutrients, but have the advantage that little or no extrapolation is needed for decisions that are relevant for humans (*6*).

Table II. Principles for Scientific Risk Assessment: Problem Formulation (*1*, *5*)

Step	*Processes*
1. nutrient hazard identification	Review literature to identify potential health problems (e.g. deficiency and excess end points)
2. nutrient hazard characterization/ quantitative evaluation of critical effects	Identify, where possible, the level at which a nutrient causes adverse effects (e.g. dose–response, clinical, epidemiological, metabolic, and case report data). Set AROI, tolerable UL, or SUL
3. dietary intake assessment	Evaluate the average intake of various population groups from food, water, and supplements, and assess variability of magnitude of intake with percentiles
4. nutrient risk characterization	Integrate intake information and AROI, UL, and SUL data, and evaluate strength and weakness of each step and identify group of greatest concern

AROI, acceptable range of oral intake; UL, upper intake level; SUL, safe upper intake levels.

A key point in the risk assessment is the identification of critical adverse health effects upon which a tolerable upper intake level (UL) is based. The process involves the identification of a no observed adverse effect level (NOAEL), from human data if possible. If the data cannot support a NOAEL, a lowest observed adverse effect level (LOAEL) may be established. Animal data are used only if appropriate human data are not available or as a guide to search for a hazard that might be identified in human data. The uncertainties in the data are assessed and uncertainty factors are applied to the identified toxicological thresholds (e.g. NOAEL or LOAEL). Numerical uncertainty factors account for the scientific uncertainties, including inadequacies in the database, interspecies extrapolation, variability and differences in susceptibility of individuals, the nature and severity of adverse effects, and whether there are short-term or long-term effects. Scientific judgment is used in the choice of the uncertainty factors, and the UL is derived by dividing the NOAEL or LOAEL by the total product of the uncertainty factors. The selection of the uncertainty factors is critical when considering the potential effects for nutritional deficiency and excess.

FAO/WHO (*5*) list the key activities in hazard identification and characterization. A major limitation of the UL method as applied by risk managers is that no UL can be set for nutrients without established adverse effects. However, an alternative approach has been developed with what is

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termed the highest observed intake (HOI) (*5*). The HOI is derived only when no adverse health effects have been identified. It is the highest level of intake observed or administered as reported in studies of acceptable quality (*5*). Hence, in the absence of a UL, the HOI is the highest intake with available data to show, with acceptable confidence, the absence of adverse effects. The HOI and UL values, even after adjustments for uncertainties related to the strength of the data set, are both risk assessment values and are both accepted by the Codex Alimentarius in its nutritional risk analysis principles and guidelines for application to the work of the Committee on Nutrition and Foods for Special Dietary Uses (*1*). With this sanction, the ULs and HOIs have acquired global policy and regulatory importance because Codex Alimentarius is recognized as the pre-eminent international authority on food safety by the World Trade Organization in its Sanitary and Phytosanitary Agreement (*7*).

In step 3, dietary intake assessment requires an estimate of the current and potential intakes of essential vitamins, minerals, or related substances from the various dietary sources. A major problem is the availability of data on nutrient intakes, and scientific committees draw on a wide array of consumption data from household surveys, recall of consumption at 24 h and 48 h, 4-day and 7-day weighed food intake data, etc. In fact, data from many days are needed to estimate the average or habitual intakes for individuals, in total or from conventional foods, water, fortified foods, and food supplements. The variability of the magnitude of intakes can be assessed with intake percentiles (e.g. percentiles 5, 50, 95, and 97.5) to represent the range of intakes from deficient to suboptimal up to high intake. In certain circumstances and in countries where intake data are limited, mathematical modeling approaches can be used, and, often, pragmatic approaches are considered to make use of the best available data from countries with the most complete sets of data and where the markets for fortified foods and food supplements are well developed, such as those from the United Kingdom National Diet and Nutrition Surveys (*8–10*) and the United States National Health and Nutrition Examination Survey (NHANES) (*11–13*). The overall objective is to obtain the best estimate of usual intakes that reflect long-term chronic exposure to the nutrients or substances in question (*14*).

In step 4, nutrient risk characterization, the nutrient intake data assessment and information on the ULs and the acceptable range of safe intake are fully integrated and applied within the context of the total diet. Wherever feasible, this step involves the evaluation of the distribution of habitual total daily intake for target populations. The approach recognizes that nutrient-related risks are often associated with total intakes from multiple dietary sources, including, for example, conventional foods, such as dairy products as major sources of calcium, liver as rich sources of vitamin A, etc, fortified foods, food supplements, and, in the case of certain minerals, water. The nutrient risk characterization might also take into account the bioavailability and stability of nutrients and related substances in the foods consumed.

The nutrient risk characterization uses quantitative and qualitative scientific assessment and identifies the proportion of the population or subpopulation likely to exceed the UL. It highlights important considerations, including the severity and nature of adverse effects, descriptions of uncertainties, and identification of

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any special subpopulation at risk (*1*, *5*). The overall nutritional risk assessment process recognizes that there may be sensitive groups, such as infants, children, certain adults, the elderly, and pregnant or lactating women. Even within relatively homogeneous life-stage groups, there can be a range of sensitivities to adverse effects, including those influenced by body weight and lean body (muscle) mass. The extent to which subpopulations are considered separately from the general population is an area of scientific judgment, and the nutrient substances are usually assessed on a case-by-case basis.

International Scientific Nutrient Risk Assessments

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Over the past 20 years, the UL and scientific risk analyses have become the internationally accepted ways to evaluate the safety of the essential nutrients and to underpin regulatory approaches to setting maximum levels of vitamins and minerals, where appropriate, in fortified foods and food supplements. Several international organizations and numerous national scientific committees have developed recommendations for UL values. The three national authoritative bodies included in the FAO/WHO model in 2006 (*5*) were:

- European Food Safety Authority, European Union, and the former Scientific Committee on Food, European Commission (EFSA/SCF) (*15*)
- Institute of Medicine of the National Academies, United States of America and Canada (IOM) (*16–20*)
- United Kingdom Expert Group on Vitamins and Minerals, Food Standards Agency (EVM) (*21*)

Table III shows the levels established by these three scientific assessment committees. For example, the EFSA (*15*) has provided scientific opinions on ULs for 29 nutrients listed in Annex 1 of the European Food Supplements Directive (*22*). This assessment resulted in numerical ULs being established for 16 nutrients. Some of the remaining nutrients showed extremely low or non-existent adverse effects even at very high levels of intake, and, for some, lack of sufficient scientific data did not permit derivation of numerical ULs. Where ULs were not established, the EFSA/SCF provided qualitative risk characterizations for the specific nutrients. The other expert committees, the EVM and IOM, have set numerical values for ULs or, in the case of the EVM, safe upper levels (SULs) and guidance levels (GLs). It should be noted that the UL values can be expressed either in terms of total dietary intake (i.e. from all sources, including conventional foods, fortified foods, and food supplements) as in the case of the IOM and EFSA risk assessments, or for long-term supplementary amounts (expressed in SULs), as in the case of the EVM assessment. As previously mentioned, these UL, SUL, and GL values have been accepted by FAO/WHO (*5*) and by the Codex Alimentarius Commission (*1*) for the purposes of being global reference points for national food control agencies, for consumers, food producers and processors, and for international trade. The Codex Alimentarius principles and guidelines together with the standards, codes, and practical guidelines from FAO/WHO provide the benchmarks against which

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national food measures and regulations are developed and evaluated within the legal parameters of the World Trade Organization (*7*).

Table III. Comparison of Established ULs and Proposed Daily Levels for Supplementation

Nutrient	*Unit*	*EFSA/SCF UL for total intake*	*IOM UL for total intake*	*EVM SUL for long-term supplementation per 60 kg adult body weight*
Vitamin A	µg	3,000	3,000	1,500 guidance and total intake
Beta-carotene	mg	Below 15	Not set	7 (not for smokers)
Vitamin D	µg	50–100[a]	50–100[a]	25 guidance
Vitamin E[b]	mg	300	1,000	540 (800 IU)
Vitamin K	µg	Not set	Not set	1,000 guidance
Thiamin (B_1)	mg	Not set	Not set	100 guidance
Riboflavin (B_2)	mg	Not set	Not set	40 guidance/ 43 total intake
Nicotinamide	mg	900	35[c]	500 guidance/ 560 total intake
Nicotinic acid	mg	10		17
Pantothenic acid	mg	Not set	Not set	200 guidance/ 210 total intake
Pyridoxine (B_6)	mg	25	100	200 (short term),[d] 10 (long term)
Folic acid	µg	1,000 (+dietary)	1,000 supplemental (+200 dietary)	1,000 guidance/ 1,500 total intake
Vitamin B12	µg	Not set	Not set	2,000 guidance
Biotin	µg	Not set	Not set	900 guidance value/ 970 total intake
Vitamin C	mg	Not set	2,000	1,000 guidance
Calcium	mg	2,500	2,500	1,500 guidance
Magnesium	mg	250 supplementary	350 supplementary (+dietary)	400 guidance
Iron	mg	Not set	45	17 guidance
Copper	mg	5	10	1 guidance/ 10 total intake

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Table III. (Continued). Comparison of Established ULs and Proposed Daily Levels for Supplementation

Nutrient	*Unit*	*EFSA/SCF UL for total intake*	*IOM UL for total intake*	*EVM SUL for long-term supplementation per 60 kg adult body weight*
Iodine	µg	600	1,100	500 guidance/ 940 total intake
Zinc	mg	25	40	25 guidance/ 42 total intake
Manganese	mg	Not set	11	4 guidance/ 9–12 total intake; 0.5 guidance for elderly
Potassium	mg	Not set	Not set	3,700 guidance
Selenium	µg	300	400	350 guidance/ 450 total intake
Chromium (trivalent)[e]	mg	Not set	Not set	10 guidance and total intake
Molybdenum	µg	600	2,000	Not set
Fluoride	mg	Not set	10	Outside terms of reference
Phosphorus	mg	Not set	4,000	250 guidance/ 2400 total intake

ESFA/SCF, European Food Safety Authority, European Union, and the former Scientific Committee on Food, European Commission. UL, upper intake level; SUL, safe upper intake levels. [a] Was 50 µg per day initially, but reassessed value was increased to 100 µg per day for adults, including pregnant and lactating women. [b] d-α-tocopherol equivalents per day. [c] Applied to total of all forms of niacin owing to IOM decision to establish a lowest observed adverse effect level based on skin flushing by nicotinic acid; in the European Union niacin supplements and niacin fortification are generally in the form of nicotinamide. [d] Implied in text of report. [e] Picolinates are excluded.

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All current methods for establishing ULs and SULs emphasize the concept of quantitative scientific risk assessment. However, disparities in the selection and interpretation of the available scientific literature on safety and the approaches to handling uncertainties has sometimes led to large differences in the values for various nutrients. The differences present a challenge to risk managers in the use of the risk assessments in nutritional risk management, especially with respect to the establishment of maximum safe levels of vitamins and minerals and related substances in fortified foods and food supplements. It is important to recognize, however, that the ULs and SULs represent an intake that can be consumed daily over a lifetime without significant risk to health, according to the available scientific evidence. The ULs are based on the assumptions and characterizations of uncertainties made by scientific risk assessment committees. They are not only safe, but safe by a comfortable margin, and they are defined and identified

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to reflect safety of chronic intake. ULs are not thresholds for adverse effects or safety limits, and they do not apply to temporarily elevated levels.

Nutritional Risk Management and Communications

Information needed for use by nutrient risk managers to take a particular action is contained in the FAO/WHO report (*5*), and any decisions have to take into account the impact on dietary patterns and consumer behavior (*1*). A key point is that risk managers should utilize scientifically based risk assessment approaches enshrined in the guidelines and principles of risk analysis, not RDAs, for the establishment of SULs. Table IV summarizes the issues related to the misuse of RDAs in the setting of maximum levels of nutrients in fortified foods and food supplements, which, unfortunately, some countries are still considering. The use of scientific nutritional risk analysis to set maximum levels of vitamins and minerals means the adoption of a uniform approach that is recognized internationally (*1*, *5*). The risk assessors can establish the risk and provide the information to equip the risk manager to determine whether the risk warrants immediate action, close monitoring, or no action at the current time. Risk management approaches can be effected through quantitative and/or qualitative guidance, with options such as the suitability of a particular category of foods based on nutritional composition (e.g. the amounts of saturated fat, free sugars, and sodium or salt), labeling advice, conditions of use, or warning statements intended to mitigate nutritional risks to public health, educational campaigns, increased dialogue with the food industry, specifying standards for product formulation, quality control, etc.

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Table IV. Issues with Use of Recommended Daily Amounts Based Safe Upper Intake Levels. SOURCE: Adapted with permission from reference (*35*). Copyright 2014 International Alliance of Dietary/ Food Supplements Associations (IADSA).

Definitions	*Descriptions of methods*
Classic requirement calculations	Classically, an individual's requirement for a nutrient has been the amount of that nutrient needed to prevent clinical signs of deficiency. While this must always be an important part of defining a requirement, scientific committees recognize that in addition to satisfying the basic need to avoid deficiency, some allowance should be made, where appropriate, to ensure nutritional adequacy. For example, a degree of storage of a nutrient to allow for periods of low intake or high demand without detriment to health
Estimated nutrient intake requirements	• Sufficient for absence of any signs of deficiency disease in individuals and groups • Sufficient to be associated with an appropriate biological marker of nutritional adequacy • Sufficient to maintain a given circulating level or degree of enzyme saturation or tissue concentration

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Table IV. (Continued). Issues with Use of Recommended Daily Amounts Based Safe Upper Intake Levels.

Definitions	*Descriptions of methods*
	• Sufficient to maintain homeostatic balance, taking into account that the period over which such balance needs to be measured differs between nutrients and individuals
Recommended daily intake	Average daily intake level that is sufficient to meet the nutrient requirement for nearly all (97–98%) of healthy individuals in a particular life stage and gender group, but not suitable to describe safety or to represent a safety limit for total or supplemental intake of a nutrient; arbitrary multiples of RDA to set maximum levels of vitamins and minerals in food supplements have no scientific validity
Scientific risk assessments and risk management	The only valid methods to identify maximum levels of vitamins and minerals (and other substances with nutritional or physiological effects) in food supplements, as well as in foods with added nutrients
Nutrient-related hazard identification and characterization	Should recognize the methodological differences in assessment of nutritional risk of inadequate and excessive intakes, and the scientific advances in these methodologies
Nutrient reference standards	Those used to characterize nutrient-related hazards related to adequacy of intake include measures of average requirement, whereas those that characterize nutrient-related hazards linked to excessive intakes include the tolerable upper intake level and highest observed intake determined by scientific risk assessment
Safe upper limits in food supplements based on recommended daily intake	Could be misleading to consumers and promote hypothetical safety concerns about a particular vitamin or mineral, for example, the natural amounts of vitamin B_{12} in conventional foods, such as liver and some shellfish, can be many times higher than the recommended daily intake

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The Codex Alimentarius Commission (*5*, *23*) has set out the general principles applicable to nutritional risk communication, which requires that the three components of nutritional risk analysis should be documented fully and systematically in a transparent manner, and that public understanding of the process is fostered so as to enhance trust and confidence in the safety of the food supply, and that all the interested parties are involved as appropriate.

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Global Regulatory Approaches to the Setting of Maximum Amounts of Vitamins and Minerals in Fortified Foods and Food Supplements

If risk managers and regulatory authorities consider the establishment of maximum levels of vitamins and minerals in fortified foods and food supplements to be appropriate, the general approaches are based on scientific nutritional risk analysis, as already described. A good example of how the approaches are being applied is in the European regulatory developments for the establishment of maximum amounts of vitamins and minerals in fortified foods and food supplements. Regulation (EC) 1925/2006 (*24*) makes provision for the harmonization of the conditions for the voluntary addition of vitamins and minerals and of certain other substances to foods (referred to informally as food fortification), and the European Commission Directive on the approximation of the laws relating to food supplements sets out the conditions for their use (*25*). Both these items of European legislation contain the criteria for setting maximum amounts of essential nutrients in these products, which are considered requisite for the risk management policy to be used in the forthcoming European-Union-wide harmonization of the maximum levels:

- upper safe levels of vitamins and minerals by scientific risk assessment based on generally accepted scientific data
- intake of vitamins and minerals from all dietary sources
- reference intakes of vitamins and minerals for the population

Another good example is the establishment of maximum levels (MLs) by the Association of Southeast Asian Nations (*26*). Both the European Union and the Association of Southeast Asian Nations regulatory developments are based on the risk assessment component derived from the FAO/WHO model (*5*) and the Codex Alimentarius Commission principles and guidelines (*1*).

Examples of Risk Management Models

A Theoretical Model for Setting Maximum Amounts of Vitamins and Minerals in Food Fortification

Theoretical models for setting maximum amounts of vitamins and minerals in fortified foods in Europe were prepared by the International Life Sciences Institute Europe. The most comprehensive model (*27*) identified several factors to be considered:

- ULs
- High micronutrient intakes in Europe at the P95 intake for each nutrient
- The proportion of foods to which micronutrients could practically be added
- A range of estimates for the fractions of foods that might actually be fortified for each nutrient

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In 2003, the model was modified (*28*, *29*) to take into account intakes from food supplements and the regulation on nutrition and health claims (*30*). The modifications retained the approach that expressed the maximum levels of the nutrients in fortified foods in weight units (mg or μg) per 100 kcal. The debate continues on whether the maximum levels in fortified foods should be based on the amount of food energy consumed or per 100 g/100 ml or per quantified portion. For food supplements, the maximum amount will be set per daily amount of consumption of the supplement (e.g. per one, two, or three tablets or capsules, or other measure indicated by the manufacturer).

Typically, the amount of nutrients added to food products are based on making nutrient content claims, and the Annex of the regulation on nutrition and health claims sets out the criteria for source and high levels for vitamins and minerals (*30*). In addition, there are technological limitations on how much of certain nutrients can be added to food with respect to color, taste, and texture, as well as implications for the shelf-life of products (*31*). The consumption of nutrient-dense conventional foods and fortified foods is also constrained by the energy density and satiating aspect of the food or meal. Hence, the risk of excessive intakes of vitamins and minerals from foods is relatively small. The use of preformed retinol (vitamin A) in foods merits further consideration when added to foods for the purposes of restoration, substitution, and fortification. As described in the next section, although concerns have been expressed, the amounts of vitamin A in foods, as well as the current levels in food supplements, appear to pose no problems in the diets of Europeans (*32*).

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Proposed Model for Setting Maximum Amounts of Vitamins and Minerals in Food Supplements

This risk management model takes into account the three risk assessments from EFSA/SCF (*15*), IOM (*16–20*) and EVM (*21*) and categorizes the essential nutrients into three groups of risk by use of quantitative and qualitative information. The evaluation takes into account the contributions to total nutrient intake from all sources, including conventional foods, fortified foods and food supplements (concentrated sources of nutrients or other substances with a nutritional or physiological effect that are intended to supplement the normal diet, alone or in combinations, marketed in dose form, such as capsules, tablets, pills, etc.). There are three categories of risk: group 1, no evidence of risk within ranges currently consumed and no risk to human health (no UL established); group 2, low risk of exceeding the UL; and group 3, potential risk at excessive intakes. The nutrients within the three groups are shown in Table V.When authoritative risk assessments show no adverse effects in healthy individuals, when there are no safety concerns about a nutrient, and when a UL cannot be established, those nutrients (vitamins B_1, B_2, B_{12}, biotin, pantothenic acid, vitamin K and chromium [trivalent form]) are placed in group 1 and no further risk management measures are required. In Europe, as there is no scientific basis for establishing a maximum level for these group 1 nutrients, the European Commission (*33*) concluded that, because of the absence of adverse effects, a proportionate risk management

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option, in line with the principles of better regulation, would not be to establish maximum amounts for these nutrients.

Table V. Proposed MLs in Food Supplements for Adults. SOURCE: Adapted with permission from reference (*35*). Copyright 2014 International Alliance of Dietary/ Food Supplements Associations (IADSA).

Group	*Maximum levels*
1. no evidence of risk to human health at levels currently consumed	No further risk management measures required
2. low risk of exceeding UL	Vitamin B_6 18 mg
	Vitamin C 1,700 mg
	Vitamin D 83 µg
	Vitamin E 270 mg
	Nicotinamide 820 mg
	Molybdenum 350 µg
	Phosphorus 1,250 mg
	Selenium 200 µg
	Magnesium 250 mg
	Folic acid 600 µg
	Potassium 1,500 mg
3. potential risk at excessive intakes	Vitamin A (retinol) 1,200 µg
	Beta-carotene 7 mg
	Calcium 1,000 mg
	Copper 2 mg
	Iodine 200 µg
	Iron 20 mg
	Manganese 4 mg
	Zinc 15 mg

MLs, maximum levels; UL, tolerable upper intake level.

For those nutrients with ULs, the categorization of the nutrients into groups 2 and 3 is based on a new methodology to determine how large the current margin of safety is and what it is likely to be in the future, which allows for different dietary contexts, new research findings, and application to food and food supplement products entering the food supply. The population safety index paradigm characterizes risk by means of the following equation:

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$$PSI = \frac{UL - (MHI + IW)}{RI}$$

where MHI is mean highest intake, IW is estimated mineral intake from water, drawn from the EFSA (*15*) and the EVM (*21*), and RI is in the labeling Recommended Daily Allowance sourced from Annex XIII of Regulation EU No 1169/2011 (*34*). The UL from all sources is obtained from the EFSA/SCF (*15*) when available, otherwise, the IOM UL values are used (*16–20*). The MHI is the "mean highest intake" from food sources (includes fortified foods but excludes food supplements) based on the 97.5 percentile mean intake data for males. The choice of males is because they generally have higher intakes than the equivalent intakes in females, both for adults and children, and hence the calculation introduces a small precautionary measure.

The labeling RI values are for the whole population and are generally higher than the reference nutrient intakes for a particular population group. The higher labeling RI denominator is used in the calculation because the value is harmonized across all 28 European Union Member States. The use of the labeling RIs and the ULs provide regulatory fixed points on the intake curve, and the higher labeling RI introduces a substantial precautionary measure for adults, and particularly for children. The categorization assumes that where the PSI of a nutrient provides a margin of safety 1.5 times the labeling RI between the 97.5 percentile intake of food (including fortified food) plus the IW (where appropriate for minerals) and the UL, the chance of exceeding the UL is low (group 2). When the margin of safety and the PSI is at or below 1.5 (i.e. the 97.5 percentile of intake from food and water is either above the UL or less than 1.5 times the labeling RI below the UL), there is a potential risk of exceeding the UL (group 3). The detailed intake data for adults and children, the PSI calculations, and the individual quantitative and qualitative risk management assessments for each nutrient are beyond the scope of this review and are in the reports published by Food Supplements Europe (*4*) and the International Alliance of Dietary Supplements Associations (*35*).

The fundamental risk management question is not only how large the margin of safety is now, but also is how large it is likely to be in the future, allowing for varying dietary contexts. To gain a measure of potential changes in consumer preferences, food supplement use and use of fortified foods, a comparison was made of dietary surveys undertaken in the United Kingdom over a period of 15 years. Based on this intake information, the current model assumes a precautionary risk management factor of a 50% increase in dietary intake for all the vitamins from foods, including fortified foods, and a 10% precautionary risk management factor for minerals. Taking into account the risk categorization of nutrients using the PSI and the quantitative estimates of future potential higher intakes from all other food sources including fortified foods, the proposed risk management model has been applied to determine MLs for vitamins and minerals in food supplements. Whenever the data are available, the following equations are used:

- For vitamins: MLS = UL – (MHI x 150%)
- For minerals: MLS = UL – [(MHI x 110%) + IW]

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The proposed maximum safe levels in food supplements for adults are shown in Table V. Reassuringly, the theoretical model for setting maximum levels of vitamins and minerals in fortified foods (27) also resulted in three categories of risk characterization for micronutrients that could be added safely to appropriate foods at specified levels similar to the categories described in Table V.

Balancing Risks of Excessive Intakes and Deficiency

Where there is a narrow range of safe intake and a potential risk that consumers might exceed the UL on a daily basis, it may not be possible for the risk manager to use the UL or GL as a reference point for establishing an ML for a particular nutrient. A good example is the preformed retinol form of vitamin A. The SCF/EFSA and IOM established a UL of 3,000 μg retinol equivalents per day, which was based on the risk of adverse effects, including birth defects, reduced bone mineral density, and liver abnormalities. Above this level of 3,000 μg retinol equivalents per day the risk of adverse effects gradually increases, and long-term vitamin toxicity is associated with levels of 7,500 to 15,000 μg preformed retinol per day. In 2003, the EVM considered the two areas of evidence regarding potential adverse effects of vitamin A, one on risk of teratogenicity and the other on the risk of bone fracture. The EVM concluded that, given the severity of the effect, it is prudent to regard 3,000 μg retinol equivalents per day as the threshold for teratogenicity. However, in setting the GL, the EVM also took into account emerging evidence from epidemiological studies and from studies in laboratory animals that vitamin A affects calcium metabolism and might increase bone fracture risk in older women and men. Despite the paucity of data, the EVM concluded that risk of hip fracture is a continuous graded response, that it was not possible to identify an intake that is without some degree of risk, and that the GL should be 1,500 μg per day. The labeling RI for vitamin A is 800 μg per day.

The example of preformed retinol illustrates that the determination of SULs is even more critical when the range of intakes for different age and gender groups is very wide indeed, reflecting the limited distribution of preformed retinol in foods. This dependency on retinol from relatively few foods (the main dietary sources are liver and liver products) results in the median intakes typically being 20–50% less than the average intakes, which highlights the risk of inadequate intakes in sizeable groups of the United Kingdom population. While the dietary intake data show that the risk of exceeding the UL could theoretically affect a very small proportion of the population (less than 3%), there are substantial groups of the population that would fail to achieve the recommended amount and thus have a real risk of deficiency.

Young women and those considering pregnancy have been advised by government scientific advisory boards to avoid consumption of liver or liver products, including fish liver oil, because of their high vitamin A contents. For example, vitamin A is not included in the United Kingdom National Health Service's Healthy Start vitamin tablets for pregnant women and mothers (*36*). The UK National Institute for Care and Health Excellence has published recommendations (*37*) based on the UK Chief Medical Officer's advice on

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vitamin D supplements for pregnant and breastfeeding women, which state that supplements containing 5–10 μg of vitamin D must not contain retinol. However, the risk of too-high vitamin A intake in the form of preformed retinol exists, if at all, only during the first 4 weeks of pregnancy and not later. Furthermore, assuming an absorption rate of 40%, it is hardly possible to consume critical amounts of vitamin A from 100 g of liver (*38*).

Strobel *et al.* (*38*) point out that the actual teratogenic substance is not retinol but its metabolite retinoic acid, which does not occur in foods and can only be synthesized from retinol in the body. Since the synthesis of retinoic acid from retinol in normal metabolism is strictly controlled, even excessive retinol intakes will not result in supra-physiological levels of retinoic acid.

The warnings against consumption of live and potential concerns over intake of preformed retinol need to be reassessed urgently as they might have caused the low consumption of liver to decrease even further, especially among young women and mothers. Not only might the health of the mother be at risk if vitamin A intake is insufficient, but also the development of the child. The overall development of the baby and especially lung development and maturation of the embryo is dependent on a sufficient supply of vitamin A. If supply is low, vitamin A stores in the lung, especially in pre-term babies, are low. It is critical to develop sufficient vitamin A stores in the lung, which happens in the third trimester of pregnancy. If not, these children will be at increased risk for bronchopulmonary dysplasia, one of the most frequent and life-threatening respiratory diseases in preterm infants (*38*).

Vitamin A is one of the more labile vitamins, and various factors, such as its sensitivity to oxygen, ultraviolet light, pH, etc, can result in significant decreases in bioactivity. The role of beta-carotene as a precursor of vitamin A also needs to be considered (*39*). Restrictions on beta-carotene that are largely relevant to smokers should be considered carefully in relation to the optimization of vitamin A intakes for children and young women, especially those considering pregnancy. Indeed, the EFSA (*40*) has recently re-evaluated the safety of beta-carotene and concluded that exposure from its use as a food additive and as a food supplement at a level below 15 mg/day does not give rise to concerns about adverse health effects in the general population, including smokers.

Clearly, nutritional risk managers will have challenging scientific, technical and policy issues to address, especially in the case of vitamin A.

Risk Management Approaches for Children Aged 4–10 Years

The risk assessment process recognizes that there may be sensitive groups, such as infants, children, certain individual adults, the elderly, and pregnant and lactating women. For children, the IOM and EFSA/SCF risk assessments addressed the setting of ULs for children, and the accepted method is, where appropriate, to extrapolate the UL derived from adult data. The extrapolations are usually made on the basis of body weights by means of either reference or metabolic body weights ($BW^{0.75}$) (*5*, *15*). The PSI risk management paradigm and methodology can also be applied to children, and the approaches are being shared

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with risk managers in Europe (*4*). The scientific data on nutrient intakes, nutrient requirements, absorption, metabolism and excretion of nutrients in children is extremely limited. In addition, there are substantial physiological changes in the velocity of growth and in endocrine status during childhood and adolescence. Over the decades there has been progressive increases in heights and weights of children that are associated with trends towards earlier puberty. The enormous variability in the rate and timing of the adolescent growth spurt influences the nutritional requirements of children at different ages and their adaptability to nutrient deficiencies and excess. For the purposes of setting MLs in fortified foods and food supplements for children, the risk managers are considering a children's age range of 4–10 years. This choice relates to the availability of scientific data, including the age ranges of reference body weights, the availability of nutrient intake data, the age ranges for dietary reference values and the extrapolated ULs from EFSA opinions. Interestingly, the IOM (*16*) described early childhood as ages 4–8 years and determined that the adolescent age group should begin at 9 years.

It should be noted that market practices for food supplements differentiate between products intended for adults and those for children, whereas when foods are fortified, the issues are complicated by the fact that foods with added nutrients are consumed both by adults and by children. For children, proposals for establishing safe maximum levels in fortified foods and food supplements will require proportionate risk management measures and scientific judgment to balance the risk of deficiency with risk of overconsumption and avoidance of any adverse effects. The main objective is to protect children and to facilitate parents and carers to make informed choices.

Discussion and Conclusions

Nutritional risk analysis provides an interpretive and analytical framework to be used for systematically dealing with the available scientific information and its associated uncertainties, and for identifying research needed to reduce those uncertainties. In this chapter I have highlighted some of the difficulties and noted that regulatory authorities are frequently confronted with a need for decision-making in the face of insufficient or inconsistent data. However, risk analysis, and particularly nutritional risk management, is about evaluating the magnitude of a possible risk and taking care not be overly restrictive.

Given the complexities, appropriate nutritional risk assessment and risk management models and methodologies can be proposed that are pragmatic, transparent and scientifically justified as well as proportionate and consistent with regulatory developments and health policies. The setting of SULs by nutritional risk assessors and the setting of MLs of vitamins and minerals in fortified foods and food supplements by nutritional risk managers build in levels of precaution and are aimed at providing the framework within which consumers can make informed decisions about intake, having confidence that harm should not ensue.

As a consequence of limited data, risk assessors apply the precautionary principle of allowing for the variable quality of information so that risk managers

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can weigh up the safety margins between necessity and adverse effects. As previously stated, risk assessment and risk management for nutrients differ from those for other substances in food because vitamins and minerals are essential for human life and, consequently, adverse effects can result from suboptimal intakes and deficiencies as well as from excessive intakes. Nutritional risk management draws together the information on the range of safe intake—sometimes referred to as the acceptable range of oral intake (*41*)—and involves the establishment of the risk to the population habitually exceeding the UL. The two values used as indicators by risk managers to establish the extent of the range of safe intake for each nutrient are, for the upper end, the UL and, for the lower end, the labeling RI. These set points are used in the proposed risk management models for setting maximum levels of vitamins and minerals in fortified foods and food supplements for adults and children. It is important to emphasize that the ULs and labeling RIs are determined by two completely different scientific conceptual approaches, and that the two values are used only as convenient indicators of the extent of safe intake and to help categorize nutrients on the basis of the risk associated with exceeding their ULs. In other words, when the UL and labeling RI are close together, the range of safe intake is relatively small; where they are further apart, the safe range of intake is relatively large.

Some countries around the world have proposed that MLs should be based on labeling RIs. However, FAO/WHO (*5*), in their model for establishing ULs for nutrients, and the Codex Alimentarius Commission (*1*) as well as the European legislation (*24*, *25*) require that the establishment of MLs be based on scientific nutritional risk analysis methods. In Europe, the use of the labeling RI approach to setting MLs has been rejected by the European Commission and condemned by the European Court of Justice.

The scientific nutritional risk assessments for determining ULs for each nutrient depend on the availability of good data on the nature, frequency, and severity of adverse effects detected at different levels of intake. The database supporting safety in use of vitamins and minerals is limited, and special care has to be taken when considering potentially vulnerable subgroups of the population such as children, the elderly, and pregnant and lactating women. It is important for risk managers to recognize that the UL is defined by risk assessors as the ML of chronic daily intake of a nutrient from all sources that is judged to have no appreciable risk of adverse effects occurring at some specified level of exposure. The EVM (*21*) defined an SUL as an intake for long-term supplementation that can be consumed daily over a lifetime without any significant risk to health, on the basis of the available evidence, and a GL as a level that represents an approximate indication of a level that would not be expected to cause adverse effects but has been drawn from limited data and is less secure than an SUL. The determination of SULs and GLs in the EVM risk assessment relate to the amounts of vitamins and minerals that potentially susceptible individuals could consume daily on a lifelong basis without medical supervision and in reasonable safety (*21*).

In conclusion, food fortification practices and current levels of nutrients used in food supplements for over three decades have been shown to be safe and effective. However, because of the increased interest in and availability of fortified foods and food supplements, it is important to continue to undertake appropriate

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nutritional risk analysis measures to ensure consumer protection. The purpose of this review is to contribute towards the development of scientifically based processes for the setting of maximum levels of essential nutrients in fortified foods and food supplements under food law. Consultation and continuing dialogue between the various interested parties are critical to ensure that proportionate measures are used to protect consumers and to facilitate informed choice.

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Chapter 10

PEPFAR – A U.S. Government Program That Is Helping To Keep Millions Alive Around the World

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In 2003, the United States President's Emergency Plan For AIDS Relief (PEPFAR) was announced with the aim of bringing much-needed medications to the millions of people infected with human immunodeficiency virus (HIV) in resource-poor countries around the world. Over the years PEPFAR has been a great success. At the end of September, 2014, PEPFAR supported 7.7 million people on treatment. In this chapter I provide a brief history of PEPFAR and describe the role that the United States Food and Drug Administration (FDA) has played in the PEPFAR program. The way in which the FDA communicates its policy to manufacturers and other interested parties and modifies its expectations and requirements to deal with the changing nature of the problem are also examined.

Introduction

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). HIV destroys the immune system over a period of 8–10 years, leaving the victim open to various opportunistic infections and neoplasms that eventually lead to death. Although the disease is thought to have arisen earlier in Africa, it first came to widespread public attention in the early 1980s. Over the course of the 1980s and 1990s a number of drugs were developed that enabled HIV to be effectively treated. However, these drugs were very expensive and not available to the millions of infected people in resource-poor

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countries around the world. In 2003, the United States President's Emergency Plan For AIDS Relief (PEPFAR) was announced with the aim of bringing much-needed medications to these people. Over the years, PEPFAR has been a great success, with 7.7 million people currently under treatment. In this chapter, I describe the role that the United States Food and Drug Administration (FDA) has played in the PEPFAR program and show how the FDA communicates its policy to manufacturers and other interested parties, and how it modifies its expectations and requirements to deal with the changing nature of the problem.

A Short History of Antiretroviral Drugs

The history of antiretroviral drugs begins in the early 1980s with the first public awareness of AIDS. The following timeline presents some key occurrences:

- 1981: although the disease appeared to have arisen earlier in Africa (*1*) AIDS first comes to public notice with reports of previously rare diseases in homosexual patients (*2*)
- 1983: the causative virus HIV-1 was discovered (*3*)
- 1987: zidovudine was introduced as the first drug against HIV (*4*)
- 1995: saquinavir was approved as the first protease inhibitor (*5*)
- 1996: nevirapine was approved as the first non-nucleoside reverse-transcriptase inhibitor (NNRTI) (*6*)
- 1996: combination drug therapy, known as highly active anti-retroviral therapy (HAART), was introduced (*7*)
- 2003: PEPFAR was announced (*8*)
- 2004: first full approval of a generic antiretroviral (didanosine delayed-release capsules) (*9*)
- 2005: first tentative approval of an antiretroviral (lamivudine/zidovudine tablets co-packaged with nevirapine tablets) (see below for a discussion of the tentative approval process) (*9*)
- 2006: FDA issued a guidance on fixed-dose combinations, co-packaged drug products, and single-entity versions of previously approved antiretrovirals for the treatment of HIV (commonly known as the PEPFAR guidance) (*10*)
- 2007: FDA issued *Guidance for Industry User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR* (*11*)
- 2009: 100th PEPFAR product tentatively approved (lamivudine tablets) (*9*)
- 2012: 150th PEPFAR product tentatively approved (lamivudine and zidovudine tablets for oral suspension) (*9*)
- 2014: PEPFAR products were supporting 7.7 million patients (*12*)
- 2015: 184th PEPFAR product tentatively approved (ritonavir tablets) (*9*)

Key FDA approval dates for drugs are as follows (the full list of drugs is available at Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/drugsatfda/):

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- Retrovir (zidovudine, AZT) March 19, 1987
- Zerit (stavudine, D4T) June 24, 1994
- Epivir (lamivudine, 3TC) November 17, 1995
- Norvir (ritonavir, RTV)March 1, 1996
- Viramune (nevirapine, NVP) June 21, 1996
- Combivir (lamivudine + zidovudine) September 27, 1997
- Ziagen (abacavir, ABV) December 17, 1998
- Kaletra (lopinavir + ritonavir) September 15, 2000
- Trizivir (abacavir + zidovudine + lamivudine) November 14, 2000
- Viread (tenofovir, TDF) October 26, 2001
- Reyataz (atazanavir, ATV) June 20, 2003
- Emtriva (emtricitabine, FTC) July 2, 2003
- Truvada (tenofovir + emtricitabine) August 2, 2004
- Prezista (darunavir, DRV) June 23, 2006
- Atripla (efavirenz + emtricitabine + tenofovir) July 12, 2006
- Stribild (elvitegravir + cobicistat + emtricitabine + tenofovir) August 27, 2012
- Tivicay (dolutegravir, DTG) August 13, 2013

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Disease Progression

After infection the HIV virus destroys CD4 T cells over a period of 8–10 years. When the CD4 cell count dips below 200 cells/mm^3, the risk of AIDS-defining illnesses developing increases. These illnesses include opportunistic infections and certain neoplasms, and death occurs as a result of one or more of them (*13*).

The Problem (at the Beginning of the 21st Century)

Millions of people were infected with HIV, and in 2001, the Centers for Disease Control and Prevention estimated that 36 million people were infected worldwide (*14*). However, most of them (25.3 million [70%]) lived in resource-poor countries in sub-Saharan Africa (*14*) and the drugs to combat HIV were very expensive (over US$20,000 per year (*15*)) and are covered by patents (*16*).

It was recognized that at least part of the solution to this problem would involve the following. Drug companies would agree not to enforce patents for drugs manufactured for use in resource-poor countries (*16*). Drugs would be manufactured in low-cost countries and applications being submitted to the FDA (*9*), which would agree to review these applications to their customary standards, as set out in *Guidance for Industry: Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* (*10*). Finally, large sums of money would be provided (*10*).

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A common treatment is a tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate that is taken once per day. It is marketed in the United States under the trade name Atripla. It contains the following active ingredients: efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg. This is a total of 1,100 mg of complex, chirally pure, synthetic chemicals per day, and is equivalent to about 400 g per person per year. For 1 million people this is about 400 tons per year. In addition there are costs associated with mixing these active ingredients with other inactive ingredients (excipients) and manufacturing tablets. These tablets then need to be packaged, shipped to the recipient countries (for example from India to Tanzania), and distributed to the patients.

Drugs intended to treat HIV infection all have complex structures. Figure 1 shows structures of the active ingredients present in Atripla.

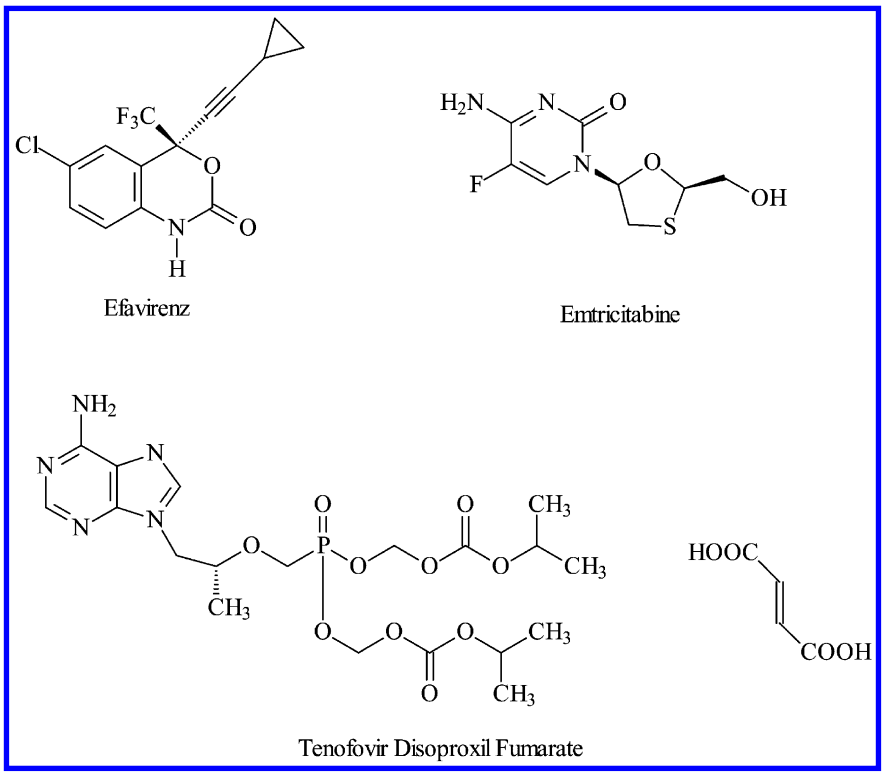

Figure 1. Chemical structures of the active ingredients in Atripla.

Of note is that each molecule has one or two chiral centers, that is, a carbon that can be bonded to other atoms in either a left-handed or a right-handed fashion. Normally, chemical reactions produce mixtures of molecules that are both left handed and right handed and special techniques are required to manufacture only one type. Other HIV drugs exhibit even more complex structures requiring

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sophisticated manufacturing processes. Nevertheless these challenges can be, and have been, overcome and these pharmaceuticals are being manufactured on the large scales required.

Enter PEPFAR (www.pepfar.gov)

PEPFAR was initiated by President Bush and passed in 2003 (*17*). It has since been reauthorized (*18*) and has received $52 billion of US Government funding to date (*17*). The *PEPFAR Annual Report: 10th Annual Report to Congress* reported that 6.7 million people were on treatment (*19*). Increasingly, patients are taking more-convenient formulations that include three separate components and are taken once per day (Figure 2).

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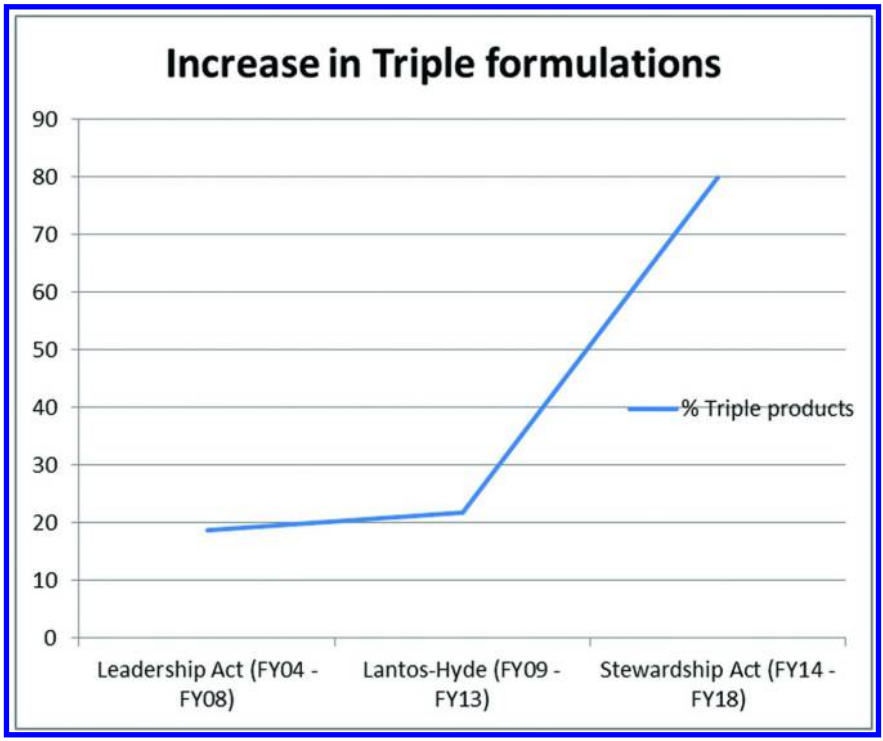

Figure 2. Improved convenience of HIV drug formulations. FY, financial year.

PEPFAR from the FDA's Point of View

Marketing applications are submitted to the FDA and they are reviewed to the FDA's customary standards (*10*). If there are no outstanding patent issues and if all the requirements are met, the applications are approved. If the applicant wanted to do so, it would be able to market this product in the United States, although in many cases, for economic or other reasons, applicants may choose not to do so. This is known as full approval.

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If patent issues would prevent marketing in the United States, the applications are tentatively approved. If the patent issues are resolved at a later date, the applicant can then apply for full approval. Tentative approval as a concept pre-dated PEPFAR, but the way in which it was applied to PEPFAR products was new.

Within the FDA, the chemistry, manufacturing, and controls (CMC) sections of the application are reviewed by two different groups. Copies of a currently marketed product that has the same active ingredient, strength, dosage formulation, route of administration, etc., are reviewed by the Office of Lifecycle Drug Products under section 505(j) of the Food, Drug, and Cosmetic Act. Other products are reviewed by the Office of New Drug Products under section 505(b)(2) of the Act (*10*).

For example, atazanavir capsules would be reviewed under section 505(j) because there is already a marketed product, Reyataz (atazanavir) capsules, marketed in the United States by the patent holder. In such a review Reyataz would be termed the reference listed drug. Tablets containing atazanavir and ritonavir (a desirable combination) would be reviewed under section 505(b)(2) of the Act because there is no product with this combination of active ingredients currently approved for marketing in the United States and, therefore, there is no reference listed drug. If all the requirements were met, both of these products would be granted tentative approval, the atazanavir capsules because there would be outstanding patent issues with the manufacturer of Reyataz.

It is very important to note that PEPFAR products are reviewed to the same standards as all other marketing applications received by the FDA. Approved products can be marketed in the United States (although the manufacturer may choose not to do so for financial or other reasons). The only reason that tentatively approved products cannot be marketed in the United States is that there are outstanding patents. Thus, it can be said, "We would give these drugs to our own people". There are currently 184 approved or tentatively approved PEPFAR products (*9*).

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How the Review Process Works

The applicant submits (mostly electronically) documentation as required by the Food, Drug and Cosmetic Act, as amended, and Title 21 of the Code of Federal Regulations. From the CMC point of view the documents will describe the manufacturing process in detail (Figure 3). FDA reviewers read these documents and produce internal reports. As required, information requests are sent to the applicant to elicit additional information or to provide clarifications. Strict deadlines govern the process. Eventually, if all requirements are met, approval or tentative approval is granted.

The review process is resource intensive and, from the CMC perspective, PEPFAR applications require the same level of effort as any other application. Because many issues, such as toxicity and clinical efficacy, will already have been settled in the context of the original applications, other review disciplines (e.g. clinical, statistics) might not be so involved in the review of PEPFAR applications.

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Figure 3. What the CMC section of an application looks like when printed out.

For PEPFAR the bulk of the work is done by chemists and biopharmaceutical specialists in the Office of Lifecycle Drug Products and the Office of New Drug Products. Clinical and toxicological issues will largely, but not entirely, have been settled during the review of the original application submitted by the patent holder. PEPFAR products do not contain new molecular entities, but they may contain new combinations of existing drugs. For administrative convenience drug substances are generally described in Drug Master Files.

Communication and the Development of Policy

Drug development and manufacture is regulated by the Food, Drug and Cosmetic Act, Title 21 of the Code of Federal Regulations, and other guidance. Many of the technical details are covered in the guidance issued by the FDA. Very briefly, the FDA cannot waive the requirements of the Act but might be able to waive the requirements of some regulations for sufficient reason. Following guidance is not mandatory, but a scientific justification might be required if it is not followed (*20*).

For PEPFAR products, a guidance issued in 2006 entitled *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of*

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Previously Approved Antiretrovirals for the Treatment of HIV (*10*) contains recommendations and procedures to speed the review process. This guidance is currently under revision.

FDA and PEPFAR Interactions

In all cases, interaction goes both ways. As previously mentioned, manufacturers submit marketing applications, and in the course of reviewing these applications FDA reviewers send information requests to the manufacturers.

Outside the application review process there are interactions between the FDA and manufacturers via public forums, such as those organized by the Clinton Health Action Initiative.

To date, the FDA has participated in six PEPFAR-related international outreach initiatives (four face to face and two via video connection). These meetings, oriented to generic and innovator manufacturers, provided critical guidance on key issues related to the successful submission of original PEPFAR applications (Abbreviated New Drug Applications and New Drug Applications) and subsequent changes after tentative approval. Additionally, these meetings presented an important opportunity to interact directly with manufacturers and collect information on other PEPFAR-related issues critical to maintaining and increasing the effectiveness of this program in the agency.

Products that have been tentatively approved or approved by the FDA are listed in the USAID Consolidated List of Approved ARVs and are eligible for procurement by US Government procurement agents, such as the Supply Chain Management System (http://scms.pfscm.org/scms). The FDA has reached out to these agents. Items such as expiration dates and packaging are of particular interest. Other outreach efforts take the form of participation in conferences, training foreign regulators, publications, and talks

FDA and Manufacturer Interactions during the Review Process

Typically, for the Office of New Drug Products a New Drug Application is reviewed and an information request is sent to the applicant requesting more details. The applicant's response is reviewed and a second (hopefully shorter) information request might or might not be required. Information requests are submitted in writing (fax and e-mail are acceptable) and are sent from the FDA by project managers after supervisory review. Companies generally have a dedicated regulatory affairs staff that compiles the responses and submits them in writing to the FDA. These communications are held in the strictest confidence by the FDA and are not made public.

It is important to note that information requests and responses do not touch on general questions. They deal with technical issues that are specific to the application. Despite their name, as well as requests for information, they might also ask for changes to be made in various aspects of the application. Hypothetical requests might be as follows:

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- Please provide the study that justifies holding bulk tablets for up to 6 months before they are packaged in bottles or blister packs.
- Please reduce the limit for impurity A from not more than 0.7% to not more than 0.5% or provide a justification for not doing so.

In response, our hypothetical applicant might provide a report that justifies a 6 month hold time and might reduce the limit of impurity A limit to not more than 0.5%. Alternatively, it might change the application to indicate that tablets should be packaged immediately and they might produce a justification for the 0.7% limit, perhaps based on toxicological data.

Both sides can learn from these interactions. In our hypothetical example the applicant may learn that the FDA expects tablet hold times to be justified and the FDA may learn about the toxicology of impurity A. In each case, this knowledge can be used to improve future applications by the company and the FDA's review of future applications.

A few years ago we analyzed the questions that we sent out in information requests related to PEPFAR applications (Figure 4). Because of the interactive nature of the interactions between the FDA and manufacturers, the questions tend to change over time as understanding improves (and, therefore, the need for questions is reduced) in some areas, whereas other parts of the application give rise to more questions because of changes in technology. Thus, the results of this exercise would probably be different if we did the study today.

For drug products (e.g. tablets, capsules), specifications and stability generated the most questions.

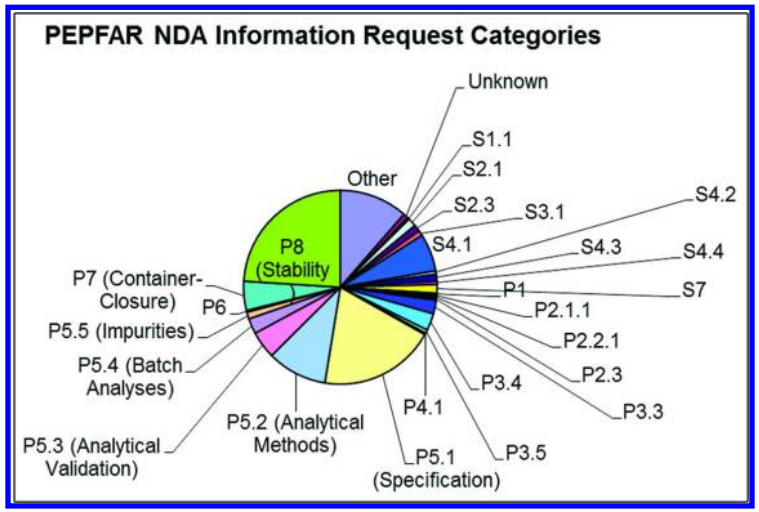

Figure 4. Types of questions from the Office of New Drug Products concerning PEPFAR products and the section of the application to which they refer. The P codes refer to the sections in the body of data in Module 3 in the Common Technical Document (21).

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For PEPFAR products, drug substances (i.e. the active pharmaceutical ingredients) are generally regulated by sending the relevant information to Drug Master Files. This is an administrative convenience only, and the level of oversight remains the same as that for information submitted under, for example, a New Drug Application. Surveying the information requests sent out in connection with drug substance Drug Master Files, we found that the control of starting materials and intermediates was most important (Figure 5).

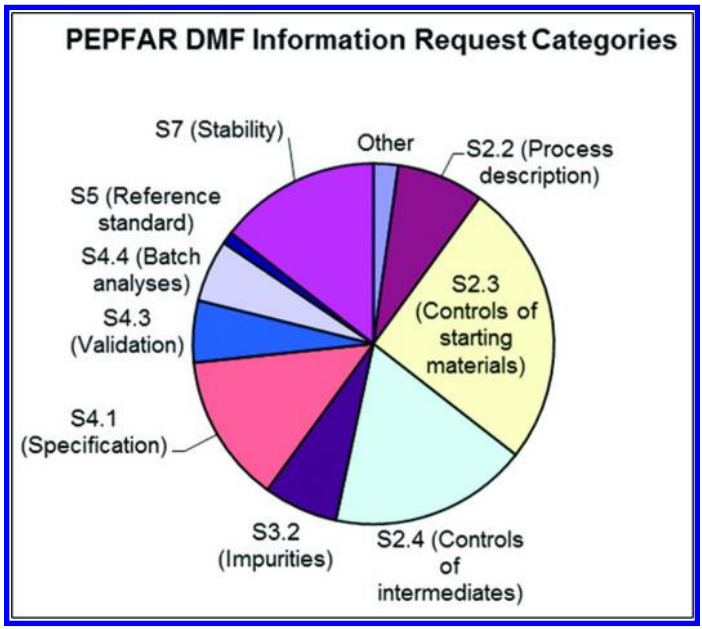

Figure 5. Information requests sent out from the Office of New Drug Products concerning PEPFAR in connection with drug substance Drug Master Files. The S codes refer to the sections in the body of data in Module 3 in the Common Technical Document (21).

Dissolution Methods

The performance of most drug products (e.g. tablets, capsules) is tested by seeing how rapidly they dissolve under tightly specified conditions. An example of these conditions might be 900 mL of 100 mM hydrochloric acid stirred at 50 rpm at 37°C, with a requirement that 80% be dissolved in 30 min. Satisfactory dissolution performance provides assurance that batches are manufactured in a consistent manner and will perform as desired. Agreement on the all aspects of the dissolution method is a crucial aspect of the drug approval process. Because the dissolution method will be used to collect information that will be presented in the marketing application, agreement should be reached some time before the marketing application is received. This will give the manufacturer a chance to accumulate data to show that the performance of the product does not change as it

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ages. In other words, samples that have reached their expiration date should have the same dissolution performance as freshly manufactured material.

To make it easier for manufacturers to develop a dissolution method for a new product, the FDA established, in 2004, an on-line database of methods that have been found to be acceptable (*22*). However, methods are dependent on the exact nature of the formulation and, therefore, the FDA might request changes from methods posted online. In this case, communication with the FDA before the New Drug Application is submitted, while there is still time to make changes, can be very helpful.

Online Information at the FDA

The FDA posts a huge amount of information on its web site, including a database of databases (*23*). Sometimes this information is redacted to preserve confidentiality.

A few examples that are particularly relevant to drugs are described below. Space does not permit a discussion of the numerous other databases that might be found on the FDA's web site.

The Inspections Database (*24*) provides a searchable listing of manufacturing facilities and dates and outcomes of FDA inspections.

Searchable Warning Letters Database (*25*) provides the text of warning letters that have been sent out by the FDA, including those sent to drug manufacturing facilities.

Drugs@FDA (*26*) is a very powerful database providing information on all FDA-approved products. Searches can be conducted by trade name, generic name, or application number. The system will provide the current package insert, which describes indications, dosages, side effects, etc. In addition, a list of changes to the application (Supplements) is provided, including the letters sent by the FDA to the company indicating that the change was acceptable and, in some cases, a copy of the FDA's internal review of the change. The letters and reviews might be redacted for reasons of commercial confidentiality. Because of patent restrictions, tentatively approved applications are not listed on this site.

The FDA PEPFAR Page (*9*) provides a list of products that are approved and tentatively approved by the FDA for the PEPFAR program.

The FDA HIV/AIDS page (*27*) provides important information for patients on regulatory issues related to HIV, including product approvals, and safety warnings.

OpenFDA adverse drug event reports (*28*) provide open application programming interfaces, raw-data downloads, documentation and examples, and a developer community for an important collection of FDA public datasets.

OpenFDA drug recall enforcement reports (*29*) provide information on drug recall enforcement for FDA-regulated products that have been deemed either defective or potentially harmful.

All drug products are formulated with inactive ingredients (excipients). These ingredients do not have a pharmacological action themselves but they are critical to the action of the drug product as a whole, for example, by ensuring that the product dissolves in an acceptable manner. A new inactive ingredient or a

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large amount of an inactive ingredient that has been used before, however, may have toxicity implications. The Inactive Ingredient Search for Approved Drug Products database (*30*) lists the inactive ingredients that have been previously used in FDA-approved products together with the amounts that were used. If an inactive ingredient has been used before at the same or a lower level with the same route of administration the FDA might require a less extensive review. It's important to note that this database has been extensively redacted so, if there is any doubt, it is probably wise for the manufacturer to consult with the FDA before submitting the marketing application, as FDA reviewers have access to a more-extensive non-redacted version.

The Orange Book (Approved Drug Products with Therapeutic Equivalence) (*31*) lists products that have been approved by the FDA. It can be searched for trade names, generic names, applicants, or application numbers. The Orange Book provides information on patents and exclusivity (exclusive marketing rights granted by the FDA) for each approved application. This information can be valuable to other companies wishing to make generic versions of a marketed product.

The World Health Organization (WHO) also publishes information that is relevant to the FDA's PEPFAR work. The WHO operates a prequalification program that aims to make quality priority medications available for the benefit of those in need (*32*). The searchable web site contains list of medicinal products for HIV/AIDS, tuberculosis, and malaria that have been assessed by this program. The list also contains FDA approved and tentatively approved antiretroviral drugs. WHO Public Assessment Reports provide publicly available evaluations of the various pre-qualified medicinal products.

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A Two-Way Street

By looking at questions that arise repeatedly, the FDA can identify issues that need to be raised in general terms through guidance or outreach. Examples of issues that have been addressed during the development of the PEPFAR process are stability conditions, naming conventions, and unidentified impurities. Conversely, by looking at the questions that they receive from the FDA, industry can modify the contents of applications

How Have Things Changed Over the Years?

To make sure that drugs will remain safe and efficacious through to the expiration date stamped on containers, samples are stored under closely controlled conditions and periodically tested to show that they comply with their approved specification. Marketing applications for products that will be sold in the United States generally involve stability testing at 25°C (77°F) and 60% relative humidity, which are thought to be reasonably representative of domestic conditions. Initially, PEPFAR applications contained stability data obtained at 25°C and 60% relative humidity, but it was felt that countries using PEPFAR products are generally hotter and more humid, and, therefore, testing at 30°C

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and 75% relative humidity would be more appropriate (when warranted by the stability of the product). Accordingly, the FDA requested that manufacturers conduct stability testing at 30°C and 75% relative humidity. Now most products are tested under these conditions and storage statements such as "Store at room temperature below 30°C" are now common.

Other changes that have occurred in the way that the FDA responds to PEPFAR applications include the following:

- a mechanism for reporting changes after tentative approval to the agency has been devised
- agreement has been reached that the expiration dating period (shelf life) may be extended on the basis of data from the batches in the original application (which are not necessarily commercial scale).
- PEPFAR applications should now be submitted with 6 months of stability data for three batches
- revised PEPFAR guidance will be issued soon
- the Office of New Drug Products has instituted a generic e-mail account for questions: newdrugCMC@fda.hhs.gov

Competition Is Good!

There are an increased numbers of tentatively approved applications, indicating that more manufacturing capacity is coming online. More competition means lower prices. For example, a bottle of 30 generic Atripla tablets, which is a 1-month supply, is now $10.51 (*33*). The cost of treating one patient has declined from $1,100 to $315, and less than half of this is the cost of the drugs (*34*). There are now 7.7 million individuals being treated.

Clinical Aspects

Current WHO guidelines recommend treatment of individuals with a CD4 count of <500 cells/mm^3. The starting regimen is usually one combination pill once per day, (e.g. efavirenz/emtricitabine/tenofovir disoproxil fumarate or efavirenz/lamivudine/tenofovir disoproxil fumarate). Another option is atazanavir/ritonavir with emtricitabine/tenofovir disoproxil fumarate once per day (thanks to Dr. Jeff Murray, Division of Anti-Viral Products, FDA).

The Future?

Forecasting the future is always risky, but perhaps some of the following developments will come to pass:

- revised PEPFAR guidance
- new combinations of drugs developed in response to clinical developments
- new formulations of existing drugs

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- move of manufacturing closer to the populations being treated
- increased collaboration between the FDA and local regulators
- increased outreach to manufacturers by the FDA
- increased interactions between manufacturers and the FDA before the submission of applications for PEPFAR products
- changes in response to evolving WHO guidelines
- other diseases, such as hepatitis, may be included in PEPFAR or similar programs

Conclusions

Over the years, PEPFAR has been a great success. At the end of September, 2014, PEPFAR supported 7.7 million people on treatment. Interactions between the FDA and manufacturers and other interested parties have been critical to the success of this program in bringing large quantities of low-cost effective medications to people in resource poor countries around the world.

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